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AN INSTRUMENTED TIMED UP AND GO IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

JESSIE HUISINGA, PhD[#1], **ADAM BRUETSCH, MS**[1], **AYLA MCCALLEY, BS**[2], **MELISSA CURRENCE, PTA**[2], **LAURA HERBELIN, CCRP**[2], **OMAR JAWDAT, MD**[2], **MAMATHA PASNOOR, MD**[2], **MAZEN DIMACHKIE, MD**[2], **RICHARD BAROHN, MD**[2], and **JEFFREY STATLAND, MD**[#2]

[1]Landon Center on Aging, University of Kansas Medical Center, 3901 Rainbow Blvd, MS 1005, Kansas City, Kansas 66160, USA

[2]Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA

[#] These authors contributed equally to this work.

Abstract

Introduction: Instrumenting timed functional motor tasks may reveal a continuum of motor disability that predicts future motor dysfunction.

Methods: We performed a prospective study of the instrumented timed up and go (iTUG) test in genetically confirmed facioscapulohumeral muscular dystrophy (FSHD) participants using a commercially available system of wireless motion sensors. Patients returned within 2 weeks to determine test–retest reliability. Gait parameters in FSHD participants were compared with a normative database, FSHD clinical severity score, manual muscle testing, and patient-reported functional disability.

Results: Gait parameters in FSHD participants were significantly ($P < 0.05$) altered compared with normative values, and reliability was excellent (intraclass correlation coefficient 0.84–0.99). Stride velocity and trunk sagittal range of motion had moderate to strong correlations to other FSHD disease measures.

Discussion: The iTUG was reliable, abnormal in FSHD, and could distinguish between participants with differing disease severities. Instrumenting timed functional tasks may prove to be useful in FSHD clinical trials.

Keywords

facioscapulohumeral muscular dystrophy; iTUG; PROMIS PF; test–retest reliability; timed up and go test

Correspondence to: J. Huisinga; jhuisinga@kumc.edu.

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The chronic progressive nature of facioscapulohumeral muscular dystrophy (FSHD) can be a major challenge when measuring a response to therapy. In a prior natural history study, no timed functional measure was sensitive to disease progression over periods as long as 3 years.[1] Most of these measures use elapsed timed to complete outcome tasks or yes/no completion of the task as the outcome and fail to quantify changes in the dynamic interplay of muscles required to perform simple coordinated motor tasks. More recently, functional tests that combine both time and distance, such as the 6-minute walk test, have proven useful in the more rapidly progressive muscular dystrophies. Further quantifying functional motor tasks may reveal a continuum of motor disability that predicts future motor dysfunction.

The recent development of portable, wireless motion sensors that provide quantitative data similar to a laboratory-based motion analysis system has made these instruments practical for use as outcome measures for clinical trials in muscular dystrophies. Commercial software is available to analyze walking parameters during a timed up and go (TUG) test while wearing the wireless motion sensors.[2] The present study evaluates specific gait metrics obtained during an instrumented TUG (iTUG) in persons with FSHD to identify the test–retest reliability of those metrics and to examine the relationship between these metrics and FSHD disease severity.

MATERIALS AND METHODS

Participants and Testing.

In this prospective study, participants were independently ambulatory, between 18 and 75 years of age, and had confirmatory genetic testing.[3] The study was approved by our institutional review board, and written informed consent was obtained from all participants. Participants came to the research center for a single day visit consisting of a physical examination, functional testing, and wireless motion analysis. Participants returned within 2 weeks for a second visit consisting only of gait testing to assess test–retest reliability of the iTUG gait metrics.

Persons with FSHD performed the iTUG test while instrumented with 6 wireless inertial sensors (Mobility Lab, Opal sensors; APDM, Portland, OR). The TUG test is a standardized, clinical test of walking during which the patient rises from a seated position, walks 9 meters, turns 180 degrees, walks back to a chair, and sits down.[4] Sensors were placed on the midline of the sternum, the lumbar spine, bilaterally superior to the ankle joint and bilaterally proximal to the wrist joint (see Supp. Info. Video). Each sensor contains a triaxis accelerometer and gyroscope to assess dynamic parameters of movement.[2] iTUG metrics have previously been validated against traditional three-dimensional motion capture systems.[5] Each FSHD participant performed the iTUG 3 times after having been given a description of the test but no training before the testing. The average value for each outcome variable was used for analysis.

The FSHD clinical score (FCS) summarizes motor impairment in 6 body regions (0 = unaffected, 15 = severely affected).[6] Manual muscle testing was performed on 8 muscle groups (bilateral hip flexors, knee flexors and extensors, and ankle dorsiflexors), and scores were averaged to create a summary score.[1] The Patient-Reported Outcomes Measurement

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Information System Physical Function (PROMIS PF) 20A is an instrument developed by the National Institutes of Health PROMIS initiative, which generates scores for physical function and their impact on daily life.[7]

Statistical Analysis.

FSHD iTUG metrics were compared to manufacturer (APDM)-provided normative database metric values ($n = 84$; 32 men, average age 52.3 ± 20.0 years). The 95% distribution upper/lower confidence limits were equal to the sample mean ± 1.96 (0.975 quintile of the Z-distribution) times the SD, using normative data-base estimates. A Z-score was calculated by dividing the difference between the FSHD metric value and normative mean by the normative SD. Z-scores were averaged to create an iTUG summary score. Test–retest reliability for iTUG metrics were determined by using intraclass correlation coefficients (ICCs) determined from a linear mixed effects model. Clinical severity scores were divided into 2 groups, mild to moderate (FCS 0–6) and moderate to severe (FCS 7–15). Differences in iTUG metrics between severity groups were assessed by using independent t tests. Correlations between iTUG metrics and FSHD clinical severity scores, manual muscle test summary scores, and PROMIS PF 20A scores were determined by using Pearson correlations. Statistical testing was performed in SAS version 9.4 (SAS Institute, Cary, NC) and SPSS Statistics 22.0 (IBM, Armonk, NY), with $\alpha = 0.05$.

RESULTS

Seventeen FSHD participants with similar demographics across sexes were included in the study (Table 1). Compared with the normative database iTUG metric values, 75% of FSHD participants had values outside the normative 95% confidence limits for 8 of 10 iTUG gait metrics (Table 2). Many gait metrics distinguished between participants with mild to moderate or moderate to severe disease severity, most notably the stride velocity and trunk sagittal range of motion. The ICC values representing reliability of major iTUG gait metrics including stride velocity, cadence, stride length, and shank range of motion were excellent (Table 2). Three people were not included in the ICC calculations because they did not return for repeat testing.

Stride velocity and trunk sagittal plane range of motion were not correlated ($r = -0.45$, $P = 0.07$), suggesting that they were measuring different aspects of temporal and spatial mobility, but both measures had moderate to strong correlations with the FSHD clinical severity score, average lower extremity manual muscle testing, and PROMIS PF 20A (Table 3). Creating an average iTUG Z-score for stride velocity and trunk sagittal plane range of motion yielded a mean score of −2.38 (SD 1.85) and improved correlations to FSHD measures of disease severity (Table 3).

DISCUSSION

Here we demonstrate the feasibility of utilizing wireless sensors to instrument a standard, timed, functional gait test. The iTUG gait metrics showed excellent test–retest reliability in FSHD, were different compared with normative values, and showed moderate to strong correlations with FSHD measures of disease severity.

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The classic model for disease progression in FSHD describes a descending pattern with early facial and shoulder girdle weakness, followed by abdominal/paraspinal weakness, and then later involvement of the lower extremity. Recent large MRI studies have questioned that temporal pattern of progression, demonstrating early involvement of shoulder girdle muscles as has been previously described and also early involvement of thigh and pelvic girdle muscles.[8] This has been assumed to be clinically asymptomatic because weakness of the pelvic and lower extremity muscles was not apparent on bedside testing. Prior studies using a formal gait laboratory revealed a subgroup of FSHD patients with abnormal stride velocity despite normal manual muscle testing.[9] The clinical importance of the early involvement of pelvic girdle and upper thigh muscles on MRI is supported by the patient impression of the disease, in that problems with mobility and ambulation are the most frequently reported areas of functional limitation.[10] Thus, a quantitative assessment of gait and mobility is appealing in FSHD.

Despite the importance of mobility to patients, our ability to perceive differences with disease progression using traditional timed functional motor measures has been limited.[1] The largest natural history study did not detect changes in the time to ascend 4 stairs or to go 30 feet over periods as long as 3 years. The iTUG allows for many more quantitative outcome variables to represent gait performance compared with the standard TUG, which measures only time to complete the test. The ability to instrument a standard functional gait test provides an attractive solution because small changes in the dynamic motion of motor tasks have a good likelihood of improving the sensitivity to change while maintaining relevance to activities of daily living, which will be appealing when seeking regulatory approval for new drugs.

Limitations to the current study include the small sample and performance at a single site. Future studies must determine the multisite reliability and responsiveness to disease progression of individual iTUG metrics.

In conclusion, motion capture systems are an appealing option for FSHD clinical trials. The system described here is commercially available, portable, takes very little training, has built-in automated protocols and scripts, requires little or no postprocessing, and requires no special facilities. Above all, if this technique proves useful in FSHD, it can serve as a blueprint for instrumenting timed functional tasks for any muscular dystrophy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

FCS	FSHD clinical score
FSHD	facioscapulohumeral muscular dystrophy
ICC	intraclass correlation coefficient
iTUG	instrumented timed up and go test
PROMIS PF	Patient-Reported Outcomes Measurement Information System Physical Function

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Table 1.

Participant demographics for persons with FSHD ($n = 17$).

Item	Men	Women	Total
N	7	10	17
Mean age in years (range)	52.6 (35–67)	54.5 (32–66)	53.7 (32–67)
Mean D4Z4 fragment kb (range)	25.1 (16–35)	23.6 (15–33)	24.3 (15–35)
Mean FSHD clinical severity (range) *	7.4 (4–10)	6.2 (2–10)	6.7 (2–10)

FSHD, facioscapulohumeral muscular dystrophy.

* FSHD clinical severity 0–15 point scale: 0 = normal, 15 = severely affected.

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Table 2.

iTUG gait metrics in FSHD participants (ICC values are for all FSHD participants).*

iTUG gait metrics	Normative *N* = 84, Mean (SD)	FSHD *n* = 17 mean, (SD)	FSHD outside normative 95% CL (%)	ICC *n* = 14	FSHD mild to mod *n* = 9, mean (SD)	FSHD mod to severe *n* = 8, mean (SD)	*P*-value*
Total duration, s	16.6 (2.2)	27.4 (7.1)	16 (94.1)	0.99	24.0 (6.4)	31.3 (6.2)	0.03*
Stride length (% stature)	84.8 (5.8)	77.4 (8.1)	12 (70.6)	0.97	81.5 (7.6)	72.8 (6.1)	0.02*
Stride velocity (% stature/s)	80.3 (8.9)	58.6 (12.8)	17 (100)	0.99	66.0 (11.4)	50.4 (8.9)	<0.01*
Cadence (steps/min)	113.4 (8.7)	90.1 (13.7)	16 (94.1)	0.99	96.7 (13.4)	82.6(10.3)	0.03*
Double support (%)*	22.2 (4.1)	31.5 (7.5)	16 (94.1)	0.99	28.3 (5.3)	35.0 (8.4)	0.07
RoM knee (degrees)	57.6 (3.7)	61.2 (7.4)	13 (76.5)	0.96	57.5 (5.6)	65.4 (7.2)	0.02*
RoM knee asymmetry (|Diff R-L |)*	0	5.5 (3.6)	-	-		-	-
RoM trunk horizontal (degrees)	9.4 (2.6)	10. 0 (9.8)	4 (23.5)	0.99	6.5 (2.2)	13.9 (13.5)	0.13
RoM trunk sagittal (degrees)	4.3 (1.0)	6.8 (3.0)	13 (76.5)	0.99	4.9 (1.3)	8.9 (2.9)	<0.01*
RoM arm (degrees)	20 (8.3)	14.1 (6.2)	13 (76.5)	0.84	13.8 (5.7)	14.4 (7.2)	0.84
RoM arm asymmetry (|Diff R-L|)*	0	11.5 (10.7)	-	-	-	-	-
Turn: duration, s	1.9 (0.3)	3.2 (1.9)	15 (88.2)	0.95	2.6 (0.4)	3.8 (2.6)	0.17

-, ; CL, confidence limit; Diff, difference; FSHD, facioscapulohumeral muscular dystrophy; ICC, intraclass correlation coefficient; iTUG, instrumented timed up and go test; mod, moderate; R-L, right-left; RoM, range of motion.

*Mild to moderate FSHD clinical severity score 0–6; moderate to severe FSHD clinical severity score 7–15.

†From t test.

‡Significant group difference between mild to moderate and moderate to severe FSHD groups.

§Double support = time spent with both feet in contact with the ground during a single stride.

//Variability for normative differences in side to side asymmetry are not available; however, the difference in normative means for left and right side = 0.

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Table 3.

Correlations between iTUG metrics and measures of FSHD disease severity; Pearson *r* value (*P*-value).

Comparison	Stride velocity	Sag trunk RoM	iTUG Z-score
FSHD clinical severity score	−0.65 (0.005)*	0.70 (0.002)*	0.79 (<0.01)*
MMT LEXT	0.52 (0.03)*	−0.68 (0.003)*	−0.72 (<0.01)*
PROMIS PF 20A	0.44 (0.07)	−0.53 (0.03)*	−0.58 (0.01)*

FSHD, facioscapulohumeral muscular dystrophy; iTUG, instrumented timed up and go test; MMT LEXT, average lower extremity manual muscle testing score; PROMIS PF, Patient-Reported Outcomes Measurement Information System Physical Function; Sag trunk RoM, range of motion of the trunk in the sagittal plane.

*Significant Pearson correlation.