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RESEARCH REPORT

Disease-specific wearable sensor algorithms for profiling activity, gait, and balance in individuals with Charcot–Marie–Tooth disease type 1A

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Abstract

Background/Aims: Charcot–Marie–Tooth Disease type 1A (CMT1A), the most common inherited peripheral neuropathy, is characterized by progressive sensory loss and weakness, which results in impaired mobility. Increased understanding of the genetics and pathophysiology of CMT1A has led to development of potential therapeutic agents, necessitating clinical trial readiness. Wearable sensors may provide useful outcome measures for future trials.

Methods: Individuals with CMT1A and unaffected controls were recruited for this 12-month study. Participants wore sensors for in-clinic assessments and at-home, from which activity, gait, and balance metrics were derived. Mann–Whitney U tests were used to analyze group differences for activity, gait, and balance parameters. Test–retest reliability of gait and balance parameters and correlations of these parameters with clinical outcome assessments (COAs) were examined.

Results: Thirty individuals, 15 CMT1A, and 15 controls, participated. Gait and balance metrics demonstrated moderate to excellent reliability. CMT1A participants had longer step durations ($p < .001$), shorter step lengths ($p = .03$), slower gait speeds ($p < .001$), and greater postural sway ($p < .001$) than healthy controls. Moderate correlations were found between CMT-Functional Outcome Measure and step length ($r = -0.59$; $p = .02$), and gait speed ($r = 0.64$; $p = .01$); 11 out of 15 CMT1A participants demonstrated significant increases in stride duration between the first and last quarter of the 6-min walk test, suggesting fatigue.

Interpretation: In this initial study, gait and balance metrics derived from wearable sensors were reliable and associated with COAs in individuals with CMT1A. Larger longitudinal studies are needed to confirm our findings and evaluate sensitivity and utility of these disease-specific algorithms for clinical trial use.

KEYWORDS
activity, balance, Charcot–Marie–Tooth (CMT), gait, wearable sensors

Sharma and Eichinger contributed equally to this study.

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1 | INTRODUCTION

Charcot–Marie–Tooth (CMT) neuropathies are inherited peripheral neuropathies that affect 1 in 2500 individuals and impact both motor and sensory nerves.[1] CMT type 1A (CMT1A) is the most common form of CMT and is a result of a 1.5 Mb duplication on chromosome 17 containing the peripheral myelin 22 (*PMP22*) gene.[2,3] Individuals with CMT1A exhibit slowly progressive weakness and sensory impairments in a distal to proximal pattern, leading to functional limitations in gait and balance and reduced quality of life.[4,5]

There have been significant advances in the understanding of the genetic basis and pathomechanisms of CMT, including CMT1A, leading to potential treatments and highlighting the urgent need for clinical trial readiness. Optimal outcome measures for clinical trials in CMT1A need to account for its slowly progressive nature.[6–10] The Inherited Neuropathies Consortium (INC) has developed and validated several disease-specific measures of neurologic impairment and function, including the CMT Neuropathy Scale and version 2-Rasch analyzed (CMTNS and CMTNSv2-R), the CMT Exam Score (CMTES) and CMTES-Rasch analyzed (CMTES-R), the CMT Pediatric Scale (CMTPedS), and the CMT Functional Outcome Measure (CMT-FOM).[6,11–16] The CMTES and CMTES-R are composite measures of disease severity and have been found to detect change over 2–6 years.[10] The CMTPedS and CMT-FOM are multi-item measures that assess distal strength, hand function, gait, mobility, and balance.[17,18] The CMTPedS has been shown to detect progression over a 2-year period in children with different CMT types, including CMT1A.[9,13] The sensitivity to change of the CMT-FOM is currently being evaluated in the Accelerate Clinical Trials in CMT study (ACT-CMT; NIH grant # U01 NS109403). In addition to these disease-specific clinical outcome assessments (COAs), activity level assessments such as timed walking tests and standardized balance measures have demonstrated modest sensitivity to change in CMT.[19,20] These measures of neurologic impairment and function will be incorporated as outcomes in late-stage clinical trials in CMT; however, biomarkers are also required to detect signals of treatment effect in early stage trials.

Gait analysis has been used to characterize, quantify, and track changes in locomotion and postural deficits in CMT over time.[21,22] Movement analysis, as a measure of locomotion function, has demonstrated good test–retest reliability[21,22] and provides information on spatiotemporal characteristics as well as kinetics and kinematics. Furthermore, lab-based movement analysis, using force plates and motion capture, found gait parameters were sensitive to change in individuals with mild to moderate CMT over 2 years with a standardized response mean (SRM) >0.80.[22] While movement analysis is sensitive to change, it requires large, expensive laboratories, making it less attractive for clinical trial application. Advances in technology and miniaturization have facilitated the development of wearable sensors, which use tri-axial accelerometers to produce quantitative metrics of gait and balance. The size and battery life of the sensors provide opportunities to collect data over longer periods of time, within the natural environment. Therefore, wearable sensors may be able to serve as biomarkers of functional change in early phase clinical trials.

Previous studies employing wearable sensors in CMT have primarily focused on measuring physical activity and have used proprietary algorithms provided with the device.[23,24] Therefore, we aimed to develop and optimize disease-specific algorithms to derive, gait, balance, and activity parameters from accelerometer data in individuals with CMT1A using wearable sensors. We also sought to assess the reliability and validity of these metrics for use as quantitative biomarkers of physical function in early stage clinical trials.

2 | MATERIALS AND METHODS

2.1 | Study overview and design

This study was conducted in individuals with CMT1A and healthy controls using wearable sensors equipped with tri-axial accelerometers, specifically BioStamp nPoint,[25] which were developed by MC10 Incorporated (Lexington, MA, USA). This study was approved by the Institutional Review Board (IRB) at the University of Rochester Medical Center (URMC). All participants provided informed consent, including consent for in-clinic video capture.

Individuals with CMT1A and controls were prospectively enrolled at the URMC. CMT1A participants were 18–65 years of age, ambulatory, CMTES score of <20, and had clinical and electrophysiologic features of CMT1A, with documentation of a *PMP22* gene duplication (personal or first degree relative). Unaffected adults were 18–65 years of age and recruited by IRB approved flyers posted in common areas at URMC. These individuals were age-sex matched and enrolled as healthy controls to perform the wearable sensor assessments at baseline. Individuals with known diabetes mellitus, or other disorders known to predispose to neuropathy were excluded from this study. Additionally, individuals were excluded if they had foot or ankle surgery performed or planned within 9 months of enrollment, unrelated known orthopedic, neurologic, or medical conditions that influenced gait or balance, or had a medical condition that precluded the administration of the functional assessments.

2.2 | Measures

2.2.1 | Clinical assessments

Individuals with CMT1A, who met all inclusion/exclusion criteria at an eligibility screening visit, were evaluated at baseline and 12-month visits. Each CMT1A participant completed the CMTES, the CMT-FOM, and standardized manual muscle testing (MMT).

The CMT-FOM is a performance-based measure comprised of 13 items that are combined to form a composite score to quantify the functional abilities of adults with CMT1A. Items include assessments of distal strength using a hand held dynamometer (HHD) (handgrip, ankle dorsiflexion [DF], and ankle plantar flexion [PF]), hand function (Functional Dexterity Test and Nine Hole Peg Test), lower extremity function/gait (10 meter walk/run, 6 minute walk test, and 4 stair climb

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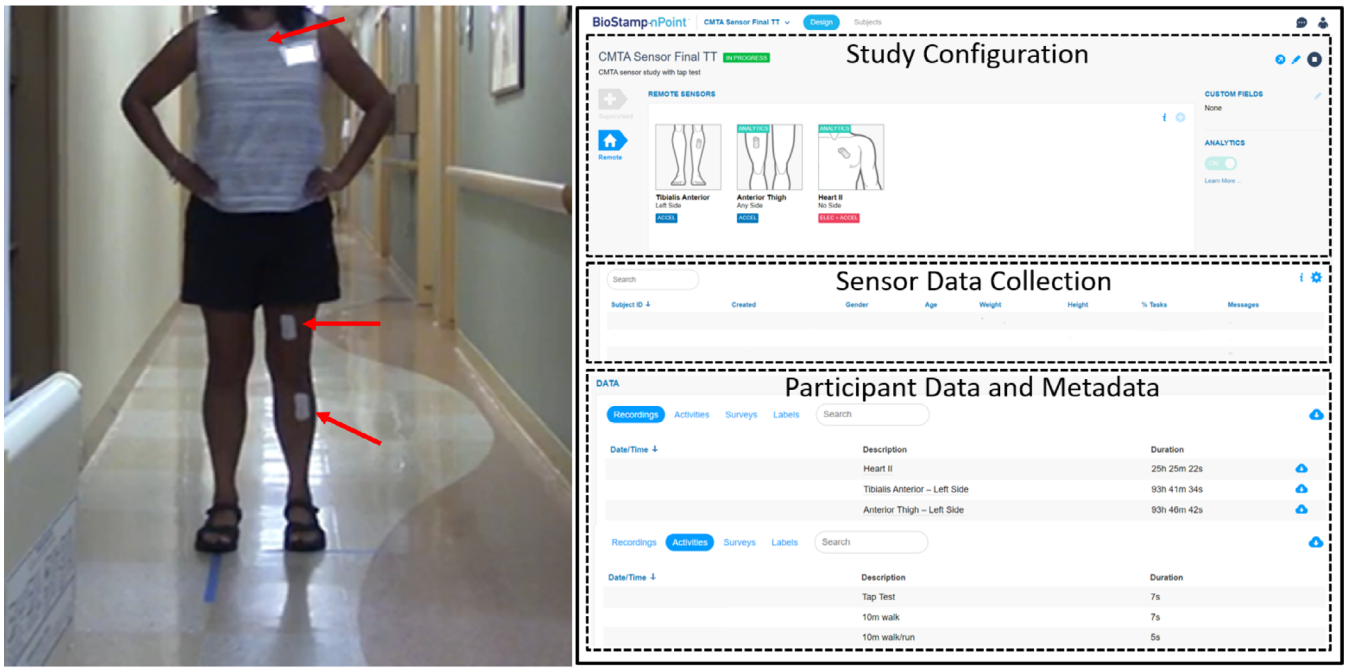

FIGURE 1 (A) A study participant wearing the sensors at the designated locations: chest, left thigh, and left proximal tibia. (B) Web-portal for accessing the recorded sensor data over the total duration of wear.

test), mobility (Timed Up and Go), and balance (stance with feet apart on line with eyes open, stances with feet apart on line with eyes closed, and single leg stance with eyes closed). Raw data are converted to *z*-scores and then assigned a score 0–4 with the total score ranging from 0 to 52; higher score indicating increased functional limitation.

Additional balance assessments were performed and measured using the modified-clinical test of sensory interaction and balance,[26,27] which includes four different scenarios: standing on firm and foam surfaces with eyes open (EO) and eyes closed (EC). This is a reliable and valid test that was created to quickly and easily assess dependence on various inputs for maintaining balance.[27–29] Participants began the test standing upright with their feet together. The goal for all trials was to maintain quiet standing for 30 s. If a participant lost their balance prematurely, the tests were stopped, and the time was recorded in seconds.

MMT was performed on seven bilateral muscle groups (hip flexors [HF], hip extensors [HE], hip abductors [HA], knee flexors [KF], knee extensors [KE], ankle plantar flexors [APF], and ankle dorsi flexors [ADF]) using standardized procedures. Muscles were graded using a modified 10-point Medical Research Council scale (0–5).[30]

2.2.2 | Sensors

BioStamp nPoint MC10 sensors are FDA 510 K approved devices to collect COA data. Three small, flexible, adhesive sensors were applied to the chest, left thigh, and left proximal tibia. Proper placement of the sensors is shown in Figure 1A. Tri-axial accelerometer data were collected from the sensors at a sampling rate of 31.25 Hz. The web-portal for accessing recorded data over the total wear duration is shown in Figure 1B. Raw data from the sensors were used to create disease-specific algorithms to capture activity states (time spent lying, sitting, standing, and walking), gait, and balance parameters.

2.3 | Data collection

BioStamp nPoint MC10 sensors were applied to all the participants during the mobility and balance tasks of the CMT-FOM and for the additional balance assessments. The 10MWRT and balance assessments were performed twice during the baseline visit, with a 10-min rest, to assess reliability. All the functional measures were video recorded for the purpose of marking raw sensor data and determining the ground truth, to facilitate the development, and optimization of the algorithms. In addition to the mobility tasks and balance assessments, CMT1A participants completed MMT and HHD strength assessments. At the end of the in-clinic assessments, participants were asked to wear the sensors until bedtime of the following day (to ensure they were worn for the entire battery life of the sensor; approximately 24 h) to measure activity and gait in the natural environment. After the 24-h period, participants were instructed to remove the sensors and return them in a prestamped envelope.

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2.4 | Activity analysis

Activity states were determined based on data from the trunk and thigh sensors. Each sensor duration was partitioned into nonoverlapping 2 s windows. For each 2 s window, activity analysis was performed using a previously described technique,[31] where a posture was determined based on the combination of dominant axis (*x*, *y*, or *z*) for the chest and thigh sensors. Activity states including lying, sitting, and standing/walking were first determined. Standing and walking durations were then divided further using a normalized autocorrelation analysis of the chest sensor data.[32]

2.5 | Gait and balance analysis

2.5.1 | Gait analysis

Using the accelerometer data obtained from chest and thigh sensors during walking assessments, three aspects of gait were analyzed. (1) Spatiotemporal gait characteristics, (2) Finer gait characteristics, and (3) Gait fatigue. The spatiotemporal and finer gait analyses were performed for both in-clinic and at-home (full) walking durations, whereas the gait fatigue analysis was only performed for in-clinic walking durations.

1. Spatiotemporal gait analysis: The analysis involved estimation of basic spatiotemporal gait parameters such as step count, step duration, step length, and gait speed. Step count and step duration were determined for each participant using previously developed techniques.[32] Periodic steps while walking result in strong auto-correlation peaks at lags corresponding to the step duration. Therefore, normalized autocorrelation of chest sensor data were used to derive step count and step duration. Unlike methods that count steps by matching against templates developed for healthy controls, the autocorrelation is computed from data for a single participant. Therefore, this methodology has the advantage as it adapts to individual impairments in gait. Although a drawback is that it may miss-count isolated steps. Step length was determined using an empirical method.[33] Step length was then divided by step duration to calculate the gait speed.

2. Finer gait analysis: Given the known distal muscular involvement of CMT, we were interested in gaining a more detailed understanding of the gait cycle and the impact of weakness. Using an existing technique,[34] a single stride in a gait cycle was identified and defined as the duration between two successive toe-offs. More specifically, the technique first created a stride template and then matched this template with a long duration gait sequence using a dynamic time warping-based matching method to identify individual strides in the gait sequence. After identifying the strides, plantar flexion and dorsi flexion intervals in the stride cycle were empirically determined. Plantar flexion occurs during toe-off, therefore the plantar flexion duration was represented as the interval in stride time ranging from 27.5% before through 15% after toe-off. Dorsi flexion occurs during foot strike, which typically occurs in stride time 40% from toe-off, so the dorsi flexion duration was represented by an interval in stride time starting at toe-off and extending 50% into the stride duration. The plantar flexion, dorsi flexion, and full stride durations in a normalized stride cycle are represented in Figure 2. To derive the finer gait metrics, accelerometer data corresponding to the plantar flexion, dorsi flexion and full stride durations from the left thigh sensor were used. The accelerometer data were calibrated and mean subtracted to account for sensor orientation artifacts and to remove the effect of gravity, respectively. Since acceleration in a forward direction is the primary source of propulsion of the body during gait, forward acceleration was chosen and the root mean square (RMS) acceleration in the forward direction was calculated. The thigh RMS forward acceleration values during the plantar flexion (RMS-PF), dorsi flexion (RMS-DF), and full stride (RMS-Full) durations represent the derived finer gait metrics.

3. Gait fatigue analysis: To assess fatigue during gait, stride duration, generated using the above-mentioned technique, was compared during the first and last quarter of the 6MWT for all participants.

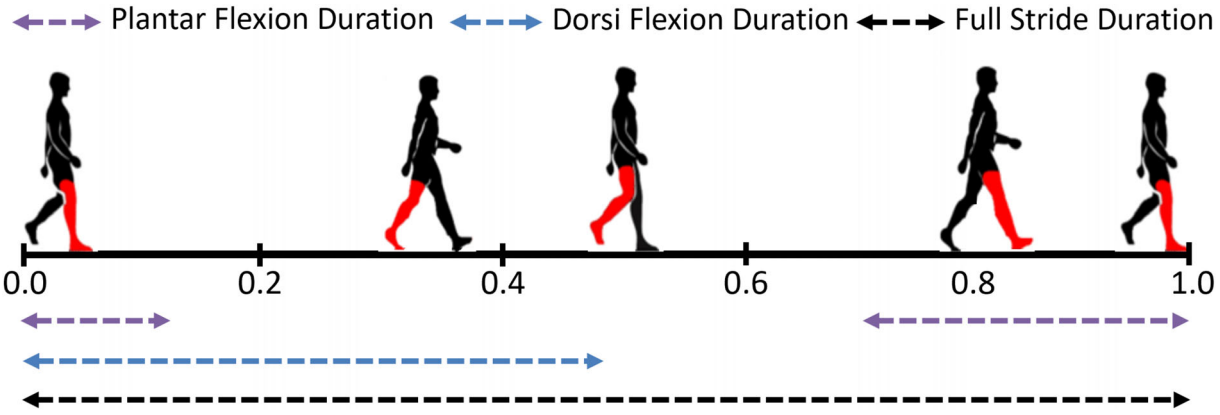

FIGURE 2 A normalized stride cycle representing the full stride duration (black dashed line), which starts at toe-off on the left side and ends with toe-off on the same left side. Also represented are the empirically chosen plantar flexion (purple dashed line) and dorsi flexion (blue dashed line) intervals. The plantar flexion duration represents an interval in stride time ranging from 27.5% before through 15% after toe-off. The dorsi flexion duration represents an interval in stride time starting at toe-off and extending 50% into the stride duration.

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2.5.2 | Balance analysis

The balance analysis derived two postural sway parameters: (1) Sway jerk, which characterized the strength of quick compensatory movements noted when an individual attempts to correct their position and (2) Sway area, which characterized the magnitude of movements while an individual attempts to maintain quiet standing. Accelerometer data from all three sensors (chest, thigh, and tibia) were used to perform the balance analysis. For each of the four different balance scenarios, postural sway parameters were generated using an existing technique.[35]

2.5.3 | CMT-FOM score prediction

A predictive model was developed by using the derived gait and balance parameters and regressing them against the CMT-FOM score. Stride duration, gait speed, RMS-PF, RMS-DF, sway jerk, and sway area derived from the in-clinic tests formed the predictor variables, from which the CMT-FOM score represented the response variable. Random Forest regression model with 100 decision trees and squared error criterion was used to measure the quality of tree split. Leave-one-out cross validation was used to assess the model performance in predicting CMT-FOM scores. CMT-FOM score prediction is of interest because it may, upon validation and improvement in larger studies, provide support for employing wearable sensor technology in study settings where in person assessments are limited.

2.6 | Statistical analysis

Following the development of algorithms, we aimed to assess the reliability and validity of these derived parameters for use as quantitative biomarkers of physical function. Test–retest reliability of the gait and balance measures were analyzed using intraclass correlation coefficients (ICC). Specifically, the two-way mixed effects, single measurement, absolute agreement model was used and reported the ICC (1, 2) coefficients.[36] Mann–Whitney U tests were used to analyze group differences in activity states (time spent lying, sitting, standing, and walking), gait metrics (step count, stride duration, step length, and gait speed), and postural sway parameters (sway jerk and sway area) and to compare stride durations during the first and last quarter of 6MWT to assess for fatigue. Wilcoxon signed rank test was used to assess change over time in parameters from baseline to the 12-month visit. Spearman or Pearson correlation coefficients were used to assess the relationship between derived parameters and ordinal or ratio clinical metrics, respectively. One-sided tests were used to assess group differences and change in parameters, and two-sided tests were used for the correlations. A p-value <.05 was considered significant. Median and range/inter-quartile range were reported as summary statistics. All statistical analyses were performed using Python.

3 | RESULTS

3.1 | Demographics

Fifteen CMT1A participants (mean [standard deviation, range] age: 37.3 [15.8, 18–64] years; 67% women) and 15 age-sex matched healthy controls (38.5 [15.1, 19–64] years; 67% women) were enrolled in the study and completed in-clinic baseline measurements. At screening, for the CMT1A participants, the mean (standard deviation, range) for the CMTES score was: 8.5 [4.4, 3–17], the CMT-FOM score was: 19.5 [10.3, 8–41], and the lower extremity strength score (average MMT for all lower extremity muscle groups) was: 4.4 [0.5, 3.4–5.0]. Data from in-clinic and at-home epochs (full duration) from 15 CMT1A participants and 15 healthy controls were used for analysis. For the in-clinic data analysis, the entire dataset (15 CMT1A and 15 controls) was used. At home, all the CMT1A participants and 9 out of 15 healthy controls wore sensors. However, sensors detached from two CMT1A participants and one healthy control therefore their full duration data were discarded, resulting in a partial dataset (13 CMT1A and 8 controls) for the analysis. Longitudinal data were collected at the 12-month visit for 12 of the 15 CMT1A participants.

3.2 | Test–retest reliability

Excellent reliability for stride duration (average [confidence interval]: 0.98 [0.94–1.00]) and stride length (0.99 [0.97–1.00]) was found. Correlations for the postural sway measures, sway jerk, and sway area, during the four different balance scenarios for all three sensors (chest, thigh, and tibia) are reported in Table 1. Moderate to excellent reliability was found for all the balance measures. More specifically, thigh and tibia sensors and EO scenarios have stronger correlations than chest sensors and EC scenarios (e.g., Sway Area – Firm EO; chest 0.56 [0.04–0.84]; thigh 1.00 [0.99–1.00]; tibia 0.99 [0.98–1.00] compared to Firm EC; chest 0.38 [0.22–0.77]; thigh 0.87 [0.62–0.96]; tibia 0.64 [0.14–0.88]).

3.3 | Activity analysis

The median [interquartile range] proportion of time spent per day in different activity states for CMT1A participants and healthy controls is reported in Table 2. Time spent lying and walking was similar for both CMT1A participants and healthy controls. Although not significant, we can observe that the CMT1A participants spent greater time sitting (CMT1A: 10.0 [9.7–11.0], controls: 8.9 [7.1–11.1], $p = .25$) and less time standing (CMT1A: 3.4 [2.9–4.0], controls: 4.6 [3.1–5.6], $p = .10$) than healthy controls. Activity patterns, using a clock visualization, were generated from one CMT participant and one healthy control over their full duration of sensor wear and are illustrated in Figure 3.

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TABLE 1 Test–retest reliability correlations for balance measures, sway jerk, and sway area during the four different in-clinic balance scenarios (firm EO, firm EC, foam EO, and foam EC) for all of the sensors.

	Sway jerk (Avg [CI])				Sway area (Avg. [CI])			
	Firm EO 1 vs. 2	Firm EC 1 vs. 2	Foam EO 1 vs. 2	Foam EC 1 vs. 2	Firm EO 1 vs. 2	Firm EC 1 vs. 2	Foam EO 1 vs. 2	Foam EC 1 vs. 2
Chest	0.55 [0.02–0.83]	0.54 [−0.02–0.84]	0.99 [0.97–1.00]	0.65 [0.13–0.89]	0.56 [0.04–0.84]	0.38 [−0.22–0.77]	1.00 [0.99–1.00]	0.52 [−0.07–0.84]
Thigh	0.98 [0.94–0.99]	0.82 [0.48–0.94]	0.98 [0.95–0.99]	0.57 [−0.01–0.86]	1.00 [0.99–1.00]	0.87 [0.62–0.96]	1.00 [1.0–1.0]	0.39 [−0.24–0.79]
Tibia	0.99 [0.95–1.00]	0.80 [0.45–0.94]	0.97 [0.89–0.99]	0.56 [−0.03–0.86]	0.99 [0.98–1.00]	0.64 [0.14–0.88]	1.00 [1.0–1.0]	0.59 [0.03–0.87]

Abbreviations: EC, eyes closed; EO, eyes open.

3.4 | Gait and balance analysis

3.4.1 | Spatiotemporal gait analysis

CMT1A participants had significantly longer step durations (median [interquartile range]: in-clinic: 0.51 [0.50–0.54) seconds/step] when compared to healthy controls (in-clinic: 0.45 [0.45–0.46] seconds/step, $p < .001$). CMT1A participants also had significantly shorter step lengths (in-clinic: 0.73 [0.67–0.74] m) when compared to healthy controls (in-clinic: 0.74 [0.72–0.78] m, $p = .03$). As a result of longer step durations and shorter step lengths, significantly slower gait speeds were seen in the CMT1A participants (in-clinic: 1.37 [1.29–1.46] m/s) when compared to healthy controls (in-clinic: 1.62 [1.57–1.76] m/s, $p < .001$). The spatiotemporal gait metrics from full durations and in-clinic 6MWT durations, for both the CMT1A participants and healthy controls, are reported in Table 2. The full durations and the in-clinic 6MWT durations showed similar trends, however we can observe that both the CMT1A participants and healthy controls had shorter step durations, longer step lengths, and faster gait speeds during the in-clinic 6MWT durations as compared to the full durations. Additionally, step length (full duration: $r = -0.57$, $p = .04$; in-clinic: $r = -0.59$, $p = .02$) and gait speed (full duration: $r = -0.66$, $p = .02$, in-clinic: $r = -0.64$, $p = .01$) were found to have statistically significant, moderate, negative correlations with CMT-FOM scores.

3.4.2 | Finer gait analysis

For both in-clinic and full durations, we can observe that RMS-PF and RMS-DF have statistically significant, strong positive correlations with the corresponding strength measures for plantar flexion and dorsi flexion collected by both HHD and MMT. These correlations are shown as heatmaps in Figure 4. In general, we found RMS-DF to have a stronger correlation with the strength measures as compared to RMS-PF, specifically with ankle plantar flexion and dorsi flexion, knee flexion, and hip flexion, extension, and abduction. The correlations for the RMS-Full fell between that of RMS-PF and RMS-DF. We can also observe that the derived measures tend to have stronger correlations with distal strength as compared to proximal strength. Additionally, RMS-DF [$r = -0.75$, $p = .001$] and RMS-Full [$r = -0.70$, $p = .004$] have statistically significant, strong negative correlations with CMT-FOM score.

3.4.3 | Fatigue analysis

Stride duration comparisons between the first and last quarter of the in-clinic 6MWT, for both CMT1A participants and healthy controls, are shown in Figure 5. From this figure, we see 11 out of 15 CMT1A participants showed statistically significant increases in median stride duration from the first to the last quarter. Whereas for the healthy controls, there were only two participants showing small positive

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TABLE 2 Comparison of activity states and gait parameters for Charcot–Marie–Tooth disease type 1A (CMT1A) participants and healthy controls.

Motor features	CMT1A participant, median [interquartile range]	Healthy controls, median [interquartile range]	*p*-Value
Activity states (baseline, full duration) (13 CMT1A and 8 controls)			
Lying proportion (h/day)	8.8 [8.2–9.1]	8.9 [6.7–9.6]	$p = .49$
Sitting proportion (h/day)	10.0 [9.7–11.0]	8.9 [7.1–11.1]	$p = .25$
Standing proportion (h/day)	3.4 [2.9–4.0]	4.6 [3.1–5.6]	$p = .10$
Walking proportion (h/day)	1.3 [1.1–1.8]	1.4 [1.2–1.6]	$p = .66$
Gait parameters (baseline, full duration) (13 CMT1A and 8 controls)			
Steps per day	8302 [6476–11 158]	9755 [8231–10 708]	$p = .22$
Step duration (s/step)	0.59 [0.56–0.61]	0.52 [0.50–0.53]	$p < .001$
Step length (m)	0.67 [0.62–0.70]	0.71 [0.69–0.74]	$p = .02$
Gait speed (m/s)	1.14 [1.10–1.24]	1.38 [1.34–1.41]	$p < .001$
Gait parameters (baseline, clinic 6MWT) (15 CMT1A and 15 controls)			
Step duration (s/step)	0.51 [0.50–0.54]	0.45 [0.45–0.46]	$p < .001$
Step length (m)	0.73 [0.67–0.74]	0.74 [0.72–0.78]	$p = .03$
Gait speed (m/s)	1.37 [1.29–1.46]	1.62 [1.57–1.76]	$p < .001$
Gait parameters (longitudinal, clinic 6MWT) (12 CMT1A)			
Step duration (s/step)	0.52 [0.50–0.53]	N/A	
Step length (m)	0.69 [0.66–0.74]	N/A	
Gait speed (m/s)	1.36 [1.25–1.45]	N/A	

Note: N/A, longitudinal data not recorded for the controls.

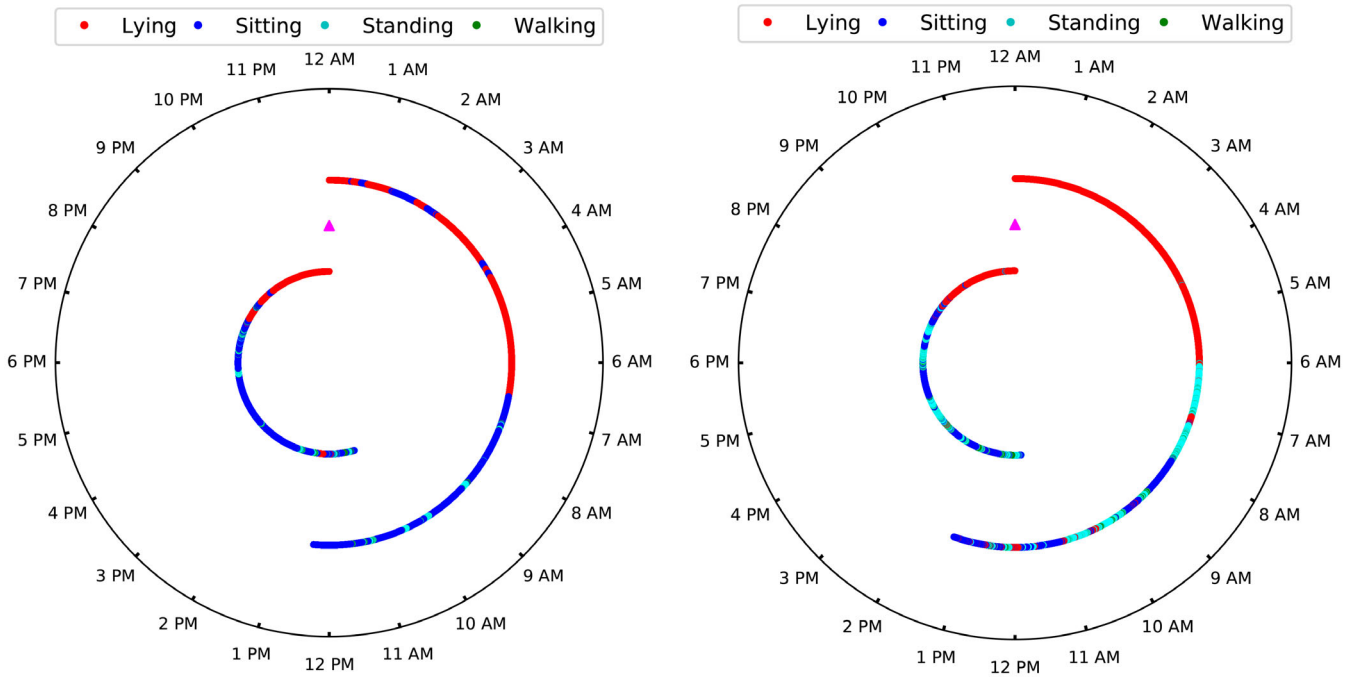

FIGURE 3 Activity states in a 24-h clock visual format for activity of a Charcot–Marie–Tooth disease type 1A participant with the highest Charcot–Marie–tooth disease functional outcome measure score (left) and a healthy control (right).

percentage increases in median stride duration. Four CMT1A participants with higher CMT-FOM scores (>25), indicating increased functional limitation, demonstrated even greater increases in median stride duration with larger distributions.

3.4.4 | Balance analysis

During the firm EO scenario, participants demonstrated the lowest sway jerk and sway area, followed by firm EC then foam EO, which both had

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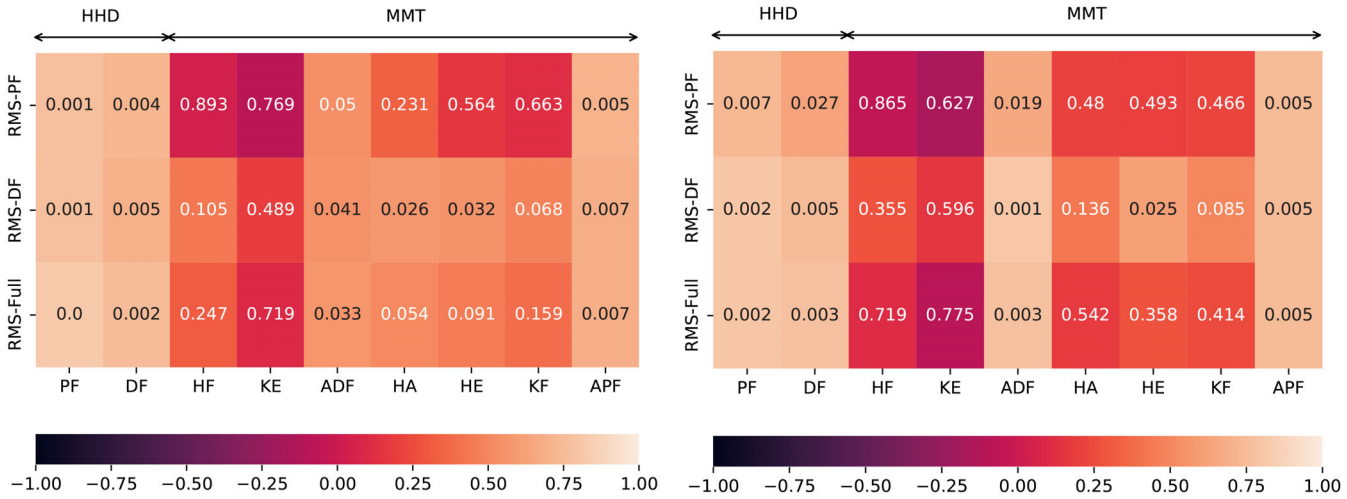

FIGURE 4 Correlation between thigh root mean square (RMS) acceleration calculated during the plantar flexion (RMS-PF), the dorsi flexion (RMS-DF), and the full stride (RMS-Full) durations and two groups of clinical measures of strength, hand held dynamometer (HHD: PF—plantar flexion; DF—dorsi flexion) and manual muscle testing (MMT: HF—hip flexion; KE—knee extension; ADF—ankle dorsi flexion; HA—hip abduction; HE—hip extension; KF—knee flexion; APF—ankle plantar flexion), for in-clinic (left) and at-home durations (right). The color in the heatmaps represents the correlation coefficient, Pearson's or Spearman's, and the numeric text represents the *p*-value.

similar distributions. The foam EC condition showed the highest sway jerk and sway area of all the balance scenarios, for both CMT1A participants and healthy controls. During all scenarios, the differences between the groups showed statistically significant, greater postural sway for the CMT1A participants. The comparison of sway jerk and sway area during the four different balance scenarios is shown in Figure 6. Additionally, correlations between the postural sway parameters and strength, function, and sensation measures for all the sensors are shown in Table 3. For the chest, thigh, and tibia sensors, sway jerk, and sway area showed statistically significant, strong negative correlations with plantar flexion (PF) strength, dorsi flexion (DF) strength, and mean lower extremity strength (MeanLE) during firm EO/EC and foam EO scenarios. We observed moderate correlations with the CMTES score and weak correlations with the CMT-FOM score and sensation measures (vibration and pinprick) during firm EO/EC and foam scenarios. Among the different sensors, the tibia sensor showed slightly stronger correlations when compared to the chest and thigh sensors, mainly during the firm EC scenario (e.g., Firm EC: chest and PF: $r = -0.72$, thigh and PF: $r = -0.74$, tibia and PF $r = -0.84$). Overall, sway jerk and sway area demonstrate the strongest correlation with the different clinical measures during the firm EC scenario.

3.4.5 | CMT-FOM prediction

The predicted CMT-FOM score was compared with the ground-truth CMT-FOM score. There was a strong positive correlation between the predicted and ground-truth CMT-FOM score ($r = 0.73$, $p = .002$). The variable that contributed the most to the predicted CMT-FOM score was RMS-DF.

3.5 | Longitudinal data analysis

Longitudinal analysis was performed for both gait and balance parameters. The in-clinic step duration, step length, and gait speed computed using the 12-month 6MWT data for CMT1A participants showed worsening, however, there were no significant changes noted as shown in Table 2. There were also no statistically significant changes from baseline to 12-months for the balance parameters.

4 | DISCUSSION

Sensitive outcome measures are urgently needed for clinical trials in CMT. Prior studies have examined the reliability, validity, and sensitivity of disease-specific CMT COAs including CMTES and CMTPeds.[8,10,13] While these measures demonstrate good reliability and validity, their sensitivity to change in natural history studies is low to moderate for most forms of CMT in which they have been evaluated. Additionally, studies using a wearable sensor to measure activity level data documented the reliability, validity, and sensitivity to change in the CMT population.[23,24] While these data are promising and shed light on the utility of accelerometers, the device only provides a picture of activity, not gait or balance. Movement analysis is an accurate way to assess locomotion function, and has been previously examined in the CMT population and demonstrated good test–retest reliability.[21,22,37,38] More specifically, a study examining lab-based movement analysis, found a higher SRM than the CMTES, when examining the biomechanical parameters derived from 3D motion analysis of walking and more demanding locomotor tasks, such as ascending and descending steps.[22] Despite the ability to track

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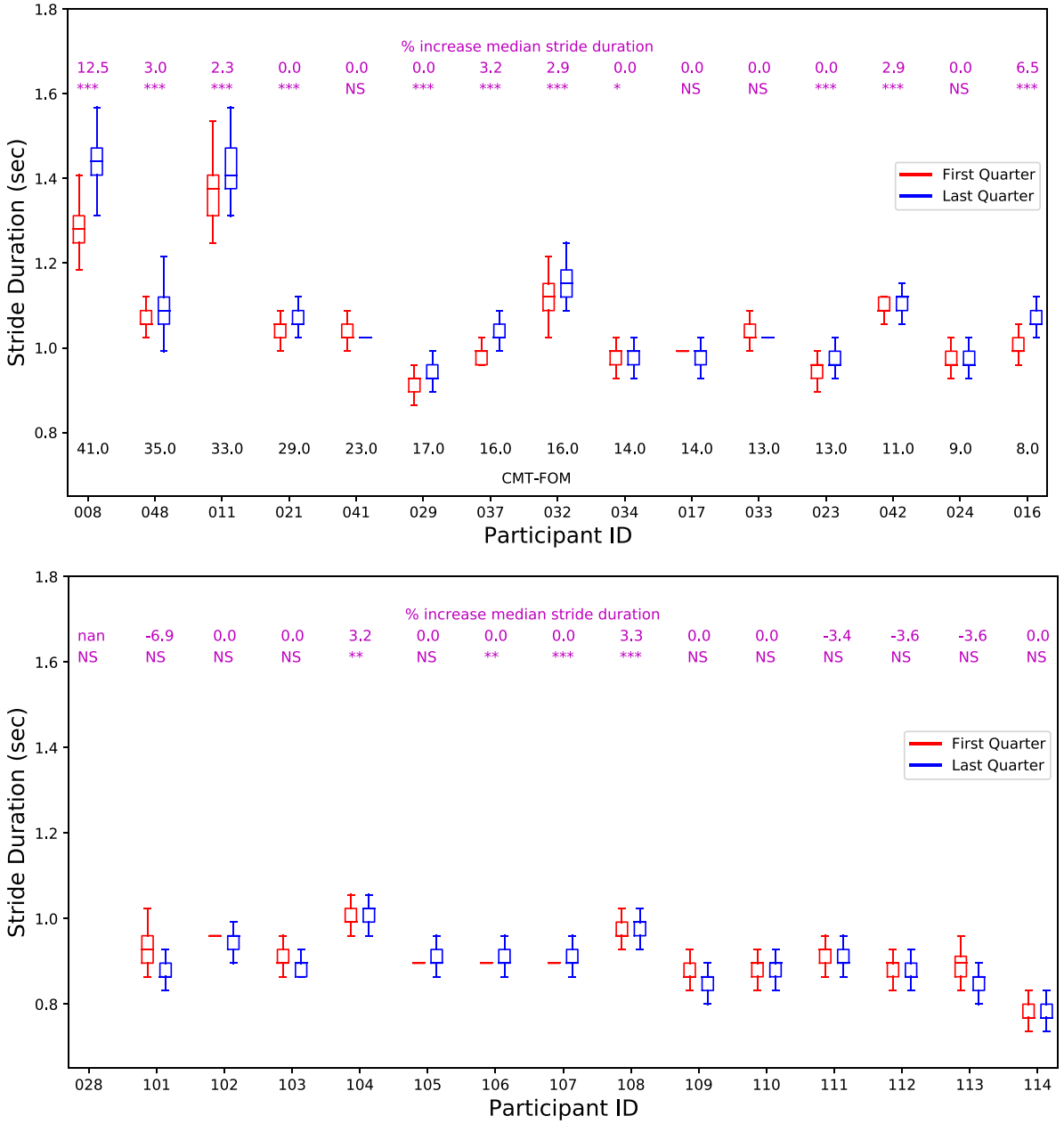

FIGURE 5 An analysis of fatigue by comparing stride duration during the first and last quarter of 6MWT for Charcot–Marie–Tooth disease type 1A participants (top) and healthy controls (bottom). The x-axis shows the participant ID and y-axis shows stride duration in seconds. For each participant, the red (first quarter) and blue (last quarter) boxplots represent the distribution of stride duration. In the top figure, the numbers below each boxplot pair represent the participant's Charcot–Marie–Tooth disease functional outcome measure score. The pink numbers above the boxplot pair show the percentage increase in median stride duration from the first quarter to the last. Also represented is a one-sided Mann–Whitney test, used to analyze the differences between stride duration in the first quarter compared to the last quarter (***: $p < .001$, **: $.001 < = p < .01$, *: $.01 < = p < = .05$, NS: $p > .05$). The boxplots appear as dashes in situations where there is extremely low variability in the stride duration.

progress over time using lab-based movement analysis, it is costly and resource intensive and not feasible for multi-center clinical trials. Wearable sensors, such as the BioStamp nPoint MC10, provide the opportunity to reliably derive similar activity, gait, and balance metrics from in-clinic assessments and at-home (full) durations.

As compared to traditional timed function tests to measure the impact of CMT1A on function, wearable sensors provide the ability to gather discrete gait and balance data during in-clinic assessments and within the natural environment. Collecting data in the natural environment provides information over time and may offer additional details beyond those gathered during an in-person visit. Clinical assessments provide a snapshot of function where subjects are often read specific instructions and not allowed to wear supportive braces, such as ankle-foot-orthotics (AFOs). Influential day-to-day factors may alter an individual's ability to complete certain assessments ultimately skewing their functional score and disease severity picture. Õunpuu et al.[39]

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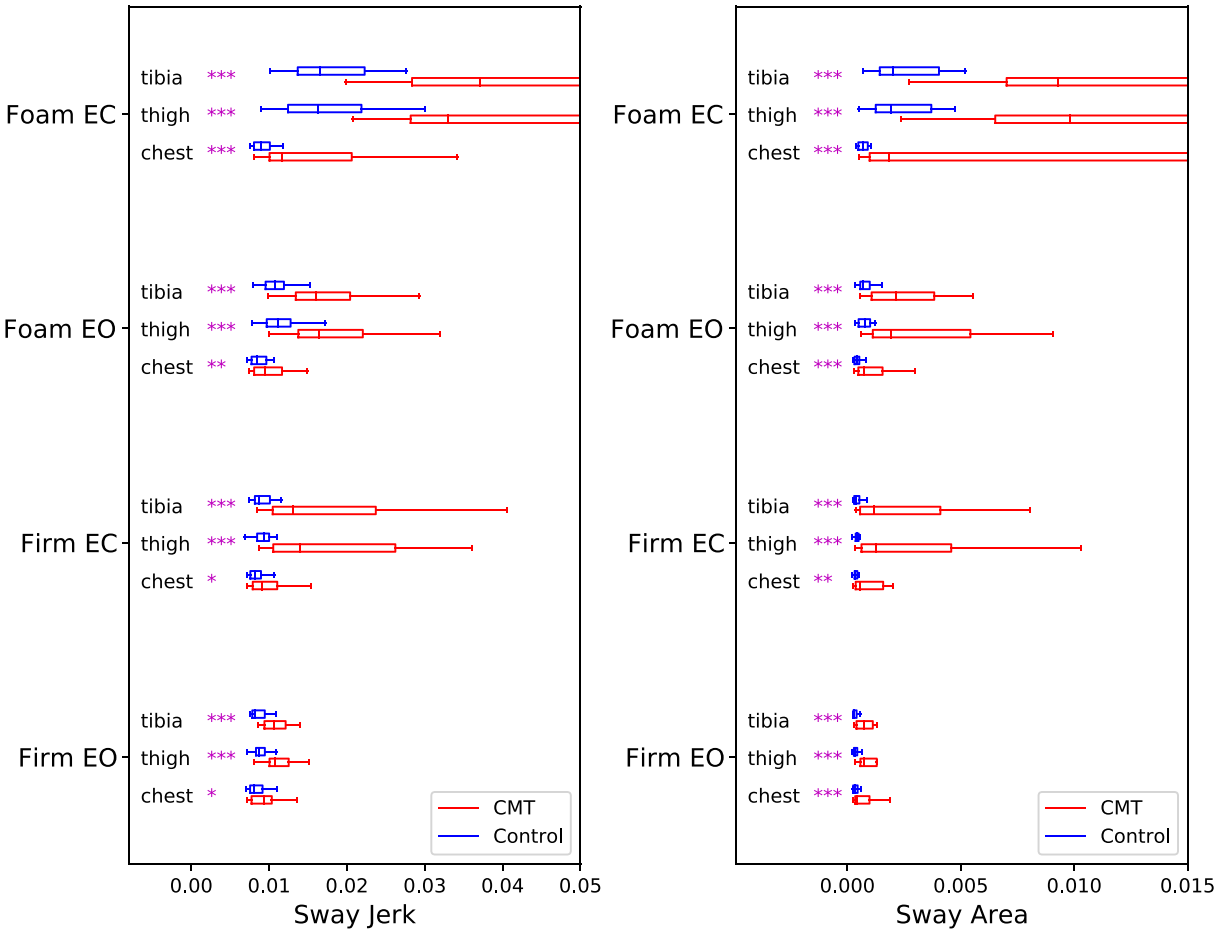

FIGURE 6 An analysis of balance by comparing sway jerk and sway area between Charcot–Marie–Tooth disease type 1A (CMT1A) participants and healthy controls during the four in-clinic balance scenarios (firm eyes open, firm eyes closed, foam eyes open, and foam eyes closed) for all of the sensors (chest, thigh, and tibia). Sway jerk and sway area values are in units of g/s and g^2, respectively, where g represents acceleration due to gravity ($g = 9.81$ m/s^2). Also represented is a one-sided Mann–Whitney test, used to analyze the differences between CMT1A participants and healthy controls in sway jerk and sway area. (***: $p < .001$, **: $.001 < = p < .01$, *: $.01 < = p < = .05$, NS: $p > .05$).

examined the impact of orthoses on gait in children with CMT. Their full study cohort showed significant increases in walking velocity when wearing AFOs versus barefoot walking due to a significant increase in stride length.[39] Therefore, assessment of activity and gait in the natural environment may provide a more consistent representation of a participant's function and subsequent progression.

When examining gait metrics, the CMT1A participants showed significantly longer step durations, shorter step lengths, and slower gait speeds when compared to healthy controls. Our results support the findings reported by Don et al.; they found CMT patients displayed a significantly longer stride duration, lower swing velocity, shorter step length, and greater step width than controls.[37] Additionally, when comparing full duration to in-clinic 6MWT duration gait metrics, our results demonstrated changes in both groups (CMT1A and healthy controls) including shorter stride duration, longer step length, and faster gait speed during the in-clinic measures. This can likely be attributed to the instructions that were provided to participants prior to starting the test. Participants were specifically instructed to "walk as quickly as you can safely, without running". This verbiage encourages fast walking. Comparatively, data from the full duration includes at-home information where participants were likely walking at their comfortable pace; this provides a likely explanation for the differences we found in both groups. We also found strong positive correlations between RMS-PF and RMS-DF with corresponding strength measures of plantar flexion and dorsi flexion as well as strong negative correlations between RMS-DF and RMS-Full and CMT-FOM scores. RMS-DF, RMS-PF, and RMS-Full provide information regarding forward acceleration during specific gait cycle intervals. Therefore, our correlations illustrate the relationship forward acceleration has with distal strength and disease severity.

A majority of the CMT1A participants demonstrated significant increases in median stride duration from the first to last quarter of the 6MWT, suggesting fatigue over time. Participants with higher CMT-FOM scores had even greater median stride duration increases. Consistent with previous literature,[37,40] this suggests that more affected individuals with CMT1A, with greater distal weakness, make compensatory changes to their gait pattern resulting in higher energy costs. The ability to detect change in gait metrics during the 6MWT suggests

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TABLE 3 Correlation of sway jerk and sway area with strength (plantar flexion [PF], dorsi flexion [DF], and mean lower extremity strength [MeanLE]), function (FOM), and sensation (pinprick [PP] and vibration [VIB]) measures for all the sensors (chest, thigh, and tibia) during the in-clinic balance scenarios (firm EO, firm EC, foam EO, and foam EC).

		Sway jerk				Sway area			
Sensor	Clinic scores	Firm EO	Firm EC	Foam EO	Foam EC	Firm EO	Firm EC	Foam EO	Foam EC
Chest	PF	−0.72**	−0.70**	−0.71**	−0.44 NS	−0.79***	−0.70**	−0.66*	−0.38 NS
	DF	−0.74**	−0.70**	−0.69**	−0.50 NS	−0.74**	−0.65*	−0.61*	−0.36 NS
	MeanLE	−0.79***	−0.71**	−0.75**	−0.38 NS	−0.77***	−0.67**	−0.65**	−0.31 NS
	FOM	0.35 NS	0.41 NS	0.39 NS	0.39 NS	0.45 NS	0.55*	0.44 NS	0.52 NS
	CMTES	0.37 NS	0.70**	0.56*	0.56*	0.32 NS	0.75**	0.50 NS	0.70**
	PP	−0.32 NS	0.06 NS	−0.10 NS	0.34 NS	−0.21 NS	0.34 NS	0.02 NS	0.39 NS
	VIB	0.07 NS	0.56*	0.37 NS	0.51 NS	0.00 NS	0.56*	0.30 NS	0.70*
Thigh	PF	−0.70**	−0.74**	−0.71**	−0.14 NS	−0.61*	−0.63*	−0.58*	−0.21 NS
	DF	−0.64*	−0.73**	−0.71**	−0.20 NS	−0.53 NS	−0.59*	−0.54*	−0.22 NS
	MeanLE	−0.71**	−0.81***	−0.76**	−0.14 NS	−0.52*	−0.63*	−0.58*	−0.15 NS
	FOM	0.20 NS	0.44 NS	0.27 NS	0.25 NS	0.07 NS	0.40 NS	0.31 NS	0.32 NS
	CMTES	0.51 NS	0.56*	0.58*	0.44 NS	0.29 NS	0.57*	0.68**	0.53 NS
	PP	−0.11 NS	0.16 NS	−0.06 NS	0.41 NS	−0.14 NS	0.36 NS	0.15 NS	0.39 NS
	VIB	0.44 NS	0.46 NS	0.52 NS	0.51 NS	0.23 NS	0.35 NS	0.46 NS	0.40 NS
Tibia	PF	−0.75**	−0.84***	−0.81***	−0.22 NS	−0.61*	−0.67**	−0.60*	−0.45 NS
	DF	−0.67**	−0.82***	−0.80***	−0.26 NS	−0.53 NS	−0.62*	−0.56*	−0.45 NS
	MeanLE	−0.66**	−0.80***	−0.82***	−0.21 NS	−0.52*	−0.65**	−0.60*	−0.37 NS
	FOM	0.40 NS	0.53*	0.39 NS	0.44 NS	0.23 NS	0.36 NS	0.28 NS	0.36 NS
	CMTES	0.43 NS	0.62*	0.53*	0.63*	0.33 NS	0.53*	0.59*	0.55 NS
	PP	0.01 NS	0.29 NS	−0.11 NS	0.43 NS	0.08 NS	0.40 NS	−0.01 NS	0.31 NS
	VIB	0.37 NS	0.46 NS	0.53 NS	0.70*	0.23 NS	0.32 NS	0.52 NS	0.54 NS

Note: Also represented are the *p*-values (***: $p < .001$, **: $.001 <= p < .01$, *: $.01 <= p <= .05$, NS: $p > .05$).
Abbreviations: EC, eyes closed; EO, eyes open.

that wearable sensors are sensitive to change and demonstrates their potential utility in early phase clinical trials.

During the four different balance scenarios, we found significantly greater sway jerk and sway area for the CMT1A participants when compared to healthy controls. The degree of postural instability increased with task complexity, as we observed the greatest between group differences during the EC scenario. These results are consistent with previous study findings. More specifically, van der Linden et al. emphasized the functional impact of somatosensory impairments on postural control even in mildly affected CMT1A patients.[41] Since the wearable sensors provide objective measures of balance, this may help document the functional impact of somatosensory involvement in individuals with CMT1A. Furthermore, the balance analysis showed strong negative correlations between sway jerk and sway area and clinical measures of strength (PF, DF, and MeanLE) most prominent during the firm EO/EC and foam EO scenarios. This indicates that greater postural sway is associated with lower levels of leg strength. These findings are in accordance with what was reported by Lencioni et al. who found a strong correlation between steady conditions and ankle plantar flexion strength suggesting that quiet standing relies more on plantar flexor strength than on dorsi flexor and/or proximal muscle strength.[38] Additionally, we found stronger, correlations between the tibia sensors and clinical measures of balance than with the thigh or chest sensors. When working to maintain balance, distal strength and the use of balance strategies are integral. The three well documented balance strategies are ankle, hip, and stepping,[42–44] and effective implementation depends on the magnitude of the perturbation and relies on proper muscle activation patterns.[42] Therefore, our results from the sway jerk and sway area computations are predictable. These relationships between strength and balance, as well as the gait metrics, support the validity of these measurements for use in future studies.

Although, measures of sway jerk and sway area can be measured similarly by force plates, these often require larger spaces with sophisticated equipment, such as 3D motion analysis labs. Wearable sensors provide a less resource intensive option with similar reliable and valid results. Other assessments of balance have not been fully explored in CMT[45] and standardized balance outcome measures including the Berg balance score, short physical performance battery, and Tinetti performance oriented mobility assessment of balance and gait may have limitations for use in clinical trials.[20,46]

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Activity levels were overall unexpectedly similar in CMT1A and controls. Although CMT1A participants and controls spent similar time walking, individuals with CMT1A showed trends toward spending more time sitting and less time standing than controls. One possible explanation for this is related to the balance impairments that individuals with CMT1A often exhibit. Nardone et al. examined the relationship between sensory fibers and stability under static and dynamic condition and found that their participants demonstrated greater instability in quiet stance than during dynamic activities.[47] Therefore, while our CMT1A participants with sensory impairments may still walk, they may opt to sit rather than stand due to static balance deficits, which may provide a potential explanation for the differences in activity found in our analysis.

4.1 | Limitations

Our study provides valuable data to support the further development of wearable sensors for use in CMT1A; however, it is not without limitations. A larger study is necessary to validate the algorithms that were created to derive the gait and balance parameters from the accelerometer data and to confirm our findings. A larger study would also allow the preliminary statistical analyses that have been presented here to be strengthened, to account, among other things, for multiple hypothesis testing, which was not currently explored with our small data set. Although a follow up visit was performed at 12 months, our study was not powered to detect change and therefore a larger longitudinal study is necessary to examine the sensitivity to change of these novel outcome measures. Lastly, our study was only performed in individuals with CMT1A and therefore, further investigations with other types of CMT are needed.

4.2 | Summary

In summary, this study illustrates the potential use of wearable sensors to assess activity, gait, and balance in individuals with CMT1A. We found the derived gait and balance parameters from these wearable sensors to have strong correlations with CMT-FOM scores and distal strength supporting their validity. Using disease-specific wearable sensor algorithms to generate quantitative gait and balance data may provide additional information regarding the impact of CMT on function for clinical trials.

AUTHOR CONTRIBUTIONS

Contributed to the study conceptualization and protocol development: Dinesh K, Sharma G, Herrmann DN, Sowden JE, Baker L, and Eichinger K. *Contributed to data collection*: Baker L, Eichinger K, Behrens-Spraggins S, Charles J, and Wood E. *Contributed to data analysis, interpretation and writing the manuscript*: Dinesh K, Sharma G, Eichinger K, Herrmann DN, Baker L, and White N. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Dinesh K, Sharma G, Charles J, Behrens-Spraggins S, Wood E, Sowden JE, Baker L, and White N have no conflicts of interest related to this manuscript. Eichinger K serves as a member (non-paid) of the CMTA Advisory Board and has served as a consultant to Acceleron, Applied Therapeutics, Fulcrum, Roche, Dyne, Avidity, and Biogen in the past 3 years. Herrmann DN has, in the last 3 years, served as a consultant or on a Scientific Advisory Board for Regenacy, Pfizer, Passage Bio, Applied Therapeutics, DTx Pharma, Sarepta, Neurogene, Swan Bio, L.E.K. Consulting, GLG and Guidepoint Global.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are publicly available.[48]

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