News Release

Title

Development of a functional composite for the evaluation of spinal and bulbar muscular atrophy

Key Points

- Spinal and bulbar muscular atrophy (SBMA) is an adult-onset X-linked neuromuscular disease caused by the expansion of a trinucleotide CAG repeat within the first exon of the A*ndrogen Receptor* gene.
- Development of new disease-modifying drugs for neurological diseases become active, but sensitive and quantitative measurements have not been sufficiently established.
- In the present study, we developed a functional measurement that combines the quantitative motor evaluation index of various body regions in patients with SBMA. (SBMA functional composite: SBMAFC).
- Our findings indicate that SBMAFC is more sensitive to disease progression than existing functional rating scales and is a potential outcome measure in clinical trials of SBMA.

Summary

A group of researchers headed by Prof. Masahisa Katsuno, Department of Neurology, and Associate Prof. Atsushi Hashizume, Department of Clinical Research Education, Nagoya University Graduate School of Medicine, have developed a new disease-specific functional composite measurement for spinal and bulbar muscular atrophy (SBMA) named SBMAFC. This work was published online in *Scientific Reports* in Octorber 19,2022.

SBMA is an adult-onset X-linked neuromuscular disease that chiefly affects adult males. SBMA is caused by the expansion of a trinucleotide CAG repeat within the first exon of the androgen receptor (AR) gene. Although there is no established disease-specific treatment for SBMA, an area of new disease-modifying drug development for neurodegenerative diseases becomes active. Precise, reliable, and sensitive outcome measurements are essential to successful clinical trials. The present study aimed to develop a functional measurement that combines the quantitative motor evaluation index of various body regions in patients with SBMA. We assessed subjects with SBMA and healthy controls with quantitative muscle strength measurements and functional scales. We selected tongue pressure, grip power, % peak expiratory flow (%PEF), timed walking test, and % forced vital capacity (%FVC) as components. We created a functional composite by combining these values with Z-score (SBMA functional composite: SBMAFC). We also calculated the standardized response mean to compare the sensitivity of SBMAFC with existing measurements. A total of 97 genetically confirmed patients with SBMA and 36 age- and sex-matched healthy controls were enrolled. In the longitudinal analysis, the standardized response mean of SBMAFC was larger than that of existing rating scales. Receiver operating characteristic (ROC) analysis demonstrated that the SBMAFC is capable of distinguishing between subjects with early-stage SBMA and healthy controls.

Our findings indicate that SBMAFC is more sensitive to disease progression than existing functional rating scales and is a potential outcome measure in clinical trials of SBMA.

Research Background

SBMA is an adult-onset X-linked hereditary neuromuscular disease caused by polyglutamine repeat expansion in the androgen receptor gene. The main symptoms are muscular weakness, muscular atrophy, and bulbar dysfunction, which manifest between 30 and 60 years of age. Although no treatments for SBMA have shown efficacy in confirmatory clinical trials, the development of disease-modifying drugs has become an active area in clinical research, facilitated by the rapid growth of studies elucidating molecular pathogenesis. Since the expected efficacy of such treatment is to slow the disease course, there is a pressing need for reliable, easy-to-use scales that can detect subtle clinical changes over short periods. Several functional scales, including the Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS) or the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), have been utilized as outcome measures in clinical trials of SBMA. However, the sensitivity and reliability of these scales are limited.

On the other hand, objective muscle strength measurements, including grip power and the 6-minute walking test, have the advantage of high objectivity and quantitatively. However, they also have the disadvantage of solely representing the physical function of a particular body region (e.g., grip power for upper limb function). An idea to overcome these issues is the development of a composite that integrates objective measurements for partial motor function and, thereby, represents the total physical function.

Research Results

We performed the present study according to the following two steps. At first, we created a new composite score by combining quantitative measurements. We selected the following tests as objective measurements to be integrated into the functional composite: tongue pressure for bulbar function, grip power for upper limb function; timed walking test for lower limb function; peak expiratory flow for truncal function; and vital capacity for respiratory function. To combine these various quantitative motor measurements with different units, we utilized Z-score, a standardized score that quantifies an individual's physical performance compared to the healthy population's average performance. We calculated Z-score as the number of standard deviation units that a patient's score differs from the average score. In short, the Z score is calculated as follows. $Z_{composite} = Z_{bulbar} + Z_{upper\ limbs} + Z_{trunk} + Z_{lower\ limb} + Z_{respiration}$. A better score on one or all components than the mean results in a higher SBMAFC score, whereas a worse score than the mean results in a lower overall SBMAFC. We enrolled 97 subjects with SBMA and 36 age- and sex-matched HCs with no diagnosed neurological disorders (Table 1). In the longitudinal study, 54 SBMA patients were followed up for 48 weeks. Based on the results of baseline data of healthy controls, we computed a composite score, SBMAFC, with the following formula;

SBMAFC = (Tongue Pressure (kPa) - 41.6) / 7.84 + (Grip Power (kgw) - 45.0) / 6.4 + (%PEF - 116.4) / 22.4 + (Timed Walking speed (km/hr) - 7.7) / 2.0 + (%FVC - 112.0) / 11.8.

The value of SBMAFC correlated well with those of SBMAFRS and ALSFRS-R. To investigate the internal validity of SBMAFC, relationships of each component of SBMAFC and the total value of SBMAFC were analyzed. The values of SBMAFC components in subjects with SBMA correlated well with the total score of SBMAFC at baseline.

In the present study, 8 of 97 subjects with SBMA were defined to be at an early stage. The mean age at evaluation and disease duration was 38.6 ± 14.1 and 2.0 ± 2.2, respectively. The score distributions of the outcome measures and the ROC curves indicated that the area under the curve of SBMAFC was larger than that of ALSFRS-R or SBMAFRS (SBMAFC, 0.948; SBMAFRS, 0.700, ALSFRS-R, 0.613, respectively) (Fig. 1). These results indicate that SBMAFC is advantageous for detecting subtle symptoms in subjects with early-stage SBMA.

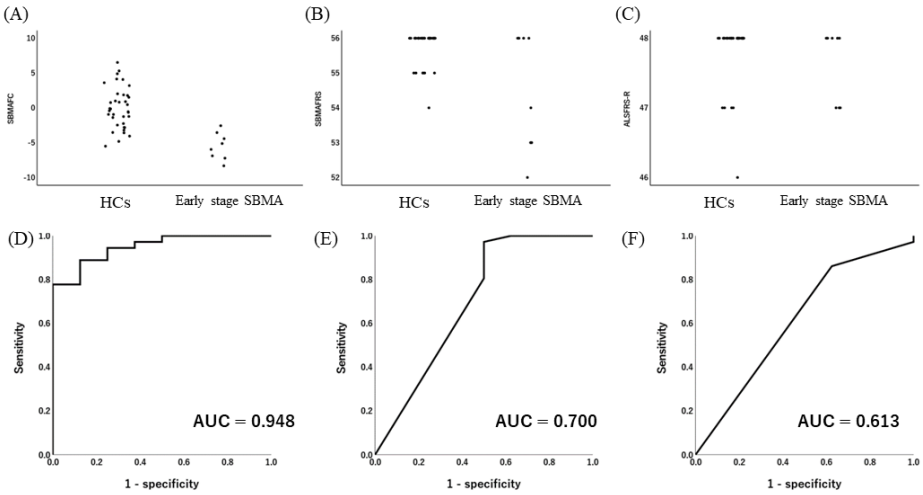


Figure 1. Distribution (A-C) and the ROC analysis (D-F) of SBMAFC, SBMAFRS, and ALSFRS-R in early-stage SBMA.

To clarify how sensitive SBMAFC is to disease progression, we analyzed the longitudinal change of SBMAFC. The results showed that the SRM of the SBMAFC was larger than SBMAFRS or ALSFRS-R in the 48-week follow-up (Tables 1).

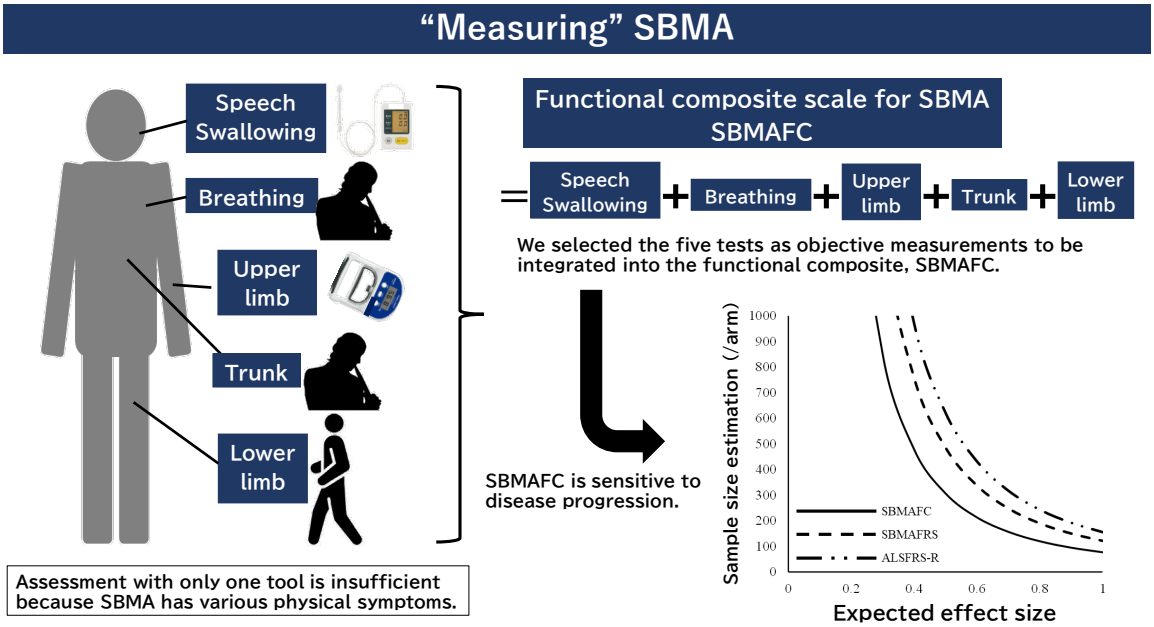
Table 1 Longitudinal change of outcome measurements in 48-week follow-up

	Baseline (n = 54) Mean ± S.D.	48 weeks follow-up (n = 54) Mean ± S.D.	Longitudinal change Mean ± S.E.	
Items of composite measurements				
Tongue pressure (kPa)	18.8 ± 7.2	17.9 ± 3.4	-0.57 ± 0.48	(
Grip power (kgw)	21.7 ± 7.0	21.1 ± 7.4	-0.61 ± 0.32	(
PEF%	85.2 ± 18.6	84.9 ± 19.6	-0.37 ± 1.70	(
Walking speed (km/hr.)	5.05 ± 1.89	4.54 ± 1.91	-0.51 ± 0.15	(
%FVC	100.0 ± 14.0	99.5 ± 13.8	-0.51 ± 0.61	(
SBMAFC	-10.34 ± 3.27	-10.83 ± 3.39	-0.487 ± 0.154	(
Existing measurements				
SBMAFRS	43.2 ± 6.2	42.0 ± 7.6	-1.24 ± 0.49	(
ALSFRS-R	41.6 ± 3.9	40.9 ± 4.4	-0.74 ± 0.33	(

The SRM of SBMAFRS was larger than that of ALSFRS-R, in agreement with a previous study showing the higher sensitivity of SBMAFRS over ALSFRS-R regarding longitudinal changes. These results indicate that responsiveness is more excellent in the SBMAFC than in the existing functional scales, SBMAFRS and ALSFRS-R. Sample size estimation based on this longitudinal analysis was the lowest for the SBMAFC, followed by the SBMAFRS and the ALSFRS-R, confirming that the SBMAFC is a sensitive clinical measure that detects disease progression over time.

Research Summary and Future Perspective

In conclusion, the functional composite SBMAFC is more sensitive to the disease progression of SBMA than existing functional scales, including SBMAFRS and ALSFRS-R, and has potential to be utilized in future clinical trials. In addition, the SBMAFC may detect subtle symptoms at an early stage of disease, and, thus, is a potential outcome measurement of clinical trials of disease-modifying therapies for SBMA.



Publication

Tomonori Inagaki, Atsushi Hashizume, Shinichiro Yamada, Daisuke Ito, Yoshiyuki Kishimoto, Ryota Torii, Hiroyuki Sato, Akihiro Hirakawa and Masahisa Katsuno

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