Poster M276

Measurement Properties of the Friedreich's Ataxia Rating Scale–Activities of Daily Living in Patients With Spinocerebellar Ataxia

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CONCLUSIONS

1. Overall, psychometric evaluation showed that Friedreich's Ataxia Rating Scale–Activities of Daily Living (FARS-ADL) performed well on a range of analyses examining the reliability and validity of the measure in subjects with spinocerebellar ataxia (SCA)
2. Furthermore, FARS-ADL demonstrated the ability to serve as a reliable assessment of disease progression over a period of ≥1 year

BACKGROUND and METHODS

Background

- SCAs are a group of rare, dominantly inherited, heterogenous disorders that cause progressive neurodegeneration of the cerebellum and spinal cord[1-2]
  - More than 50 distinct genetic subtypes have been identified, with the most prevalent worldwide being SCA3 (25%-50%), SCA2 (13%-18%), and SCA6 (13%-15%)[3–5]
  - Health-related quality of life is severely impacted by SCA, and patients experience a high clinical burden due to limited independence, reliance on caregivers, and impacts on social and physical function[6,7]
  - There is interest in improving the measurement of clinically meaningful ataxia symptoms for use in clinical trial settings[8,9]
- The Friedreich's Ataxia Rating Scale (FARS) is a validated outcome measure used widely in patients with Friedreich ataxia and consists of subscales assessing (1) functional staging (FARS-FUNC), (2) activities of daily living (FARS-ADL), (3) neurological features (sections A-E) (FARSn), and (4) timed performance outcomes[10,11]
- FARS-ADL has been used in SCA natural history studies[12]; however, its measurement properties within this population have not been evaluated

Objective

- To examine the psychometric validity and measurement properties of FARS-ADL in patients with SCA

Methods

- Psychometric measurement properties of the FARS-ADL were evaluated using data from a cohort of SCA subjects enrolled in the PROM-Ataxia validation study from Massachusetts General Hospital (cross-sectional; MGH cohort) and subjects enrolled in BHV4157-206 (NCT03701399; 48-week study; Study BHV4157-206 cohort)[13]
  - The MGH psychometric cohort (n=33) represented patients in a real-world clinical setting; the Study BHV4157-206 cohort (n=217) allowed evaluation of the SCA3 genotype separately due to its large size, thus enabling psychometric assessments that required longitudinal data
    - Key inclusion criteria for the validation subset (MGH) were age of ≥18 years and diagnosis of SCA (SCA types 1, 2, 3, 6, 7, 8, or 10)
- Psychometric properties evaluated included data acceptability (ceiling and floor effects), internal consistency (Cronbach α), convergent and divergent validity, and responsiveness
  - Data acceptability was determined by examining the distributions (minimum and maximum values and IQR) of the total score and scores for each item. Acceptability is supported when observed scores are well distributed, mean scores are near the scale midpoint, and floor and/or ceiling effects are minimized
    - A threshold of >15% of subjects with scores at either the minimum or maximum item value was used to indicate floor and ceiling effects, respectively
  - Internal consistency reliability was assessed by the Cronbach α coefficient (raw and standardized) and item-to-total correlations (Spearman r). An α of ≥0.70 and item-to-total correlation of ≥0.30 served as thresholds of acceptable internal consistency
  - Convergent and divergent validity was assessed through a correlation matrix of FARS-ADL scores and a number of clinician-assessed measures and patient-reported outcomes measures
    - Domains examined included upper limb mobility, lower limb mobility, fatigue, overall ataxia symptoms, anxiety, depression, overall physical abilities, ADLs, overall mental or emotional state, and speech
  - Known-groups validity was examined by comparing mean values between 2 groups of differing disease severity (least severe [presymptomatic and mild] vs most severe [severe] based on Klockgether severity score) using an independent *t* test and FARS-ADL item, domain, and total scores across disease categories based on quartiles of the FARS-FUNC total score
  - Responsiveness data were derived primarily through anchor-based analytics, with known-groups findings considered as supportive
- Intra-individual meaningful change thresholds were examined by leveraging subjects enrolled in BHV4157-206 (Study BHV4157-206 cohort)
  - Minimum important change values were derived using distribution-based and anchor-based methods
    - Distribution-based methods: 0.5×SD and standard error of measurement (SEM)
    - Anchor-based methods, with Clinical Global Impression–Global Improvement Scale (CGI-I) as anchor: empirical cumulative distribution function (eCDF) and probability density function (PDF) curves

RESULTS

Demographics and Clinical Characteristics

- A total of 33 subjects comprised the MGH psychometric cohort, representing SCA genotypes SCA1, SCA2, SCA3, SCA6, SCA6/8, and SCA8, with the most common ataxias being SCA3 (54.5%), SCA2 (15.2%), and SCA6 (15.2%) (**Table 1**)
- The mean (SD) total FARS-ADL score was 11.9 (6.6), with a range of 0.0 to 25.0
- Study BHV4157-206 enrolled 217 subjects with SCA; mean (SD) age was 47.6 (12.8) years, 51.2% were female, mean (SD) age at symptom onset was 38.3 (12.3) years, and mean (SD) total FARS-ADL score was 9.7 (4.9), with a range of 1.0 to 23.0
  - In a subgroup of 89 subjects with an SCA3 genotype, baseline characteristics were as follows: mean (SD) age was 46.7 (12.1) years, 51.7% were female, mean (SD) age at symptom onset was 39.1 (11.8) years, and mean (SD) total FARS-ADL score was 9.2 (5.3), with a range of 1.0 to 22.0

Table 1. Demographics and Clinical Characteristics (MGH Psychometric Cohort)

Characteristics	MGH psychometric cohort (n=33)
Known genotype, n (%)	
SCA1	2 (6.1)
SCA2	5 (15.2)
SCA3	18 (54.5)
SCA6	5 (15.2)
SCA6/8	2 (6.1)
SCA7	0
SCA8	1 (3.0)
SCA10	0
Klockgether severity, n (%)	
Presymptomatic (stage 0)	2 (6.1)
Mild (stage 1)	13 (39.4)
Moderate (stage 2)	7 (21.2)
Severe (stage 3)	11 (33.3)
Baseline total FARS-ADL score	
Mean (SD)	11.9 (6.6)
Median (range)	13.0 (0.0–25.0)

FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living; MGH, Massachusetts General Hospital; SCA, spinocerebellar ataxia.

Psychometric Properties (MGH Cohort)

- Among subjects enrolled in the MGH cohort (n=33), ceiling effects were absent while floor effects were observed for 8 of 9 items (floor effects were not observed for the walking item). IQRs were skewed toward the lower end of response options (**Table 2**)

Table 2. FARS-ADL Data Acceptability (MGH Psychometric Cohort)

FARS-ADL domain (item statistic)	MGH psychometric cohort (n=33)
Speech (#1 speech)	
Mean (SD)	1.5 (0.9)
Median (IQR)	2.0 (1.0–2.0)
Swallowing (#2 swallowing)	
Mean (SD)	1.2 (1.0)
Median (IQR)	1.0 (0.0–2.0)
Cutting food and handling utensils (#3 cutting food and handling utensils)	
Mean (SD)	1.1 (1.1)
Median (IQR)	1.0 (0.0–2.0)
Dressing (#4 dressing)	
Mean (SD)	1.0 (0.9)
Median (IQR)	1.0 (0.0–2.0)
Personal hygiene (#5 personal hygiene)	
Mean (SD)	1.1 (1.0)
Median (IQR)	1.0 (0.0–2.0)
Falling (#6 falling)	
Mean (SD)	1.7 (1.2)
Median (IQR)	2.0 (1.0–3.0)
Walking (#7 walking)	
Mean (SD)	2.3 (1.2)
Median (IQR)	3.0 (1.0–3.0)
Quality of sitting position (#8 quality of sitting position)	
Mean (SD)	0.6 (0.7)
Median (IQR)	0.0 (0.0–1.0)
Bladder function (#9 bladder function)	
Mean (SD)	1.3 (1.2)
Median (IQR)	1.0 (0.0–2.0)

FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living; MGH, Massachusetts General Hospital.

Psychometric Properties (MGH Cohort)

- Excellent internal consistency was demonstrated, with an overall raw Cronbach α of 0.88 (α_{total}=0.88; $\alpha_{items\text{-}removed}$=0.86-0.87), and item-to-total correlations were acceptable (r=0.55-0.89 per item) (**Table 3**)

Table 3. FARS-ADL Internal Consistency Reliability (MGH Psychometric Cohort)

FARS-ADL domain (item statistic)	Cronbach α, standardized (raw)[a]	Item-to-total correlation[b]
Speech (#1 speech)	0.87 (0.87)	0.55
Swallowing (#2 swallowing)	0.88 (0.88)	0.57
Cutting food and handling utensils (#3 cutting food and handling utensil)	0.86 (0.85)	0.89
Dressing (#4 dressing)	0.86 (0.85)	0.89
Personal hygiene (#5 personal hygiene)	0.86 (0.86)	0.83
Falling (#6 falling)	0.87 (0.86)	0.78
Walking (#7 walking)	0.87 (0.87)	0.65
Quality of sitting position (#8 quality of sitting position)	0.88 (0.88)	0.60
Bladder function (#9 bladder function)	0.88 (0.88)	0.55
FARS-ADL total score	**0.88 (0.88)**	—

FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living; MGH, Massachusetts General Hospital.
[a] Cronbach α overall and per item if item deleted, raw and standardized.
[b] Spearman r.

- Convergent and divergent validity were supported, with stronger correlations observed between FARS-ADL and scales of similar constructs (*P*<0.001) (e.g., Neuro-QOL [upper], r=−0.90; Neuro-QOL [lower], r=−0.81; PROM-ADL, r=0.83; PROM-PHYS, r=0.82; and FARS-FUNC, r=0.78) and weaker correlations among measures of differing constructs (e.g., PROM-MENTAL, r=0.54 [*P*=0.001]) (**Table 4**)
- Similar trends were observed in Study BHV4157-206 in all SCA subjects and the SCA3 subgroup

Table 4. FARS-ADL Construct Validity—Convergent Validity (MGH Psychometric Cohort)

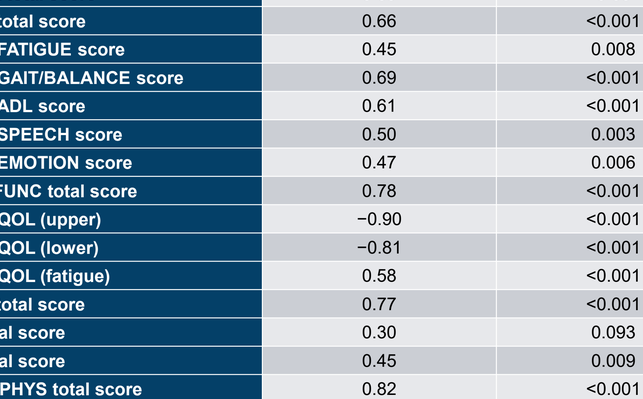
Instrument	Spearman correlation with FARS-ADL total score	*P* value
f-SARA total score	0.69	<0.001
PIFAS total score	0.66	<0.001
PIFAS-FATIGUE score	0.45	0.008
PIFAS-GAIT/BALANCE score	0.69	<0.001
PIFAS-ADL score	0.61	<0.001
PIFAS-SPEECH score	0.50	0.003
PIFAS-EMOTION score	0.47	0.006
FARS-FUNC total score	0.78	<0.001
Neuro-QOL (upper)	−0.90	<0.001
Neuro-QOL (lower)	−0.81	<0.001
Neuro-QOL (fatigue)	0.58	<0.001
BARS total score	0.77	<0.001
BDI total score	0.30	0.093
BAI total score	0.45	0.009
PROM-PHYS total score	0.82	<0.001
PROM-ADL total score	0.83	<0.001
PROM-MENTAL total score	0.54	0.001

ADL, activities of daily living; BAI, Beck Anxiety Inventory; BARS, Brief Ataxia Rating Scale; BDI, Beck Depression Inventory; FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living; FARS-FUNC, Friedreich's Ataxia Rating Scale–Function; f-SARA, modified functional Scale for the Assessment and Rating of Ataxia; Neuro-QOL (fatigue), Neurology Quality of Life Fatigue Scale; Neuro-QOL (lower), Neurology Quality of Life Lower Extremity Scale; Neuro-QOL (upper), Neurology Quality of Life Upper Extremity Scale; PIFAS, Patient Impression of Function and Activities of Daily Living Scale; PROM, patient-reported outcome measure.

Anchor-Based Analysis by CGI-I Status

- Using Study BHV4157-206 data, eCDF curves by CGI-I status (improved, no change, or deteriorated) in the −2 to +3 change range clearly differentiated between meaningful improvements and deterioration (**Figure 1**)
  - The median 48-week change scores in subjects divided by anchor category was −1 point in subjects with improvement, 0 points in those with no change, and +1 point in those with deterioration

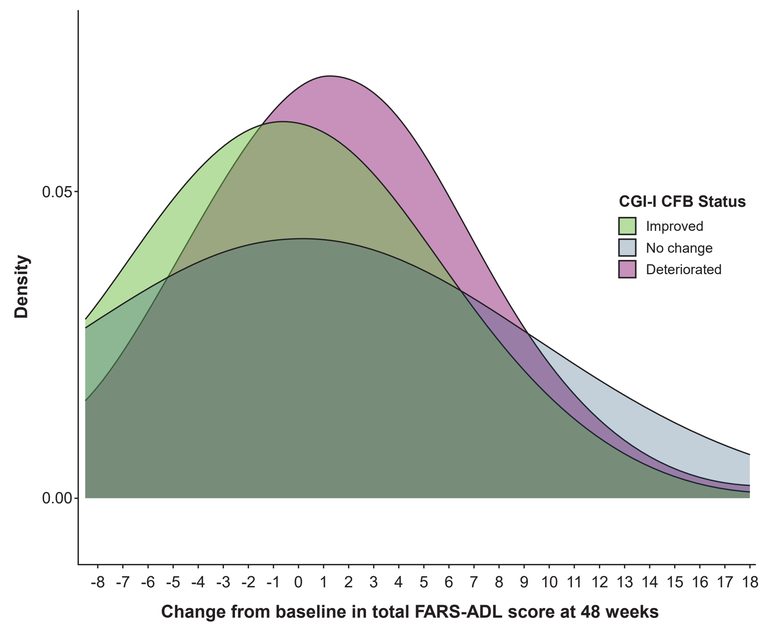
Figure 1. FARS-ADL eCDF by CGI-I Status (Study BHV4157-206)[a]



CFB, change from baseline; CGI-I, Clinical Global Impression–Global Improvement Scale; eCDF, empirical cumulative distribution function; FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living.
[a] All SCA subjects examined in this analysis.

- The anchor-based PDF curves are supportive of the findings in the eCDF curve analysis (**Figure 2**)

Figure 2. FARS-ADL PDF by CGI-I Anchor Status



CFB, change from baseline; CGI-I, Clinical Global Impression–Global Improvement Scale; FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living; PDF, probability density function.

- Distribution-based findings were 0.5×SD=2.43 and SEM=2.19 (**Table 5**)

Table 5. FARS-ADL Distribution-Based Statistics to Inform Minimal Detectable Change (Study BHV4157-206)

	All SCA (n=217)
FARS-ADL total score	
0.5×SD	2.43
SEM	2.19

FARS-ADL, Friedreich's Ataxia Rating Scale–Activities of Daily Living; MGH, Massachusetts General Hospital.

- *Additional Context*: Data from semi-structured interviews (poster M277 presented at MDA 2024) indicate a 1- to 3-point range for worsening or improvement in the total score was considered meaningful to clinicians interviewed (median values, 2-point worsening and 1-point improvement)[14]
- Data triangulation across distribution-based methods and anchor-based methods (presented herein), and clinician interviews (data presented elsewhere, poster M277 presented at MDA 2024) support a 2- to 3-point range as a minimally important change

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DISCLOSURES

Disclosures: MHP, AM, MWB, VC, and GL are employees of Biohaven Pharmaceuticals, Inc. **EP and LP** are employees of Broadstreet HEOR, which received funds from Biohaven Pharmaceuticals, Inc, for this work. **JDS** is a consultant for Biohaven Pharmaceuticals and site PI for Biohaven Pharmaceuticals clinical trials (NCT03701399, NCT02960893, and NCT03952806); receives royalties from Oxford University Press, Elsevier, Mac Keith Press, and Springer; and is the inventor of the Brief Ataxia Rating Scale, Cerebellar Cognitive Affective/Schmahmann Syndrome Scale, Patient-Reported Outcome Measure of Ataxia, and Cerebellar Neuropsychiatry Rating Scale, which are licensed to the General Hospital Corporation. **SS** has received research support from the National Ataxia Foundation, Biohaven Pharmaceuticals, Inc, National Institutes of Health, US Food and Drug Administration, Muscular Dystrophy Association, Wyck Foundation, Friedreich's Ataxia Research Alliance, Reata, PTC Therapeutics, Retrotope, Avidity Biosciences, Fulcrum Therapeutics, Reneo Pharma, and AavantiBio; and has served on scientific advisory boards for Reata, Avidity, and Dyne Therapeutics.

Acknowledgements: Medical writing support was provided by James Glen, of Nucleus Global and funded by Biohaven Pharmaceuticals, Inc. This presentation was developed in accordance with Good Publication Practice (GPP2022) guidelines. Authors had full control of the content and made the final decision on all aspects of this presentation.

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Presented at the Muscular Dystrophy Association (MDA) Clinical and Scientific Conference; March 3-6, 2024 · Orlando, FL