Distinct acoustic features in spinal and bulbar muscular atrophy patients with laryngospasm

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ABSTRACT

Objective: Laryngospasm is a sudden onset of transient respiratory difficulty that is perceived as life-threatening by patients with spinal and bulbar muscular atrophy (SBMA). The purpose of the study was to analyze the voice characteristics of SBMA patients with laryngospasm using acoustic voice analysis.

Methods: Acoustic measurements were obtained from 39 consecutive Japanese patients with genetically confirmed SBMA. A comparison was made between the acoustic voice profiles of 16 patients with laryngospasm and 23 patients without laryngospasm within 6 months before the evaluation. Computerized acoustic analysis was performed for a prolonged vowel (/a:/) using the Multi-Dimensional Voice Program (MDVP).

Results: SBMA patients with laryngospasm had smaller fluctuations of vocal fold vibration and the turbulent noise component, indicating stronger vocal fold closure than in those without laryngospasm. Receiver operating characteristic curve analysis showed that the noise-to-harmonic ratio, which globally measures the noise components of voice, is the most useful acoustic parameter to distinguish laryngospasm (area under the curve=0.767, $p=0.007$).

Conclusions: The smaller noise component in patients with laryngospasm suggests that the vocal folds of these patients are more adducted during phonation than those of the patients without laryngospasm, even in the absence of laryngospasm. Quantitative laryngeal analysis using the MDVP helps to detect laryngeal dysfunction and provides physiological insight into the pathophysiology of laryngospasm in SBMA.

INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a hereditary neurodegenerative disorder caused by the expansion of "CAG" repeats in the first exon of the androgen receptor (AR) gene. SBMA is classified as a lower motor neuron disease characterized by muscular atrophy, bulbar involvement, contraction fasciculations, and hand tremor. Patients occasionally demonstrate signs of androgen insensitivity such as gynecomastia [1-3]. Due to progressive bulbar muscular weakness, the majority of SBMA patients develop dysphagia and dysarthria [2-5].

Laryngeal involvement often occurs in subjects with SBMA, and it may lead to laryngospasm, which can be perceived as being life-threatening by patients [6,7]. Laryngospasm is defined as a sudden-onset episode with the sensation that air cannot be moved in and out of the lungs, which usually lasts for a few seconds and is followed by stridor, due to the rapid and forceful contraction of the laryngeal muscles [8], **apparently resulting in close approximation of the arytenoid cartilages and vocal folds.** In SBMA patients, laryngospasm can last from a few seconds to 1 minute. An SBMA patient who developed bilateral abductor vocal fold paralysis and respiratory distress, which was improved after tracheostomy, has also been reported [9]. Although it is clinically well-known that SBMA patients have a nasal voice [1], the voice characteristics of SBMA patients have not been evaluated using perceptual and acoustical analyses. It is clinically important to investigate the laryngeal function of SBMA patients in detail since this symptom is perceived as life-threatening by all SBMA patients with laryngospasm [6,10].

In the assessment of laryngeal function during phonation, perceptual and acoustical measures provide substantial information. Acoustic analysis has been used in Parkinson's disease and amyotrophic lateral sclerosis (ALS) **to quantify**

1 **characteristics** of voice production, which cannot be conceived by auditory perceptual
2 impression [11,12]. Particularly, Multi-Dimensional Voice Program (MDVP) **analyses**
3 **have been** applied extensively for voice analysis of patients with dysarthria [13], **and**
4 **will be used here.**

5 The purpose of this study was to perform perceptual assessment and acoustic
6 analysis to clarify the differences in the voice characteristics of SBMA patients with
7 and without laryngospasm.

8 9 **METHODS**

10 **Ethics.** This study was approved by the ethics committees of Aichi-Gakuin
11 University School of Health Science and Nagoya University Graduate School of
12 Medicine. All participants gave their written informed consent prior to the interviews
13 and examinations.

14 **Subjects.** Thirty-nine SBMA patients genetically diagnosed as having CAG repeat
15 expansion (≥ 38) in the first exon of the AR gene were included in this study [14]. No
16 patients had definite symptoms or took medication for gastroesophageal reflux disease,
17 although we did not perform endoscopic examinations. No subjects had tracheostomy
18 or underwent recent intubation for any surgery. Age of onset was defined as the age at
19 which the patient became aware of muscular weakness in any part of the body,
20 including bulbar symptoms. The patients were divided into 2 groups according to
21 their history of laryngospasm, i.e., patients who experienced laryngospasm within 6
22 months before the acoustic examination and those without such an episode. The
23 frequency and trigger factors of laryngospasm and disease severity were evaluated in
24 each patient through history taking (Table 1). All SBMA patients were subjected to
25 perceptual assessments and MDVP analysis to assess current laryngeal function.

However, 2 patients who had difficulty in vocalization and breathing during voice recording of the prolonged vowel /a:/ (Patients no. 1 and 7) were excluded from the MDVP analysis.

Comprehensive disease severity scales. The disease severity of each SBMA patient was assessed using functional scales such as the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R), Limb Norris score, and Norris Bulbar score [15,16]. These scales have been used for SBMA and are strongly correlated with each other [17,18].

Genetic analysis. Genetic analysis was done to confirm the diagnosis of SBMA. Genomic DNA was extracted from the peripheral blood of SBMA patients using conventional techniques. PCR amplification of the CAG repeat in the AR gene was performed using a fluorescein-labeled forward primer (5'-TCCAGAATCTGTTCCAGAAATGC-3') and a non-labeled reverse primer (5'-TGGCCTCGCTCAGGATGTCTTTAAG-3'). The detailed PCR method has been described previously [19]. Aliquots of the PCR products were combined with a loading dye and separated by electrophoresis using an autoread sequencer (SQ-5500; Hitachi Electronics Engineering, Tokyo, Japan). The CAG repeat size of the PCR standards was determined by direct sequencing, as described previously [19].

Auditory perceptual voice assessments

The speech of each SBMA patient included in the present study was evaluated perceptually to define their voice characteristics.

GRBAS analysis. Perceptual voice analysis for dysphonia was performed using the

Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale, in which the voice properties were evaluated with respect to dysphonia: Grade (G), the overall degree of the deviance of voice; Roughness (R), irregular fluctuation of the fundamental frequency; Breathiness (B), turbulent noise produced by air leakage; Asthenia (A), overall weakness of the voice; and Strain (S), impression of tenseness or excess effort. Each component was scored using a four-point scale: 0, normal; 1, mild deviance; 2, moderate deviance; and 3, severe deviance [20-22].

Hypernasality. Perceptual assessment of hypernasality was performed according to a previous study [23]. Speech sound was scored using a four-point scale: 1, normal; 2, mild presence of hypernasality; 3, moderate presence of hypernasality; and 4, severe presence of hypernasality.

Procedures of perceptual assessments. Three types of speech samples (the prolonged vowel /a:/, reading the passage “The North Wind and the Sun,” and conversation) were used for the perceptual assessments. Each speech sample, which had been recorded in a randomized order, was rated independently by two judges (certified speech-language pathologists) using the above dimensions. The judges had an unlimited time to listen to and rate the speech samples. The measurement values were calculated from the average score of the two judges. After the independent rating of the speech samples, the two judges conferred to reach an agreement on each speech dimension [23]. Before the consensus rating, the ratings of the judges did not vary by more than 1 point.

Acoustic analysis

Recording procedures and signal processing. Voice recordings were performed at a sampling frequency of 44,100 Hz and a resolution of 16 bits using a liner PCM

recorder (R-09HR; Roland Corporation, Shizuoka, Japan) and a condenser microphone (ECM-23F5; Sony, Tokyo, Japan) in a quiet room with a noise level below 35 dB. The distance from the microphone to the mouth was 15 cm.

The subjects were asked to phonate a sustained /a:/ vowel for approximately 5 s at a comfortable loudness and constant pitch [13]. This task was performed twice.

MDVP. Computerized acoustic analyses of the sustained vowel were performed using MDVP Model 4300 (Kay Electrometrics, Lincoln Park, NJ, USA). Voice was analyzed for 3 s in the mid-portion of the sustained vowel, excluding the first and last 25 ms of the vowel according to a previous report [13].

We calculated 33 out of 34 parameters of MDVP, most of which have been validated with regard to the reliability in previous studies of other neurological diseases [11,13,24]. Values lying outside the normal range of these parameters suggest dysphonia (mostly audible as hoarseness) [24-26]. We did not use Tsam, the parameter which evaluate the time length of voice samples, since we analyzed 3-second voice samples for each patient in the present study.

The measurement values were calculated from an average of two consecutive phonations, as described previously [13]. All MDVP measurements were performed at Nagoya University Hospital.

Statistical analysis. We analyzed the data using the non-parametric Mann-Whitney test for statistical comparisons. Correlations among the parameters were analyzed using Spearman's rank correlation coefficient. To investigate the reliability of the acoustic analysis, the intra-class correlation coefficient (ICC) was calculated between the two samples. A receiver operating characteristic (ROC) curve, which is obtained by plotting the sensitivity of a test on the y-axis against 1-specificity on the x-axis,

was used to determine the validity of the screening test. The area under the curve (AUC), a measure of the accuracy of the screening tool calculated from the ROC curve, was applied for the detection of laryngospasm. The optimal cut-off point was determined on the point of the ROC curve closest to the upper left-hand corner (0, 1) [27]. *P*-values below 0.05 were considered to be statistically significant. Calculations were performed using the statistical software package IBM SPSS ver.19.

RESULTS

The 39 male Japanese patients with SBMA were analyzed consecutively, as shown in Tables 1 and 2. Among the patients, 16 (41.0%) had a recent episode of laryngospasm. The clinical and genetic backgrounds, such as age, number of CAG repeats, disease duration, testosterone levels, and disease severity, were equivalent between the SBMA patients with and without laryngospasm (Table 2).

The most common trigger of laryngospasm in the SBMA patients was aspiration (12 patients/16 patients, 75.0%), followed by phonation in 4/16 patients (25.0%). Laryngospasm also occurred spontaneously (without subjective triggers) in 2/16 patients (12.5%). As for frequency, laryngospasm occurred more than once per day in 2 patients (2/16, 12.5%), more than once per week in 1 patient (1/16, 6.3%), more than once per month in 6 patients (6/16, 37.5%), and more than once per 6 months in 7 patients (7/16, 43.8%) during the 6 months before the acoustic evaluation.

Perceptual features of the SBMA patients with laryngospasm. Table 3 shows the auditory perceptual parameters for hoarseness and hypernasality in the SBMA patients. In the present study, 28 of the 39 (71.2%) patients were confirmed to have dysphonia by perceptual voice analysis with GRBAS. In the majority of SBMA patients with

dysphonia, the severity of dysphonia was mild (G: 0.5–1). There was no significant difference in the perpetual assessment values between the SBMA patients with and without laryngospasm.

Acoustic features of the SBMA patients with laryngospasm. Table 4 shows the comparisons of the MDVP parameters between the SBMA patients with and without laryngospasm. Overall, the differences between the groups were predominantly observed in the parameters regarding frequency perturbation rather than those related to amplitude perturbation. The patients with laryngospasm showed decreased values of the indices regarding frequency perturbation, such as Jitt. Noise-related indices, VTI and NHR, were also altered in the SBMA patients with laryngospasm. As for amplitude perturbation, although Shim was decreased in the patients with laryngospasm, other parameters showed no differences between the groups.

The 7 parameters (Jita, Jitt, APQ, PPQ, Shim, VTI and NHR), which showed a significant difference in the comparison of the two groups, showed a strong intra-class correlation between the duplicated samples, except for Jitt; Jita, ICC=0.82 (95% CI=0.67-0.90, $p < 0.001$); Jitt, ICC=0.57 (95% CI=0.18-0.77, $p=0.005$); Shim: ICC=0.81 (95% CI=0.64-0.90, $p < 0.001$); APQ, ICC=0.85 (95% CI=0.72-0.92, $p=0.005$); PPQ, ICC=0.84 (95% CI=0.69-0.92, $p=0.005$); VTI, ICC=0.71 (95% CI=0.47-0.84, $p=0.001$); and NHR, ICC=0.83 (95% CI=0.70-0.91, $p < 0.001$). These results indicate the high reliability of our acoustic assessments. From these parameters, we selected the following indices for further analyses: (1) frequency perturbation of vocal fold vibration (Jita: absolute Jitter, and Jitt: jitter percent): when dysfunction of the intrinsic laryngeal muscles occurs, fundamental frequency may become less stable, causing a rise in Jita and Jitt; (2) amplitude perturbation of vocal fold vibration (Shim:

shimmer percent): when dysfunction of the intrinsic laryngeal muscles and respiratory muscles occurs, cycle amplitudes may become less stable, causing a rise in Shim; (3) turbulent noise (VTI: voice turbulence index): when vocal fold closure is incomplete, the turbulent noise produced by the aperture between the vocal folds may increase, causing a rise in VTI; and (4) various noises-related index (NHR: noise-to-harmonic ratio): an increase in any of the noise components, i.e., Jita, Jitt, ShdB, Shim, or VTI, may lead to elevated NHR [11-13,25,28]. We did not use RAP or PPQ for the detailed analysis, as the clinical implication of these indices is less established than that of the other parameters [24].

As for the relationships between the MDVP parameters and clinical background, Jitt, Shim, and NHR were inversely and mildly correlated with the frequency of laryngospasm ($r=-0.346$, $p=0.036$; $r=-0.328$, $p=0.047$; and $r=-0.460$, $p=0.004$; respectively). Shim was also inversely and mildly correlated with Limb Norris score ($r=-0.447$, $p=0.022$). There was no clinically relevant correlation between clinical background and the other MDVP parameters (Table 5).

ROC curve analysis was applied between the SBMA patients with and without laryngospasm. The results demonstrated that Jita, Jitt, Shim and NHR were significantly lower in the patients with laryngospasm than in those without (Table 6 and Figure 1). The AUC data suggest that NHR was the acoustic parameter most strongly associated with laryngospasm in SBMA patients.

DISCUSSION

In the present study, although perceptual assessments did not show a significant difference between the SBMA patients with laryngospasm and those without laryngospasm, quantitative acoustic analysis identified the acoustic characteristics of

voice production in SBMA patients with laryngospasm. Our results suggest that NHR, which evaluates various noises due to frequency and amplitude perturbation, turbulent noise and/or voice breaks during phonation, appears to be a useful acoustic parameter for distinguishing the SBMA patients with laryngospasm from those without laryngospasm.

This study is the first to investigate the voice characteristics in individuals with SBMA. A laryngeal fiberscope can be used to visualize the larynx for any vocal fold pathology, but the procedure can trigger laryngospasm [29]. Conversely, acoustic analysis, particularly the MDVP used in the present study, is a quantitative assessment tool for patients, and has a low risk of inducing laryngospasm by virtue of its non-invasive nature. The absence of a strong relationship between the acoustic parameters and the ALSFRS-R and Norris scales suggests that laryngeal dysfunction in SBMA cannot be evaluated precisely using motor function scales, but that acoustic measurements appear to be helpful in assessing vocal function in this disorder.

SBMA patients with laryngospasm, compared with those without laryngospasm, showed significantly smaller values in frequency perturbation indices, such as Jitt, and noise-related indices, such as VTI and NHR, during phonation. In consideration of its correlation coefficient and ROC curve, NHR is useful to understand the mechanism of laryngospasm in SBMA patients. As for frequency perturbation indices, abnormal increases of these parameters are explained by several factors, including a reduction in the number of motor neurons, decreased mean firing rate of the motor units of the laryngeal muscles, and variation in the size of motor units and action potentials [30]. Some of these factors are likely present in the limbs of SBMA patients [18]. Abnormalities in the frequency and amplitude of voice have been shown to be related to lesions of the nucleus ambiguus [31]. The low values of frequency and

1 amplitude perturbation indices in the SBMA patients with laryngospasm suggest the
2 relatively mild loss of lower motor neurons innervating the laryngeal muscles
3 compared to those without laryngospasm.

4 The degree of vocal fold closure is determined by a balance of forces between the
5 vocal fold abductor and adductor muscles [32,33]. Either the decreased activity of the
6 abductor muscle or increased activity of the adductor muscles results in the stronger
7 closure of the vocal folds [29]. Given that VTI may be related to the size of the
8 aperture between the vocal folds during phonation, our finding that SBMA patients
9 with laryngospasm had lower VT1 values than those without laryngospasm suggests
10 the greater closure of the vocal folds, which is indicative of an imbalance of force
11 between the vocal fold abductor and adductor muscles during phonation. This
12 hypothesis is supported by the observation that a bilateral reduction in the amplitude
13 of the abduction of the vocal folds may occur in SBMA patients [9,34]. Histological
14 examination of the intrinsic laryngeal muscles of such patients revealed severe
15 neurogenic changes in the abductor muscle rather than in the adductor muscles [35].

16 The main causes of the noise used to calculate the NHR values are incomplete
17 glottal closure (VTI) and voice signal instability, such as frequency and amplitude
18 perturbation [24]. Increased NHR values are consistent with increased Jita, Jitt, Shim,
19 or VTI values. Therefore, our finding that NHR is the most useful acoustic parameter
20 for laryngospasm agrees with the changes of both important parameters in SBMA
21 patients with laryngospasm, i.e., low values of frequency perturbation indices indicate
22 milder neuronal loss, and a low VTI value suggests an imbalance of force between the
23 abductor and adductor muscles.

24 In the majority of patients with SBMA in our study, laryngospasm was observed
25 after a trigger, such as aspiration or phonation. It is suggested that obvious triggers

leading to strong vocal fold closure are required for laryngospasm to occur. In an experimental study using animals, increased excitability of the motor neurons innervating the laryngeal adductor muscles was detected during and after the cough reflex [36]. The results of the present study suggest that the vocal folds are more adducted during phonation, even in the absence of laryngospasm, in SBMA patients with laryngospasm. Additional stimuli, such as the cough reflex to expel aspirated materials, may further intensify the spastic closure of the vocal folds, which is sustained because of a limitation in the range of the opening movement of the vocal folds, resulting from an imbalance of force between the abductor and adductor muscles. These findings are likely to represent one of the mechanisms underlying laryngospasm in SBMA. In the present study, 16 of the 39 patients (41.0%) with SBMA had a recent episode of laryngospasm. Agreeing with our data, laryngospasm reportedly occurs in 47% of SBMA patients, while it only occurs in 2% of ALS patients [6], although the clinical motor neuron symptoms of SBMA overlap with those of ALS [37]. Severe adductor muscle dysfunction is reported in ALS patients [38], suggesting that ALS patients have difficulty in completely closing their vocal folds due to the hypoactivity of their adductor muscles compared with SBMA patients.

In conclusion, we applied the MDVP, which is a simple, objective, quantitative, and non-invasive tool, to assess voice disorders in SBMA patients. Our results suggest the hypothesis that laryngospasm may occur in patients who develop excessive vocal fold closure due to the imbalance of force between the abductor and adductor muscles. Quantitative laryngeal analysis using the MDVP appears to provide mechanistic insight into the pathophysiology of laryngospasm in SBMA patients.

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Individual contributions to the manuscript

Mr. Tanaka made the study concept and design, analysis and interpretation of data, contribution of vital tools, acquisition of data, and statistical analysis.

Dr. Banno made the study concept and design, drafting and revising the manuscript, analysis and interpretation of data, acquisition of data, and statistical analysis.

Dr. Katsuno made the study concept and design, drafting and revising the manuscript, analysis and interpretation of data, acquisition of data, and statistical analysis.

- 1 Dr. Suzuki made the study concept and acquisition of data.
- 2 Dr. Suga made the study concept and acquisition of data.
- 3 Dr. Hashizume made the study concept and acquisition of data.
- 4 Dr. Mano made the study concept and acquisition of data.
- 5 Dr. Araki made the study concept and acquisition of data.
- 6 Dr. Watanabe made the study concept and acquisition of data.
- 7 Dr. Adachi made the study concept and acquisition of data.
- 8 Mr. Tatsumi made the study concept.
- 9 Dr. Yamamoto made the study concept and design, drafting and revising the
- 10 manuscript, analysis and interpretation of data, and study supervision.
- 11 Dr. Sobue made the study concept, drafting and revising the manuscript, analysis and
- 12 interpretation of data, and study supervision.
- 13
- 14

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Figure legends

Figure 1. Receiver operating characteristic curve analysis in the SBMA patients with and without laryngospasm

ROC curve analysis of SBMA patients with and without laryngospasm using (A) Jita, (B) Jitt, (C) Shim, (D) VTI, and (E) NHR is shown. The curve is obtained by calculating the sensitivity and specificity of the test at every possible cut-off point, and plotting sensitivity against 1-specificity. Sensitivity (the proportion of true positive results) is shown on the y-axis, going from 0 to 1 (0–100%), and 1-specificity (the proportion of false positive results) is shown on the x-axis, going from 0 to 1 (0–100%). The best cut-off point to balance the sensitivity and specificity of a test is the one closest to the (0, 1) point. The two circles show each statistically significant optimal cut-off point, as demonstrated in Table 6.

Abbreviations: Jita, absolute jitter; Jitt, jitter percent; Shim, shimmer percent; VTI, voice turbulence index; NHR, noise-to-harmonic ratio.

1 **Table 1. Profiles of the SBMA patients**

Patient no.	Frequency of laryngospasm during 6 months before evaluation ^a	Age at evaluation, years	Age at onset ^b , years	Disease duration from onset ^c , years	CAG-repeat length in the AR gene, number	Testosterone, ng/dL	ALSFRS-R		Norris Scale	
							Bulbar subscore ^d	Total	LNS	NBS
1	++++	58	36	22	60	4.59	8	37	55	21
2	++++	68	35	33	48	5.69	8	34	NA	NA
3	+++	63	36	27	53	4.65	9	36	NA	NA
4	++	58	55	3	54	5.61	12	48	62	39
5	++	62	50	12	51	6.75	10	42	59	33
6	++	72	67	5	43	4.95	10	41	52	31
7	++	58	48	10	45	3.75	8	35	39	26
8	++	58	49	9	NA	7.68	10	38	NA	NA
9	++	60	45	15	NA	3.83	8	34	NA	NA
10	+	29	23	6	53	10.85	11	45	60	39
11	+	43	33	10	48	9.53	11	45	60	38
12	+	63	44	19	48	7.07	9	37	46	33
13	+	71	66	5	43	6.42	11	43	53	30
14	+	50	30	20	46	5.13	10	36	41	24
15	+	63	59	4	46	6.67	9	38	48	28
16	+	53	38	15	NA	7.92	9	41	NA	NA
17	-	40	37	3	50	12.02	12	44	59	38
18	-	48	46	2	47	10.29	10	44	57	34
19	-	40	34	6	49	8.04	12	48	58	37
20	-	73	14	59	46	8.01	11	45	60	38
21	-	59	50	9	51	4.78	12	43	54	37
22	-	39	22	17	52	4.55	11	44	62	38
23	-	37	30	7	54	4.54	12	45	59	37
24	-	72	60	12	45	4.78	11	42	56	36
25	-	50	30	20	49	4.60	10	43	61	36
26	-	69	54	15	49	5.47	11	39	43	34
27	-	48	38	10	45	9.44	11	41	61	28
28	-	73	69	4	40	6.46	11	43	58	32
29	-	61	55	6	46	10.03	12	43	49	32
30	-	47	38	9	50	13.11	10	39	51	26
31	-	54	40	14	51	6.82	12	41	53	32
32	-	47	38	9	50	4.31	10	42	53	28
33	-	77	63	14	46	5.80	5	26	27	21
34	-	56	40	16	51	4.55	10	39	50	30
35	-	58	48	10	45	4.53	8	37	45	27
36	-	55	48	7	NA	11.94	8	31	NA	NA
37	-	61	49	12	NA	8.54	10	40	NA	NA
38	-	58	39	19	48	6.99	10	37	NA	NA
39	-	70	55	15	NA	5.96	8	35	NA	NA

2 Abbreviations: NA, not available; ALSFRS-R, revised amyotrophic lateral sclerosis

3 functional rating scale; LNS, Limb Norris score; NBS, Norris Bulbar score.

^aFrequency of laryngospasm during the 6 months before the evaluation: +++, more than once per day; ++, more than once per week; +, more than once per month; 0, more than once per 6 months; and –, without laryngospasm.

^bAge at onset was defined as the age at which a patient became aware of muscular weakness in any part of the body, including bulbar symptoms.

^cDisease duration from onset was defined as the period of time between the age at onset and evaluation.

^dThe bulbar subscore was calculated as the total number of items related to bulbar signs consisting of speech, salivation, and swallowing.

Table 2. Clinical and genetic features of the 39 SBMA patients with and without laryngospasm

Demographic	SBMA patients (n=39)			
	All (n=39)	Without laryngospasm (n=23)	With laryngospasm (n=16)	With vs. without laryngospasm
	mean $\pm$ SD (range)	mean $\pm$ SD (range)	mean $\pm$ SD (range)	<i>p</i>
Age at evaluation, years	56.9 $\pm$ 11.4 (29–77)	56.2 $\pm$ 12.1 (37–77)	58.1 $\pm$ 10.7 (29–72)	0.423
Age at onset ^a , years	43.5 $\pm$ 12.2 (14–66)	42.9 $\pm$ 12.3 (14–63)	44.4 $\pm$ 12.5 (23–66)	0.943
Disease duration from onset ^b , years	13.1 $\pm$ 10.2 (2–59)	12.8 $\pm$ 11.2 (2–59)	13.4 $\pm$ 8.8 (3–33)	0.667
CAG-repeat length in the AR gene, number	48.5 $\pm$ 3.9 (40–60)	48.2 $\pm$ 3.2 (40–54)	49.1 $\pm$ 4.9 (43–60)	0.853
Testosterone, ng/dL	6.8 $\pm$ 2.5 (3.8–13.1)	7.2 $\pm$ 2.8 (4.3–13.1)	6.3 $\pm$ 2.0 (3.8–10.9)	0.493
ALSFRS-R				
Speech	3.4 $\pm$ 0.6 (2–4)	3.5 $\pm$ 0.6 (2–4)	3.4 $\pm$ 0.5 (3–4)	0.473
Salivation	3.2 $\pm$ 0.9 (0–4)	3.3 $\pm$ 1.0 (0–4)	3.0 $\pm$ 0.7 (2–4)	0.074
Swallowing	3.4 $\pm$ 0.6 (2–4)	3.5 $\pm$ 0.6 (2–4)	3.2 $\pm$ 0.5 (2–4)	0.108
Bulbar subscore ^c	10.0 $\pm$ 1.6 (5–12)	10.3 $\pm$ 1.7 (5–12)	9.6 $\pm$ 1.3 (8–12)	0.054
Total	40.0 $\pm$ 4.6 (26–48)	40.5 $\pm$ 4.9 (26–48)	39.4 $\pm$ 4.3 (34–48)	0.229
Norris Scales				
Limb Norris score	53.0 $\pm$ 8.1 (27–62)	53.5 $\pm$ 8.4 (27–62)	52.3 $\pm$ 7.9 (39–62)	0.961
Norris Bulbar score	32.1 $\pm$ 5.3 (21–39)	32.7 $\pm$ 4.9 (21–38)	31.1 $\pm$ 6.1 (21–39)	0.844

Abbreviation: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale.

^aAge at onset was defined as the age at which a patient became aware of muscular weakness in any part of the body, including bulbar symptoms.

^bDisease duration from onset was defined as the period of time between the age at onset and evaluation.

^cThe Bulbar subscore was calculated as the total number of items related to bulbar signs consisting of speech, salivation, and swallowing.

Table 3. Perceptual assessments of the 39 SBMA patients with and without laryngospasm

Parameters	SBMA patients (n=39)			
	All (n=39)	Without laryngospasm (n=23)	With laryngospasm (n=16)	With vs. without laryngospasm
	mean $\pm$ SD (range)	mean $\pm$ SD (range)	mean $\pm$ SD (range)	<i>p</i>
Hypernasality	1.86 $\pm$ 1.74 (1–3.5)	1.89 $\pm$ 1.69 (1–3.5)	1.81 $\pm$ 1.86 (1–3)	0.662
Hoarseness (GRBAS scale)				
G	1.14 $\pm$ 0.84 (0–3)	1.13 $\pm$ 0.71 (0–2)	1.17 $\pm$ 1.03 (0–3)	0.921
R	1.04 $\pm$ 0.89 (0–3)	1.04 $\pm$ 0.60 (0–2)	1.03 $\pm$ 1.07 (0–3)	0.724
B	0.35 $\pm$ 0.54 (0–2)	0.39 $\pm$ 0.60 (0–2)	0.28 $\pm$ 0.45 (0–1)	0.746
A	0.19 $\pm$ 0.44 (0–1.5)	0.28 $\pm$ 0.51 (0–1.5)	0.06 $\pm$ 0.25 (0–1)	0.301
S	0.51 $\pm$ 0.68 (0–3)	0.30 $\pm$ 0.39 (0–1)	0.81 $\pm$ 0.89 (0–3)	0.084

Abbreviations: G, grade; R, roughness; B, breathiness; A, asthenia; S, strain.

Hypernasality scale: 1, normal; 2, mild hypernasality; 3, moderate hypernasality; and 4, severe hypernasality. GRBAS scale: 0, normal; 1, mild deviance; 2, moderate deviance; and 3, severe deviance.

1 **Table 4. Acoustic analysis in SBMA using the MDVP analysis**

Parameters (Symbols)	SBMA (n=37)		
	Without laryngospasm (n=23)	With laryngospasm (n=14)	With vs. without laryngospasm
	mean $\pm$ SD (range)	mean $\pm$ SD (range)	<i>p</i>
Fundamental Frequency measurements			
Fo (Hz)	147.77 $\pm$ 18.31 (114.39-178.53)	155.56 $\pm$ 39.26 (103.52-265.26)	0.654
MFo (Hz)	147.64 $\pm$ 18.25 (114.26-178.40)	155.50 $\pm$ 39.26 (103.48-265.24)	0.676
To (ms)	9.79 $\pm$ 14.01 (5.61-73.93)	6.75 $\pm$ 1.45 (3.77-9.67)	0.541
Fhi (Hz)	159.80 $\pm$ 21.19 (127.07-198.38)	167.73 $\pm$ 37.55 (121.17-272.64)	0.676
Flo (Hz)	135.66 $\pm$ 18.62 (99.17-169.69)	145.45 $\pm$ 40.62 (89.19-256.17)	0.377
STD (Hz)	3.59 $\pm$ 3.38 (1.10-18.02)	2.64 $\pm$ 0.90 (1.28-5.00)	0.526
PFR	3.83 $\pm$ 1.87 (1.50-9.50)	3.79 $\pm$ 1.59 (2.00-6.00)	0.546
SEG	99.95 $\pm$ 0.15(99.50-100.00)	99.96 $\pm$ 0.14(99.50-100.00)	0.914
PER	440.85 $\pm$ 55.36 (341.50-533.50)	464.76 $\pm$ 128.23 (309.00-795.50)	0.654
Frequency perturbation measurements			
Jita (μm)	103.83 $\pm$ 63.37 (19.51-247.12)	60.28 $\pm$ 35.85 (16.85-131.51)	0.039
Jitt (%)	1.70 $\pm$ 1.15 (0.34-4.39)	0.85 $\pm$ 0.39 (0.40-1.56)	0.022
RAP (%)	0.91 $\pm$ 0.63 (0.16-2.54)	0.48 $\pm$ 0.24 (0.17-0.89)	0.039
PPQ (%)	0.92 $\pm$ 0.59 (0.20-2.28)	0.51 $\pm$ 0.25 (0.22-0.97)	0.042
sPPQ (%)	1.44 $\pm$ 0.86 (0.64-4.72)	1.02 $\pm$ 0.31 (0.43-1.43)	0.060
vFo (%)	2.39 $\pm$ 2.19 (0.86-11.88)	1.76 $\pm$ 0.62 (0.79-2.65)	0.196
Amplitude perturbation measurements			
ShdB (dB)	0.40 $\pm$ 0.16 (0.13-0.77)	0.30 $\pm$ 0.15 (0.11-0.72)	0.050
Shim (%)	4.62 $\pm$ 1.81 (1.54-8.72)	3.54 $\pm$ 1.87 (1.26-9.01)	0.045
APQ (%)	3.89 $\pm$ 1.31 (1.72-6.35)	3.26 $\pm$ 1.53 (1.07-7.05)	0.125
sAPQ (%)	5.94 $\pm$ 2.04 (3.04-10.92)	5.68 $\pm$ 2.00 (2.47-9.31)	0.511
vAm (%)	13.52 $\pm$ 5.31 (6.02-27.26)	13.99 $\pm$ 5.23 (5.91-20.72)	0.925
Voice break-related measurements			
DVB (%)	0.00 $\pm$ 0.00 (0.00-0.00)	0.00 $\pm$ 0.00 (0.00-0.00)	1.000
NVB	0.00 $\pm$ 0.00 (0.00-0.00)	0.00 $\pm$ 0.00 (0.00-0.00)	1.000
Subharmonic component-related measurements			
DSH (%)	1.24 $\pm$ 3.12 (0.00-11.50)	0.00 $\pm$ 0.00 (0.00-0.00)	0.130
NSH	1.22 $\pm$ 3.06 (0.00-11.50)	0.00 $\pm$ 0.00 (0.00-0.00)	0.130
Voice irregularity-related measurements			
DUV (%)	0.31 $\pm$ 1.07 (0.00-5.00)	0.54 $\pm$ 1.28 (0.00-4.50)	0.495
NUV	0.30 $\pm$ 1.07 (0.00-5.00)	0.54 $\pm$ 1.28 (0.00-4.50)	0.495
Noise-related measurements			
NHR	0.15 $\pm$ 0.02 (0.11-0.19)	0.13 $\pm$ 0.01 (0.11-0.15)	0.007
VTI	0.04 $\pm$ 0.01 (0.02-0.07)	0.03 $\pm$ 0.01 (0.01-0.05)	0.039
SPI	20.97 $\pm$ 9.31 (4.91-42.99)	21.42 $\pm$ 10.26 (5.92-34.87)	0.876
Tremor-related measurements			
FTRI (%)	0.58 $\pm$ 0.24 (0.24-1.34)	0.56 $\pm$ 0.28 (0.15-0.98)	0.511
ATRI (%)	4.64 $\pm$ 2.74 (0.63-12.80)	5.13 $\pm$ 2.16 (1.02-7.71)	0.391
Fftr (Hz)	5.10 $\pm$ 2.14 (2.07-9.90)	4.16 $\pm$ 1.59 (2.44-8.00)	0.260
Fatr (Hz)	3.91 $\pm$ 1.36 (2.18-7.26)	5.11 $\pm$ 2.71 (2.27-10.53)	0.125

Abbreviation: Fo, average fundamental frequency; M Fo, mean fundamental frequency; To, average pitch period; Fhi, highest fundamental frequency; Flo, lowest fundamental frequency; STD, standard deviation of Fo; PFR, phonatory Fo-range in semi-tones; SEG, number of segments computed; PER, total number detected pitch periods; Jita, absolute jitter; Jitt, jitter percent; RAP, relative average perturbation; PPQ; pitch perturbation quotient; sPPQ, smoothed pitch perturbation quotient; vFo, fundamental frequency variation; ShdB, shimmer in dB; Shim, shimmer percent; APQ, amplitude perturbation quotient; sAPQ, smoothed amplitude perturbation quotient; vAm, peak-to-peak amplitude variation; DVB, degree of voice breaks; NVB, number of voice breaks; DSH, degree of sub-harmonics; NSH, number of sub-harmonic segments; DUV, degree of voiceless; NUV, number of unvoiced segments; NHR, noise to harmonic ratio; VTI, voice turbulence index; SPI, soft phonation index; FTRI, Fo-tremor intensity index; ATRI, amplitude tremor intensity index; Fftr, Fo-tremor frequency; Fatr, amplitude tremor frequency.

Table 5. Relationships between the acoustic parameters and clinical background in the patients with SBMA

Demographic	Jita		Jitt		Shim		VTI		NHR	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age at evaluation, years	0.059	0.727	0.012	0.942	0.218	0.194	0.146	0.388	-0.108	0.526
Disease duration from onset ^a , years	0.221	0.189	0.105	0.538	0.100	0.556	-0.210	0.211	-0.090	0.596
Testosterone, ng/dL	0.061	0.721	0.119	0.484	0.093	0.584	-0.069	0.683	0.069	0.683
Frequency for the last 6 months of laryngospasm	-0.319	0.055	-0.346	0.036	-0.328	0.047	-0.305	0.066	-0.460	0.004
ALSFRS-R										
Speech	-0.061	0.719	0.063	0.710	0.025	0.881	0.056	0.742	-0.074	0.665
Salivation	0.129	0.447	0.204	0.225	0.116	0.492	0.078	0.647	0.106	0.532
Swallowing	-0.062	0.714	-0.010	0.953	0.029	0.863	-0.111	0.514	0.224	0.182
Bulbar subscore ^b	0.029	0.863	0.136	0.421	0.105	0.535	0.034	0.841	0.115	0.497
Total	-0.075	0.659	-0.028	0.870	-0.005	0.977	0.028	0.867	0.047	0.783
Norris Scales										
Limb Norris score	-0.240	0.219	-0.310	0.123	-0.447	0.022	-0.194	0.342	-0.382	0.054
Norris Bulbar score	-0.048	0.810	-0.027	0.879	-0.149	0.467	-0.255	0.208	-0.084	0.682

Abbreviations: ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale; Jita, absolute jitter; Jitt, jitter percent; Shim, shimmer percent; VTI, voice turbulence index; NHR, noise-to-harmonic ratio.

^aDisease duration from onset was defined as the period of time between the age at

1 onset and evaluation.

2 ^bThe bulbar subscore was calculated as the total number of items related to bulbar
3 signs consisting of speech, salivation, and swallowing.

4

Table 6. Receiver operating characteristic curves for laryngospasm

Variables	Jita	Jitt	Shim	VTI	NHR
Optimal cutoff point	70.799	1.231	4.203	0.302	0.142
Sensitivity, %	78.6	85.7	78.6	69.2	71.4
Specificity, %	65.2	60.9	65.2	42.9	78.3
AUC	0.705	0.727	0.699	0.674	0.767
(95% CI)	(0.536–0.874)	(0.565–0.888)	(0.518–0.879)	(0.498–0.849)	(0.615–0.919)
SE	0.086	0.091	0.092	0.090	0.077
<i>p</i> value	0.017	0.022	0.045	0.079	0.007

Abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; SE, standard error; Jita, absolute jitter; Jitt, jitter percent; Shim, shimmer percent; VTI, voice turbulence index; NHR, noise-to-harmonic ratio.

The AUC, which goes from 0.5 to 1.0, is a measurement value reflecting how good the test is for distinguishing between patients with and without a specific symptom. The closer the AUC is toward 1, the better the overall diagnostic performance of the test (greater than 0.9, high accuracy; 0.7–0.9, moderate accuracy; and 0.5–0.7, low accuracy). When the value of an MDVP parameter is lower than each optimal cut-off point, laryngospasm is considered to be present. The actual receiver operating characteristic curves are shown in Figure 1.

Figure 1

Figure 1