Reliability and Validity of the Korean Version of the Spinal and Bulbar Muscular Atrophy Functional Rating Scale

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Background and Purpose The Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS) is a reliable and valid instrument for evaluating the functional status of patients with spinal and bulbar muscular atrophy (SBMA). This study aimed to validate a Korean version of the SBMAFRS in an SBMA population.

Methods We applied the SBMAFRS to 64 SBMA patients at their regular follow-up clinical visits. The patients underwent clinical evaluations that included the 6-minute walking test (6MWT), forced vital capacity (FVC), manual muscle test, and the Penetration-Aspiration Scale (PAS). To estimate the stability of the SBMAFRS, the scale was reapplied to a subset of 31 randomly selected patients within 4 weeks of the initial test. The convergent validity was evaluated, and correlations were examined between SBMAFRS items and the muscular force, the total and subscores on the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), FVC, PAS score, age at onset, disease duration, and 6MWT results.

Results The internal consistency of the scale was confirmed by a high Cronbach's alpha (total raw alpha=0.867, total standardized alpha=0.863). The test-retest reliability as assessed by Spearman's rho was also high. The total score and subscores of the SBMAFRS were strongly correlated with the respective items and subscores of the ALSFRS-R, respiratory function, and the 6MWT.

Conclusions We have performed a validation study of the Korean version of a disease-specific functional rating scale for SBMA patients. The SBMAFRS is a useful tool for clinical practice and as a potential outcome measure for Korean SBMA patients.

Key Words spinal and bulbar muscular atrophy, translations, validity and reliability.

INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA), also referred to as Kennedy's disease, is an adult-onset, X-linked, lower motor neuron disease (MND).[1-4] This disease is clinically characterized by slowly progressive muscle weakness, with the early involvement of the bulbar, facial, and limb muscles, and it is caused by a CAG-repeats expansion, which encodes a polyglutamine (polyQ) tract in the first exon of the *androgen receptor (AR)* gene.[1,3-5]

SBMA is understood to be a prototypical genetic MND, but its progression is relatively slow compared with that of amyotrophic lateral sclerosis (ALS).[4] Recent SBMA clinical trials have been based on assessments made using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). The disease progression of SBMA is progressive but slow compared to ALS, which usually shows rapid progression. Although the ALSFRS-R is a valid clinical tool to use in various MNDs, differences in the rate of deterioration might not reflect the true functional deterioration of SBMA.[6,7]

Based on the need for an SBMA-specific rating scale, the Spinal and Bulbar Muscular

Atrophy Functional Rating Scale (SBMAFRS) was developed,[7] which has recently been validated in Italy.[8] The SBMAFRS is a questionnaire-based clinical scale that measures physical function associated with activities of daily living in five primary domains: bulbar, upper-limb, lower-limb, truncal, and respiratory functions.[7] This makes the SBMAFRS more appropriate for SBMA patients than the ALSFRS-R, whose measurement domains reflect the functional status of ALS.

The aim of this study was to determine the reliability and validity of a Korean version of the SBMAFRS in a large cohort of SBMA patients.

METHODS

Patients

Patients with SBMA were recruited from two MND/SBMA clinics in Korea (at Kyungpook National University Chilgok Hospital and Inje University Busan Paik Hospital) between April 2019 and November 2019. Sixty-four consecutive patients with genetically confirmed SBMA were recruited to participate in the study.

This study was approved by the Internal Review Boards of Kyungpook National University Chilgok Hospital (KNUCH 2019-04-023) and Inje University Busan Paik Hospital (IRB No. 19-0057). The following inclusion criteria were applied: 1) aged 18 years or older, 2) presence of genetically confirmed SBMA, with more than 38 CAG repeats in the *AR* gene, and 3) gave written informed consent.

We applied the SBMAFRS during routine follow-up clinical evaluations. To estimate the test-retest reliability, the scale was re-administered by the same examiners to a subset of 31 randomly selected patients within 4 weeks of its first administration.

Translation of the SBMAFRS into Korean

Permission was obtained from the original corresponding author of the SBMAFRS to translate the scale into Korean. The SBMAFRS was first translated from English to Korean by a Korean individual who was fluent in English. The Korean-translated version was then reviewed and compared with the original English version by four researchers to obtain a Korean version of the SBMAFRS that was consistent with the English version. A native English speaker who was fluent in Korean and unaware of the aims of this study translated the Korean scale back into English. Finally, this back-translated version was compared against the English original by two Korean examiners who were fluent in English to check its consistency, to produce the final Korean version of the SBMAFRS (Supplementary Material in the online-only Data Supplement) that was consistent with the English version.

Measurements

Demographic and clinical data

Demographic and clinical data including the age, age at onset, age at diagnosis, sex, site of symptom onset [upper limbs, lower limbs, bulbar, or no muscular weakness (cramps, tremors, or breast enlargement)], disease duration (duration from the time of symptom onset to the time of data collection), and the ALSFRS-R score[9] were collected by reviewing medical charts.

The Medical Research Council Sum Score (MRCSS) was used to assess the motor function of the patients. We calculated the manual muscle testing (MMT) total score (maximum value=60) for the following actions of the upper and lower limbs: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. Pulmonary function was measured using the forced vital capacity (FVC), which was expressed as a percentage of the predicted value, and the 6-minute walking test (6MWT). Additionally, the swallowing function was evaluated based on videofluoroscopic swallowing using the Penetration-Aspiration Scale (PAS), where 1 reflects poor function and 8 reflects the best function. Creatine phosphokinase (CPK) levels and the number of CAG repeats were retrieved.

Korean version of the SBMAFRS

The Korean version of the SBMAFRS, like the English version,[7] is a 14-item instrument in which the total possible score ranges from 0 (worst) to 56 (normal). Each item is scored on a scale from 0 to 4, with a higher score indicating a better functional status. The 14 items are divided into 5 subscore categories: bulbar (5 items), upper limbs (2 items), trunk (4 items), lower limbs (2 items), and breathing (1 item).

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics software (version 25.0, IBM, Armonk, NY, USA). Descriptive statistics for the demographic and clinical data were used to analyze the study data. A two-sided alpha of 0.05 was used as the cutoff for significance in all statistical tests. The psychometric analysis of the Korean version of the SBMAFRS comprised an evaluation of its internal consistency (Cronbach's alpha), test-retest reliability, and convergent validity.

Cronbach's alpha for each item and Cronbach's alpha if an item was deleted from the test were used to evaluate the internal consistency of the total SBMAFRS score. Spearman's rank-order correlation coefficients and the agreement percentages were calculated to determine the test-retest reliabil-

ity. For construct validity, domain-to-domain and domain-to-total correlations were evaluated by calculating Pearson's correlation coefficients. Convergent validity was examined using Pearson's correlation coefficients between SBMAFRS, ALSFRS-R, MRCSS, and 6MWT, swallowing function, and pulmonary function.

RESULTS

Demographics

This study enrolled 64 patients with SBMA from 2 specialized MND/SBMA clinics. The characteristics of the patients are listed in Table 1. They were aged 55.5±9.8 years (mean± SD; range=34–77 years) and all of them were male. Their age at onset was 44.9±10.1 years (range=22–68 years), their disease duration was 118.7±81.7 months (range=12–396 months), and their SBMAFRS and ALSFRS-R scores were 40.9±6.4 and 39.5±3.6, respectively (Table 1). The CAG repeat length was 46.1±4.1 (range=39–60) and the CPK level was 995.6±

642.0 U/L (range=46–2,923 U/L). The site of weakness onset was most commonly identified as the lower limbs (47/64, 73.4%), followed by the upper limbs (16/64, 25.0%) and the bulbar region (1/64, 1.6%).

Reliability

The internal consistency of the SBMAFRS was adequate, based on raw and standardized Cronbach's alpha values of 0.867 and 0.863, respectively. The removal of any single item did not improve the overall Cronbach's alpha for the scale (Table 2). A test-retest comparison was conducted for 31 subjects within 4 weeks of the initial test. No significant differences were observed for the demographic data, the ALSFRS-R, SBMAFRS, 6MWT, PAS, MRCSS, and the FVC between the test group (n=64) and the retest group (n=31). Spearman's rank-order correlation coefficients for test-retest reliability performed at the baseline and within 4 weeks showed a strong positive correlation, and the coefficients for the subscores were also significant (Table 3). The agreement between test and retest scores obtained within 4 weeks on the subscore level also revealed a high test-retest reliability (89.4% for the bulbar subscore, 93.1% for the fine-motor subscore, 91.5% for the gross-motor subscore, 95.3% for walking, and 88.0% for the respiration evaluation). The agreement in the total scores for the test and retest was 94.1% (Table 4).

Table 1. Demographic and clinical characteristics of patients with spinal and bulbar muscular atrophy (n=64)

Characteristic	Value
Age, years	55.5±9.8 (34–77)
Age at onset, years	44.9±10.1 (22–68)
Number of CAG repeats	46.1±4.1 (39–60)
Creatine phosphokinase, U/L	995.6±642.0 (46–2923)
Disease duration, months	118.7±81.7 (12–396)
Onset site	
Upper limbs	16 (25.0)
Lower limbs	47 (73.4)
Bulbar	1 (1.6)
No muscular weakness	0 (0)
SBMAFRS total score	40.9±6.4 (23–53)
ALSFRS-R total score	39.5±3.6 (29–47)
ALSFRS-R bulbar (1–3 subscore)	10.2±1.0 (6–12)
ALSFRS-R fine motor (4/5 subscore)	6.9±0.9 (5–8)
ALSFRS-R gross motor (6/7 subscore)	6.8±1.2 (4–8)
ALSFRS-R walking (8/9 subscore)	4.1±1.3 (2–8)
ALSFRS-R respiration (10–12 subscore)	11.4±0.7 (10–12)
FVC, %	81.1±14.4 (42–109)
6MWT (n=60)	345.7±119.3 (79.0–612.5)
PAS score (n=60)	2.3±1.4 (1–8)
MRCSS total score	54.7±6.1 (26–60)
MRCSS upper limbs	28.7±2.4 (16–30)
MRCSS lower limbs	26.1±4.5 (10–30)

Data are mean±SD (range) or n (%) values.
ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, FVC: forced vital capacity, MRCSS: Medical Research Council Sum Score, PAS: Penetration-Aspiration Scale, SBMAFRS: Spinal and Bulbar Muscular Atrophy Functional Rating Scale, 6MWT: 6-minute walking test.

Table 2. Descriptive statistics and Cronbach's alpha values for the SBMAFRS

Variable	Value	Cronbach's alpha if item deleted
Bulbar subscore		
Speech	2.89±0.74	0.870
Control of salivation	3.48±0.67	0.869
Swallowing	3.27±0.80	0.866
Tongue	2.77±0.50	0.863
Puffing cheeks	2.63±0.63	0.866
Upper-limbs subscore (fine motor)		
Writing	2.95±0.90	0.856
Eating action	3.05±0.74	0.849
Trunk subscore (gross motor)		
Dressing activity	3.08±0.76	0.844
Rising from a sitting position	2.56±0.89	0.844
Rising from a supine position	2.55±0.85	0.860
Bowing	3.53±0.59	0.859
Lower-limbs subscore (walking)		
Walking	2.53±0.78	0.850
Stairs	1.97±1.04	0.845
Breathing subscore		
Respiration	3.66±0.54	0.865

Data are mean±SD values.

Validity

The score on the walking subscore of the SBMAFRS was significantly correlated with those on the corresponding ALS-FRS-R subscore (rho=0.904, $p<0.001$), the 6MWT (rho=0.624, $p<0.001$), the MMT for the lower limbs (rho=0.762, $p<0.001$), and the total MMT (rho=0.693, $p<0.001$) (Table 5).

Similar results were obtained for the score on the gross-motor subscore, which was significantly correlated with the scores on the respective ALSFRS-R subscore (rho=0.712, $p<0.001$), the 6MWT (rho=0.555, $p<0.001$), the MRCSS for the lower limbs (rho=0.600, $p<0.001$), and the total MRCSS (rho=0.586, $p<0.001$).

The score on the fine-motor subscore of the SBMAFRS was significantly correlated with those on the respective ALSFRS-R subscore (rho=0.733, $p<0.001$), the 6MWT (rho=0.276, $p=0.033$), the MMT for the upper limbs (rho=0.413, $p<0.001$), and the total MMT (rho=0.495, $p<0.001$).

The CPK level and swallowing function (PAS score) were not correlated with the score on any subscore or the total SBMAFRS score.

DISCUSSION

SBMA is a slowly progressive disease with no definite treatment that is known to slow the progression of the disease,[1,4,6] although recent clinical trials have shown promising results.[10]

Table 3. Test-retest reliability of the Spinal and Bulbar Muscular Atrophy Functional Rating Scale (n=31)

Variable	Spearman's rho	p
Bulbar subscore	0.744	<0.001
Upper-limbs subscore (fine motor)	0.736	<0.001
Trunk subscore (gross motor)	0.911	<0.001
Lower-limbs subscores (walking)	0.850	<0.001
Breathing subscore	0.493	<0.001

Table 4. Rate of perfect agreement between test and retest

Bulbar	Fine motor (upper limbs)	Gross motor (trunk)	Walking (lower limbs)	Breathing	Total
89.4%	93.1%	91.5%	95.3%	88.0%	94.1%

Table 5. Convergent validity of the SBMAFRS

	SBMAFRS					
	Bulbar	Fine motor (upper limbs)	Gross motor (trunk)	Walking (lower limbs)	Breathing	Total score
SBMAFRS						
Fine motor (upper limbs)	0.464[†]					
Gross motor (trunk)	0.580[†]	0.618[†]				
Walking (lower limbs)	0.496[†]	0.581[†]	0.791[†]			
Breathing	0.346*	0.319*	0.381*	0.350*		
Total score	0.747[†]	0.746[†]	0.915[†]	0.854[†]	0.498[†]	
ALSFRS-R						
Bulbar	0.711[†]	0.350*	0.296*	0.323*	0.147	0.483[†]
Fine motor (upper limbs)	0.313*	0.733[†]	0.559[†]	0.656[†]	0.202	0.648[†]
Gross motor (trunk)	0.398*	0.640[†]	0.712[†]	0.639[†]	0.254*	0.724[†]
Walking (lower limbs)	0.410*	0.506[†]	0.713[†]	0.904[†]	0.302*	0.759[†]
Respiration	0.389*	0.292*	0.342*	0.314*	0.723[†]	0.436[†]
Total	0.599[†]	0.710[†]	0.778[†]	0.848[†]	0.455[†]	0.886[†]
6MWT	0.307*	0.276*	0.555[†]	0.624[†]	0.202	0.543[†]
Upper-limb MRCSS score	0.249*	0.413[†]	0.388*	0.403[†]	0.012	0.428[†]
Lower-limb MRCSS score	0.371*	0.452[†]	0.600[†]	0.762[†]	0.215	0.653[†]
Total MRCSS score	0.336*	0.495[†]	0.586[†]	0.693[†]	0.161	0.632[†]
Age at onset	-0.244	0.071	-0.031	0.128	0.171	-0.020
Disease duration	-0.250*	-0.307*	-0.499[†]	-0.590[†]	-0.293*	-0.496[†]
Creatine phosphokinase	-0.103	-0.166	-0.012	-0.028	-0.186	-0.082
FVC	0.206	0.001	0.308*	0.321*	0.102	0.260*
PAS (n=60)	0.092	-0.020	-0.130	-0.125	0.011	-0.052

*$p<0.05$, [†]$p<0.001$.
ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, FVC: forced vital capacity, MRCSS: Medical Research Council Sum Score, PAS: Penetration Aspiration Score, SBMAFRS: Spinal and Bulbar Muscular Atrophy Functional Rating Scale, 6MWT: 6-minute walk test.

However, these studies have used the ALSFRS-R as one of the clinical parameters for establishing the effects of medication. Previous SBMA clinical trials failed to show significant improvements when using the ALSFRS-R as a clinical parameter, probably because that scale is specific to ALS and the progression of ALS differs from that of SBMA. This limitation reduces the statistical power of the ALSFRS-R for evaluating SBMA, and so an SBMA-specific functional rating scale is needed for use as a primary endpoint in future clinical trials.

The SBMAFRS is a clinical scale that is specific to SBMA and has been developed and validated in Japanese, United States, and Italian populations.[7,8] The SBMAFRS was modified from the ALSFRS-R scale while focusing on the functional status of the bulbar and truncal muscles.

The SBMAFRS was modified from the ALSFRS-R to better reflect the characteristics of SBMA. Among the subscores, the bulbar subscore was fragmented into more detail, including evaluations of the tongue and buccal power. SBMA manifests early bulbar involvement, such as tongue atrophy and mastication weakness in the early stage of the disease, and this has been appropriately incorporated in the SBMAFRS. A truncal motor evaluation was also added to the SBMAFRS, including rising from sitting and supine positions. SBMA usually involves the proximal leg muscles during the early stages of the disease, which is a specific manifestation that distinguishes SMBA from ALS patients.[2,5] Bowing is another subitem that reflects the neck and trunk muscles, and was added to increase the specificity when evaluating SBMA patients. These modifications strengthen the statistical power of the SBMAFRS in describing the functional status of SBMA patients. The SBMAFRS total score is strongly correlated with other clinical parameters such as the 6MWT score (rho=0.543, $p<0.001$), MRCSS (rho=0.632, $p<0.001$), and disease duration (rho=0.496, $p<0.001$). However, more studies are needed to consolidate the benefits and usefulness of the SBMAFRS, such as by performing validation studies involving cohorts from different countries.

The total score for the Korean version of the SBMAFRS in this study was 40.8±6.4, which was lower than that found in an Italian study (41.0±4.05)[8] and higher than that found in the original Japanese study (39.1±4.2).[7] The consistency of these results with mean SBMAFRS scores ranging from 39 to 41—confirms the reliability of the SBMAFRS, with an overall Cronbach's alpha of 0.867 and with Cronbach's alpha ranging between 0.844 and 0.870 when any one item was deleted, and the high internal consistency of the clinical scale. Cronbach's alpha is commonly used to assess the internal consistency of psychometric scales, and the total scores and the scores for the single items in our Korean version of the SB-MAFRS exceeded the generally accepted standard of 0.70,

suggesting that this scale is reliable. Moreover, our test-retest reliability assessments demonstrated the high stability of this scale over a 4-week period.

Among the clinical parameters, disease duration was strongly correlated with all of the subscores except for breathing. The breathing subscores was also not correlated with the pulmonary function test. This discrepancy indicates the need to identify more-useful parameters. Recent ALS studies have produced similar results, and other studies have shown that phrenic nerve conduction and diaphragmatic ultrasonography can reflect the respiratory function in ALS.[11] Further studies are warranted to consolidate these findings in SBMA patients.

While SBMA is a polyQ disease that is known to show anticipation, the length of CAG repeats was not correlated with the SBMAFRS scores, which reflected the functional status of the SBMA patients. Similar findings have also been observed for other triplet repeat diseases, such as Huntington's disease and spinocerebellar ataxia,[12,13] which may be explained by differences in the somatic instability found in different tissue types, and can cause discrepancies between the severity of clinical symptoms and the length of tandem repeats.

The 6MWT is a globally accepted motor function scale that is used to evaluate various neuromuscular diseases, both in terms of progression and treatment endpoints.[10,14] The 6MWT score was strongly correlated with the fine-motor, gross-motor, and walking abilities assessed by the SBMAFRS. However, CPK levels, which are usually elevated in SBMA, were not significantly correlated with the total SBMAFRS score or the scores on any of its subscores.

This study has demonstrated that the SBMAFRS is a valuable tool for reflecting the global physical condition of Korean SBMA patients, with adequate reliability and strong correlations with other clinical parameters, while showing high specificity toward SBMA. Our results show that the Korean version of the SBMAFRS is a reliable and valid scoring system with good internal consistency. Our translation process has generated a tool that can be administered to Korean SBMA patients. Further longitudinal studies involving larger populations are warranted to confirm the reliability (including the interrater reliability) of the SBMAFRS.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.4.586.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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