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Authors

Hall, Deborah A
Stebbins, Glenn T
Jacquemont, Sebastien
et al.

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Clinimetric Properties of the Fragile X-associated Tremor Ataxia Syndrome Rating Scale

Deborah A. Hall, MD, PhD,[1,*] Glenn T. Stebbins, PhD,[1] Sebastien Jacquemont, MD,[2] Elizabeth Berry-Kravis, MD, PhD,[1,3] Christopher G. Goetz, MD,[1] Randi Hagerman, MD,[4] Lin Zhang, MD, PhD,[5] and Maureen A. Leehey, MD[6]

ABSTRACT: Background: There are currently no proven treatments for fragile X-associated tremor and ataxia syndrome (FXTAS). Validated outcome measures are needed in order to plan and conduct clinical trials to aid in the development of therapy.
Methods: This study examined the reliability and construct validity of the FXTAS Rating Scale. The study was conducted by using ratings from movement disorder specialists, who were blinded to gene status, on the FXTAS Rating Scale.
Results: In 295 premutation carriers with and without FXTAS, 33 scale items showed a high level of overall reliability, adequate item-to-total correlations and construct validity. Factor analysis revealed four components.
Conclusions: The result demonstrates that many items in the scale meet standard clinimetric criteria, but modification of the scale improved the overall utility.

Introduction

Fragile X-associated tremor and ataxia syndrome (FXTAS) is a progressive neurodegenerative movement disorder characterized by tremor, cerebellar gait ataxia, parkinsonism, and cognitive decline.[1] It is caused by a "premutation" (55–200 CGG repeats) in the 5' untranslated region of the fragile X mental retardation 1 (FMR1) gene. FXTAS is often mistaken for other movement disorders such as Parkinson's disease and essential tremor.[2] When diagnosed, FXTAS is found in FMR1 carrier men typically over the age of 50; however, it sometimes occurs in women who present with a kinetic tremor and cerebellar gait ataxia. Other clinical features of FXTAS may include peripheral neuropathy, bowel and bladder dysfunction, impotence, memory loss, and problems with executive functioning.[1] Patients with FXTAS demonstrate moderate-to-severe generalized brain atrophy with ventricular enlargement, cerebellar atrophy, and subcortical and/or pontocerebellar white matter lesions.[3] Approximately 60% of men with FXTAS have T2 hyperintensities in the middle cerebellar peduncles and the splenium of the corpus callosum.[3,4]

The FXTAS Rating Scale (FXTAS-RS) is a tool that has been used by clinical researchers to measure the clinical motor signs of FXTAS, including tremor, ataxia, and parkinsonism.[5] The scale was originally constructed simply by combining items from three published rating scales commonly used to assess these motor signs in other neurological conditions, eliminating and reordering overlapping items so that patients could be assessed in a logical sequence. The source scales were the Clinical Rating Scale for Tremor (CRST) assessment,[6] the International Cooperative Ataxia Rating Scale (ICARS) for ataxia assessment,[7] and the Unified Parkinson's Disease Rating Scale (UPDRS) part III for parkinsonism assessment.[8] An item testing tandem gait was also adapted from the Unified Huntington's Disease Rating Scale.[9] The resultant FXTAS-RS has 44 items; the total score ranges from zero to 226. The tremor subdomain (score range 0–53) assesses action and postural tremor, including head (1 item), arm

[1]Department of Neurological Sciences and Pediatrics, Rush University, Chicago, Illinois, United States; [2]Department of Pediatrics, University of Montreal, Montreal, Canada; [3]Department of Pediatrics, Rush University, Chicago, Illinois, United States; [4]MIND Institute and Department of Pediatrics, University of California Davis School of Medicine, Sacramento, CA, United States; [5]Department of Neurology, University of California Davis School of Medicine, Sacramento, CA, United States; [6]Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado, United States

*Correspondence to: Deborah Hall, MD PhD, Department of Neurological Sciences and Pediatrics, Rush University, 1725 West Harrison St, Suite 755, Chicago, IL 60611; Deborah_A_Hall@rush.edu
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(4 items), and leg (2 items) tremor. Testing includes assessment of drawing and handwriting. The ataxia sub-domain (score range 0–73) assesses posture and gait (7 items), limb ataxia (9 items), dysarthria (2 items), and oculomotor disturbances (2 items). The parkinsonism sub-domain (score range 0–100) assesses bradykinesia (4 items), gait and balance (7 items), rest tremor (3 items), and rigidity (1 item).

Fragile X-associated tremor ataxia syndrome is a disease associated with significant morbidity and mortality, with difficulties in activities of daily living by the second decade of disease.[10] To date, there have been no clinical trials showing efficacy of symptomatic or disease-modifying agents for FXTAS. Validated outcome measures are needed to plan and conduct clinical trials to aid the development of therapy. The goal of this study was to examine the reliability, and construct validity of the FXTAS-RS. Based on these analyses, potential modifications to the scale could be identified to improve the overall utility of the FXTAS-RS. With an established and clinimetrically sound scale that captures the overall disability and the subcomponents of impairment, the long-term goal will be to test responsivity in interventional studies.

Methods

Subjects and Ratings

A video protocol with the items on the FXTAS-RS was administered to FMR1 premutation carriers. The structured video protocol was developed to capture the performance of the items on the FXTAS-RS. Videographers were trained at three participating university centers: University of California Davis School of Medicine, Rush University Medical Center, and the University of Colorado at Denver and Health Sciences Center. Videos of premutation carriers with FXTAS, and premutation carriers unaffected with FXTAS, were obtained. The videos were coded and sent de-identified to one of the other two institutions for rating. The FXTAS-RS is a free scale and is available from the first author of this paper.

Movement disorder specialists (MDS) at the three institutions (DH, ML, LZ, CG) were trained during an in-person meeting in the administration and scoring of the scale. Each MDS rated videos from another institution so that no specialist rated a patient with whom they were familiar. Results were submitted to a common database. This study was approved by the respective Institutional Review Boards (Rush University, University of Colorado, and University of California Davis; ORA: L01061203) and all subjects signed informed consent.

Statistical Analyses

Demographic and disease-related variables were examined using parametric and nonparametric models as appropriate. Examination of the clinimetric properties of the FXTAS-RS proceeded in a staged manner. First, scale items with excessive missing values, defined as ≥20% of the sample, were deemed problematic. Next, item-to-total correlation coefficients were examined for the remaining items and any item with correlations less than 0.40 were considered problematic.[11]

All items identified as problematic at each stage of the examination of clinimetric properties were reviewed by the MDS and the clinimetrician (GTS) to determine if they should be dropped from the scale. This determination was based on both the statistical result as well as the potential clinical import of the item. Thus, some items may have had poor clinimetric properties, but were deemed clinically important enough to warrant inclusion in the scale.

Once the problematic items were adjudicated by the MDS, the remaining items were reexamined for internal consistency (Cronbach's alpha, item-to-total correlation), and construct validity using exploratory factor analyses. Due to the ordinal level nature of the ratings, an unweighted least squares extraction was employed,[12] and varimax rotation was used to improve interpretation of the factor structure. The criterion for significant factor loadings was set at 0.40.[13] Additionally, remaining items were examined for discrimination, thresholds, and item characteristic curves using Item Response Theory (IRT) approaches, which used a maximum likelihood parameter estimation.[14] IRT measures of discrimination indicate the relative importance of the item in relation to the underlying construct measured; in this case FXTAS motor severity. Items with a discrimination score ≥1 indicate adequate relative importance.[15] IRT measures of threshold and item characteristic curves provide an indicator of scaling adequacy in the measurement of the underlying construct of FXTAS motor severity.[16]

Results

Two hundred and ninety-five individuals were videotaped and rated by the respective MDS. The mean age was 62.9 ± 9.9 years, and 45% were women. Subjects were 97% Caucasian with a mean mental status exam score of 27.5 ± 3.1 and mean CGG repeat size of 82.2 ± 21.6.

Items with ≥20% missing values included many ICARS (standing capacity, spread of feet with eyes closed, all drawing items, pouring measures, action, and intention measures) and all measures of rigidity. Items with ≤0.40 item-to-total correlations included additional ICARS measures (dysmetria of saccade, ocular pursuit, quality of sitting position); measures of dystonia (walk with dystonic posturing, arm dystonic posture, face dystonia, voice dystonia, trunk dystonia, arm dystonia, leg dystonia, gait dystonia); and the measure of face, lip and jaw rest tremor. Items assessing head postural tremor, upper extremity rest tremor, and lower extremity rest tremor had item-to-total correlations below the threshold, but they were deemed clinically important measures and were retained.

The remaining 33 items demonstrated a high level of overall reliability (Cronbach's alpha = 0.94). Item-to-total correlations met the threshold of ≥0.40 for all items with the exception of head postural tremor (0.38), upper extremity rest tremor (right hand = 0.30; left hand = 0.36), lower extremity rest tremor (right leg = 0.22; left leg = 0.12). Construct validity was adequate. IRT

TABLE 1 *Results of exploratory factor analysis*

ITEM	Factor 1	Factor 2	Factor 3	Factor 4
Facial expression (UPDRS)	0.464			
Postural head tremor (CRST)		0.407	0.475	
Speech (UPDRS)	0.617			
Dysarthria: fluency of speech (ICARS)	0.495			
Dysarthria: clarity of speech (ICARS)	0.479			
Upper extremity tremor at rest (UPDRS) R hand				0.408
Upper extremity tremor at rest (UPDRS) L hand				0.624
Action or postural tremor of hands (UPDRS) R hand			0.684	
Action or postural tremor of hands (UPDRS) L hand			0.744	
Finger-to-nose: intention tremor of finger (ICARS) R arm			0.785	
Finger-to-nose: intention tremor of finger (ICARS) L arm			0.793	
Finger taps (UPDRS) R hand		0.574		
Finger taps (UPDRS) L hand		0.650		
Hand movements (UPDRS) R hand		0.706		
Hand movements (UPDRS) L hand		0.591		
Rapid alternating movements of hands (UPDRS) R hand		0.764		
Rapid alternating movements of hands (UPDRS) L hand		0.791		
Pronation-supination alternating movements (ICARS) R arm	0.417	0.554		
Pronation-supination alternating movements (ICARS) L arm		0.544		
Leg tremor at rest (UPDRS) R foot				0.840
Leg tremor at rest (UPDRS) L foot				0.829
Leg agility (UPDRS) R leg	0.482	0.504		
Leg agility (UPDRS) L leg	0.430	0.541		
Arising from chair (UPDRS)	0.671			
Postural stability (UPDRS)	0.650			
Body bradykinesia and hypokinesia (UPDRS)	0.817			
Posture (UPDRS)	0.585	0.403		
Gait (UPDRS)	0.861			
Walking capacities (ICARS)	0.877			
Gait speed (ICARS)	0.776			
Tandem walking (UPDRS)	0.616			
Handwriting (CRST)			0.531	
Archimedes' spiral on pre-drawn pattern (ICARS)			0.660	

Note: Factor with the highest factor loading is highlighted in gray. Significant factor loading set at ≥ 0.40.

indicators of discrimination met the criterion of ≥1.00 and thresholds and item characteristic curves indicated acceptable scaling for all items. Exploratory factor analysis resulted in an acceptable Kaiser-Meyer-Olkin sampling adequacy (0.88) and a significant Bartlett's Test of Sphericity ($X^2 = 5011.67$, $P < 0.0005$). Factor extraction revealed four components, accounting for 59.6% of the cumulative variance. The rotated four factors provided measures of axial function, appendicular speed, postural tremor and rest tremor (Table 1).

Conclusions

The FXTAS-RS was created by combining components of four scales commonly used by MDSs, in order to capture the salient features of the disease. The results of this study show that some features of the scale are positive and others that may need to be modified. Once problematic items were identified and removed, there was a high degree of internal consistency of the scale, which indicates that the internal structure of the scale is appropriate. However, this value of alpha may be inflated due to the large number of items, which tends to increase alpha estimate. The evaluation of the factor structure of the scale suggested that there was a consistent clustering for four factors measuring axial function, appendicular speed, postural tremor, and rest tremor. However, ideal construct validity is found when greater than 75% of the scale variance is accounted for by the principal component analysis. In our study, approximately 60% of the scale variance was accounted for by the four components identified, suggesting modification of the scale items may be necessary. Five items demonstrated significant factor loading on multiple factors, suggesting that some redundancy is present and the scale might be simplified.

There are several strengths and weaknesses to this study. This is the first study to evaluate the clinimetric properties of this new scale for FXTAS. There was a large sample size for the first phase of the study, and it is highly unlikely that such sample sizes of premutation carriers can be amassed again. A clinimetrician (GTS) was involved in the development and validation of the scale.

There also are several weaknesses to this study. The first is that the FXTAS-RS was developed as a scale to be used with a video protocol and has not been validated in direct examination of the patient. Not all subjects in the first phase of the study were imaged, and the diagnostic criteria for FXTAS could not be performed. Given that FXTAS is known to be an X linked disorder and sex could not be disguised, some of the MDS may have been more likely to rate men in the study higher on the FXTAS-RS. In later stages of scale development, potential sex effects will need to be examined for differential item functioning. Finally, the examination of clinimetric properties of the penultimate scale with 33 items

was based on the same sample of ratings as used in the initial identification of problematic items. This analysis undoubtedly capitalized on the identical variance structure of the initial sample. Therefore, the results for the penultimate scale need to be replicated in a new sample of individuals with FXTAS.

The next step in the development of a modified version of the FXTAS-RS will require adding, omitting, and/or altering items on the scale and testing this modified version on a second cohort of premutation carriers with and without FXTAS. In addition to the comments above, some considerations may be taken into account in the modified version. A total score in the next version would be very helpful clinically in gauging change from visit to visit. Longitudinal change of the scale over time and minimal clinically significant change need to be established. Future testing on this scale will likely be accomplished by the large groups originally involved in this study who are highly motivated to collaborate so that the field has a readily available and validated outcome measure when compounds are available for testing in clinical trials in this population. Until the final validation is completed, clinicians and researchers will have the option of using the original FXTAS-RS or the modified version. Given the clinimetric strength of the modified version, the authors are currently using the modified version in research and clinical settings.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

D.A.H.: 1A, 1B, 2C, 3A, 3B
R.P.: 1A, 1B, 1C, 2B, 3B
S.A.: 2A, 2B, 2C, 3B
M.P.: 2C, 3A, 3B
G.T.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3B
S.J.: 1C
E.B.K.: 2B, 1C, 3B
C.G.G.: 1A, 1B, 1C, 3B
R.J.H.: 2B, 1C
L.Z.: 2B, 1C
M.L.: 1A, 1B, 1C, 2B, 3B

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Disclosures

Ethical Compliance Statement: This study was approved by the respective Institutional Review Boards (Rush University, University of Colorado, and University of California Davis; ORA: L01061203) and all subjects signed informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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