RESEARCH ARTICLE

Swallowing markers in spinal and bulbar muscular atrophy

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Abstract

Objective: We examined the characteristics of dysphagia in spinal and bulbar muscular atrophy, a hereditary neuromuscular disease causing weakness of limb, facial, and oropharyngeal muscles via a videofluoroscopic swallowing study, and investigated the plausibility of using these outcome measures for quantitative analysis. **Methods**: A videofluoroscopic swallowing study was performed on 111 consecutive patients with genetically confirmed spinal and bulbar muscular atrophy and 53 age- and sex-matched healthy controls. Swallowing of 3-mL liquid barium was analyzed by the *Logemann's Videofluorographic Examination of Swallowing* worksheet. **Results**: Of more than 40 radiographic findings, the most pertinent abnormal findings in patients with spinal and bulbar muscular atrophy, included *vallecular residue after swallow* (residue just behind the tongue base), *nasal penetration,* and *insufficient tongue movement* ($P < 0.001$ for each) compared with healthy controls. Quantitative analyses showed that *pharyngeal residue after initial swallowing, oral residue after initial swallowing, multiple swallowing sessions,* and the *penetration–aspiration scale* were significantly worse in these patients ($P \leq 0.005$ for each) than in controls. In patients with spinal and bulbar muscular atrophy, *laryngeal penetration* was observed more frequently in those without subjective dysphagia. **Interpretation**: Dysphagia of spinal and bulbar muscular atrophy was characterized by impaired tongue movement in the oral phase and nasal penetration followed by pharyngeal residues, which resulted in multiple swallowing sessions and laryngeal penetration. Although major limitations of reproducibility and radiation exposure still exist with videofluoroscopy, *pharyngeal residue after initial swallowing* and the *penetration–aspiration scale* might serve as potential outcome measures in clinical studies.

Introduction

Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a hereditary neuromuscular disease characterized by muscle atrophy, weakness, dysarthria, and dysphagia.[1–3] SBMA exclusively affects adult males, and the disease progression is slow. Dysphagia develops after ~10 years of muscle weakness, followed by the need of a cane and a wheelchair.[4] As a study of the natural history of SBMA showed that the most common cause of death is aspiration pneumonia (53%) due to bulbar palsy,[4] dysphagia is an important prognostic factor.

SBMA is caused by the expansion of a trinucleotide CAG repeat in the androgen receptor gene.[5] Lower motor neurons are markedly depleted throughout all spinal segments, and neurons in the hypoglossal, facial, and trigeminal motor nuclei are severely depleted or atrophic.[6] The nuclei of the remaining neurons have abnormal protein deposits due to lengthened CAG repeats.[7,8] Androgen deprivation therapy using leuprorelin, a luteinizing hormone-releasing hormone agonist, decreased abnormal protein deposits and attenuated neurodegeneration in a transgenic mouse model of SBMA.[9] The potential effect of this therapy has also been suggested in clinical trials.[10,11]

Despite its importance for patient prognosis, reliable clinical markers to assess dysphagia have not been established. Investigating dysphagia in SBMA patients has several advantages: the disease is accurately diagnosed by CAG expansion, patients have virtually none of the cognitive dysfunction or upper motor neuron involvement that are associated with pseudobulbar palsy, and there is a topographical simplicity of the affected neurons to understanding the characteristics and pathophysiology of dysphagia. Here, we examined the findings of a videofluoroscopic swallowing study (VFSS) in SBMA patients to identify the characteristics of dysphagia that might help to clarify its mechanism, and to investigate the plausibility of using VFSS-based outcome measures for quantitative analyses. We also examined the differences between patients with and without subjective dysphagia to determine patients who are at risk of developing pneumonia in a clinical setting.

Methods

Participants

The participants comprised 111 consecutive patients with genetically confirmed SBMA and 53 age- and sex-matched healthy controls; all were Japanese males. All the SBMA patients and healthy control subjects underwent VFSS at Nagoya University Hospital. We also evaluated the backgrounds of the participants as well as their motor functions at the time of the VFSS. None of the SBMA participants had received leuprorelin for the treatment of dysphagia at the time of the VFSS. All patients were positive for SBMA by genetic analyses, and the CAG repeat number was calculated for 104 patients. None of the control participants had any medical history of dysphagia or dysphagia-related diseases.

Ethics

The Ethics Committee of Nagoya University Graduate School of Medicine approved the study. Written informed consent was obtained from each participant for both the main study and ad hoc study. All the SBMA patients gave their written informed consent for the genetic analyses.

Videofluoroscopic swallowing study

During the VFSS, participants were instructed to swallow 3 mL of 40% w/v barium sulfate twice in a standing position, which was viewed in the lateral plane. Each swallowing was recorded and included at least 20 sec after the initial swallow. To eliminate unnecessary irradiation exposure, the irradiation area was confined to the oral, pharyngeal, laryngeal, and upper esophageal areas. VFSS data were recorded on MiniDV digital videotape (Sony, Japan) at 30 frames/s from August 2003 to September 2010. Readings of VFSS were performed from November 2009 to February 2011 and quantitative and qualitative findings were analyzed. All parameters were measured by two independent evaluators (MD and SLP), who were blinded to details of the participants' backgrounds, according to standard procedures.[12,13] Confidentiality was ensured by assigning a study code to each participant.

Qualitative and quantitative findings from the swallowing examination were measured using Logemann's *Videofluorographic Examination of Swallowing* worksheet, containing more than 40 qualitative and quantitative radiographic findings.[14] Qualitative items consisted of six items in the preparation to swallow; 15 items in the oral phase; 15 items in the pharyngeal phase; and three items in the cervical esophageal phase (Table S1). For quantitative analyses, the oral and pharyngeal residues were measured using semiquantitative scales: 0, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100%. Given that piecemeal deglutition, a VFSS finding of multiple repeated swallows to empty a bolus from the oral cavity, is often observed in patients with SBMA, we measured pharyngeal residues *after initial swallowing* as well as those *after piecemeal deglutition*. We also measured times (sessions) of piecemeal deglutition for the first 3-mL barium swallow. Details of the temporal measurements are in Table S2.

For qualitative analyses, the two evaluators discussed and agreed on the details of the definitions[14] of radiographic findings before the measurement, as described previously. The radiographic findings were read by the two evaluators independently and any discrepancies between the two were discussed until a consensus was reached. To assure intra- and interrater reliabilities, we trained the evaluators for this method. The concordance rates of quantitative measurements by two evaluators in the middle of and again after the study were 0.95, and 0.90, respectively.

For aspiration and penetration findings, we used the Rosenbek penetration–aspiration scale. Scores were determined primarily by the depth to which material passed into the airway and by whether or not material entering the airway was expelled (score 8 being the worst aspiration) as described previously.[15]

Functional severity score

At the time appointed for the VFSS, we also evaluated the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R),[16,17] using the total score and the sum of three bulbar-related subscores (speech, salivation, and swallowing) for analysis. The swallowing subscore was used to judge the patient's subjective dysphagia. We defined overt subjective dysphagia as a score of less than 4 (normal eating habits) on the swallowing subscore of the ALSFRS-R.

Statistics

Statistical analyses were performed with IBM SPSS Statistics, version 21 (IBM Japan). Descriptive variables such as the mean, standard deviation, and range were used to summarize the quantitative measures. For qualitative analyses, we used chi-square comparisons to determine whether there were differences between SBMA patients and controls and between those with and without subjective dysphagia. For quantitative measures, we analyzed the data by Spearman's rank correlation and Student's *t*-test. We considered *P*-values less than 0.05 as indicative of significant differences and correlation coefficients (R) greater than 0.3 as strong correlation. For the analysis of relationships between subjective dysphagia and penetration, the McNemar test was performed.

Ad hoc study

To evaluate the reproducibility and validity of the VFSS measurement for barium residues, 20 consecutive patients with SBMA were enrolled in an ad hoc study from May 2010 to August 2010. The first and second VFSSs were conducted at intervals of 7 to 30 days. The participants were instructed to swallow 3 mL of 40% w/v barium three times and 10 mL barium once. To avoid unfavorable carryover of residues to the next barium swallows, participants were instructed to conduct 10-mL water swallowing once and saliva swallowing twice after each barium swallow. Pharyngeal barium residue and times of piecemeal deglutition (multiple repeated swallows) were measured blindly by two independent evaluators as described previously. To evaluate the validity of the measurements, the SBMA functional rating scale (SBMAFRS),[18] SWAL-QOL symptom subscores,[19,20] and Swallowing Disturbance Questionnaire–Japanese (SDQ-J) were used.[21,22] Data were analyzed by intraclass correlation (1, 1) for reproducibility and Spearman's rank correlation for validity.

Results

The study included 111 SBMA patients (53.2 ± 10.4 years of age) and 53 healthy controls (50.8 ± 9.0 years of age). There was no significant difference in age between the two groups ($P = 0.16$). The characteristics of this study population, including age, CAG repeat length, disease duration, and ALSFRS-R scores, were similar to those of previous studies.[11,23,24] Fifty-three of the 111 SBMA patients reported having subjective dysphagia (Table 1).

Qualitative analyses

Those qualitative radiographic findings that were observed in a significantly higher frequency in SBMA patients than in control subjects are shown in bold in Figure 1A ($P < 0.05$ for all). Ten of these 14 significantly abnormal findings occurred during the *pharyngeal* phase of swallowing. In addition, of these 14 abnormal findings, eight were found significantly more frequently in patients with subjective dysphagia than in those without ($P < 0.05$ for all; Fig. 1B, in bold). Half of these occurred during the *oral* phase of swallowing.

Quantitative analyses

Four quantitative parameters were found to be characteristic of SBMA patients compared with controls (Table 2). Patients with subjective dysphagia showed a significantly greater amount of *oral residue after initial swallowing* and more frequent *piecemeal deglutition* (Table 3), both of which are classified as oral and voluntary measures. In contrast, the *pharyngeal residue after initial swallowing* and *penetration–aspiration scale* items, both classified as pharyngeal and involuntary measures, were not

Table 1. Demographics of study population at baseline.

Characteristic	SBMA with subjective dysphagia (N = 53)	SBMA without subjective dysphagia (N = 58)	P	Total SBMA (N = 111)
Age (years)	55.8 ± 9.8 (33–81)	50.8 ± 10.4 (27–74)	**0.011**	53.2 ± 10.4 (27–81)
CAG repeat length (number)	47.9 ± 3.3[1] (40–57)	48.5 ± 3.5[2] (42–57)	0.39	48.2 ± 3.4[3] (40–57)
Disease duration (years)	11.3 ± 8.5 (1–57)	10.7 ± 7.5 (1–33)	0.71	11.0 ± 8.0 (1–57)
Disease onset (years)	44.5 ± 11.0 (14–66)	40.0 ± 12.2 (8–68)	**0.045**	42.2 ± 11.8 (8–68)
ALSFRS-R	39.3 ± 4.1 (29–47)	43.2 ± 3.0 (36–48)	**<0.001**	41.4 ± 4.0 (29–48)
ALSFRS-R bulbar subscores	9.7 ± 1.4 (5–11)	11.5 ± 0.8 (9–12)	**<0.001**	10.6 ± 1.5 (5–12)

Values represent means ± SD; ranges are in parentheses. [1]N = 48; [2]N = 56; [3]N = 104. P-values in bold indicate significant differences between with and without subjective dysphagia. ALSFRS-R = revised amyotrophic lateral sclerosis functional rating scale.

significantly different between the groups with and without subjective dysphagia.

Laryngeal penetration

The scores on the *penetration–aspiration scale* revealed that there were no aspiration episodes in our study patients. However, laryngeal penetration was found in 29 of the 111 SBMA patients (26%). Patients with laryngeal penetration were older and had later disease onsets, but there were no differences in either the ALSFRS-R total scores or bulbar subscores between those with and without laryngeal penetration (Table S3). Although not statistically significant, the *penetration–aspiration scale* scores tended to be higher in those SBMA patients without subjective dysphagia (Table 3). Furthermore, although counterintuitive, laryngeal penetration was noted significantly more often in patients *without* subjective dysphagia than in those *with* subjective dysphagia ($P < 0.001$; Table 4).

Reproducibility and validity of pharyngeal residues

In the 20 consecutive SBMA patients in the ad hoc study (Table S4 and Table S5), the reproducibility of detecting pharyngeal residues was higher in the means of three swallows than in the first swallows (Table S6). Compared with single swallows, better correlations were noted between the amount of pharyngeal residue after initial swallowing (the mean of three swallows) and swallowing-related severity scores, especially the SDQ-J. No remarkable differences were found between the 3-mL barium swallow and the 10-mL barium swallow in terms of external validity of pharyngeal residues (Table S7).

Discussion

This study examined the characteristics of dysphagia in 111 patients with SBMA compared with those of 53 healthy control participants via VFSS. ALSFRS-R bulbar scores were associated with subjective dysphagia, but not to bolus penetration into the airway, in the SBMA group. Laryngeal penetration was significantly more frequent in the patients without subjective dysphagia.

Mechanism of dysphagia in SBMA

This study identified several characteristic radiographic findings in SBMA patients that differed from those of controls, including the presence of *vallecular residue after swallow* (residue just behind the tongue base), *residue (stasis) in both pyriform sinuses* (residue in both sides of the laryngeal orifice), *piecemeal deglutition* (multiple swallowing sessions), *poor epiglottic inversion, residue (stasis) on tongue*, and *nasal penetration*. These findings were found in more than 40% of the SBMA patients and more frequently observed in SBMA patients than in control participants. Other less frequent but statistically significant findings were related to tongue movement dysfunction, pharyngeal residue, and bolus penetration into the airway.

Considering these findings together, we speculate that dysphagia in SBMA patients functions as shown in Figure 2. Laryngeal penetration is defined as entry of material into the laryngeal vestibule but not below the true vocal folds.[25] Laryngeal penetrations were reported to be significantly more frequent after the age of 50 during normal aging.[26] Despite the fact that laryngeal penetration is also observed in healthy controls, people without laryngeal penetration were reported to have the lowest risk of developing pneumonia compared with patients with laryngeal penetration or aspiration.[27] A previous report using fiberoptic endoscopy also found that patients with SBMA have pharyngeal residues.[28] Our VFSS findings provide further characteristics, such as oral residues and repetitive swallow, that might help to identify the potential mechanisms of dysphagia in SBMA patients.
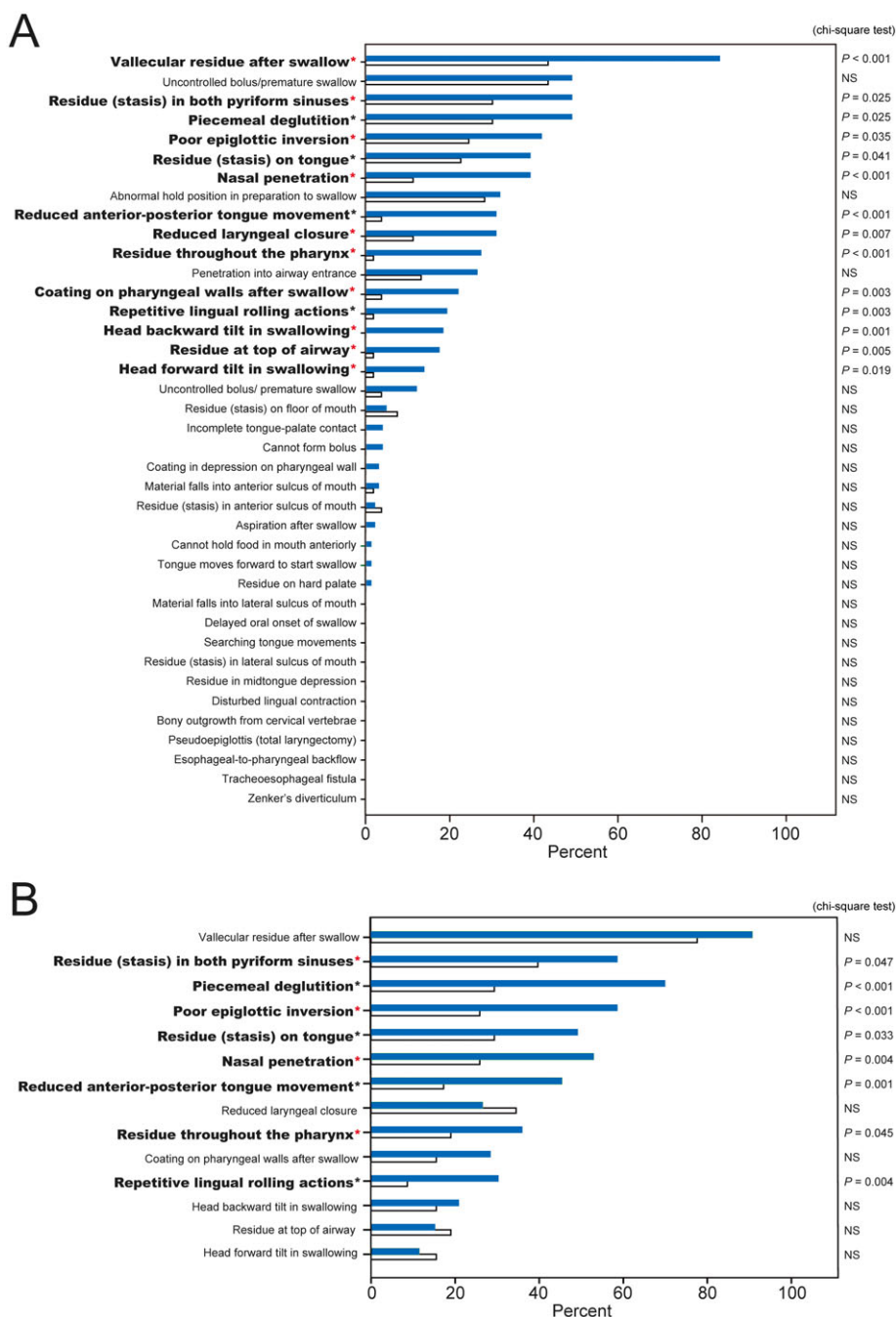
Figure 1. Results of qualitative analyses. (A) We compared the qualitative radiographic findings of SBMA patients with those of the control group. Qualitative videofluoroscopic swallowing study (VFSS) findings found significantly more frequently in the SBMA group than the control group are shown in bold. More than 80% of SBMA patients had vallecular residue after swallowing (residue just behind the tongue base); approximately 50% of patients had residue (stasis) in both pyriform sinuses (residue in both sides of the laryngeal orifice), and piecemeal deglutition (multiple swallowing sessions). Ten of the 14 findings that differentiate SBMA patients from the control group were pharyngeal phase findings. Solid bars denote SBMA patients ($N = 111$). Open bars denote control participants ($N = 53$). *Statistically significant difference between SBMA and control groups; chi-square test. Red asterisks indicate pharyngeal phase findings. (B) For the SBMA-related qualitative radiographic findings, we also compared their occurrences in patients with and without subjective dysphagia. Significant differences between these two groups are shown in bold. Half of the findings that differentiate the with (solid bars; $N = 53$) and without (open bars; $N = 58$) subjective dysphagia groups were oral-phase findings. *Statistically significant difference between the with and without subjective dysphagia groups; chi-square test. Red asterisks indicate oral-phase findings.

Table 2. Quantitative analyses between control and SBMA patients.

Characteristic	Control (N = 53)	SBMA Total (N = 111)	P
Pharyngeal residue after initial swallowing (%)	6.6 ± 10.8 (0–60)	14.0 ± 18.2 (0–75)	**0.001**
Oral residue after initial swallowing (%)	3.8 ± 2.9 (0–15)	5.2 ± 4.7 (0–30)	**0.005**
Pharyngeal residue after piecemeal deglutition (%)	6.1 ± 10.6 (0–60)	8.0 ± 9.6 (0–55)	0.26
Oral residue after piecemeal deglutition (%)	3.5 ± 2.8 (0–15)	3.9 ± 2.9 (0–15)	0.46
Piecemeal deglutition (number of multiple swallowing sessions)	1.2 ± 0.4 (1–2)	1.5 ± 0.8 (1–4)	**<0.001**
Oropharyngeal swallowing efficiency (%)	54.2 ± 17.7 (13–99)	59.8 ± 26.6 (4–132)	0.12
Stage transition duration (s)	0.34 ± 1.13 (−0.58–8.07)	0.37 ± 0.84 (−0.19–4.83)	0.81
Laryngeal elevation duration (s)	0.23 ± 0.07 (0.12–0.43)	0.23 ± 0.10 (0.09–0.63)	0.74
Duration of cricopharyngeal opening (s)	0.39 ± 0.06 (0.30–0.54)	0.39 ± 0.07 (0.25–0.67)	0.83
Oral transit duration (s)	1.03 ± 0.52 (0.30–2.70)	0.82 ± 0.66 (0.20–4.90)	0.47
Pharyngeal transit duration (s)	0.78 ± 0.19 (0.49–1.31)	0.76 ± 0.35 (0.48–3.13)	0.75
Penetration–aspiration scale	1.1 ± 0.3 (1–2)	1.4 ± 0.8 (1–6)	**0.003**

Values represent means ± SD; ranges are in parentheses. P-values in bold indicate significant differences between with and without subjective dysphagia.

Table 3. Quantitative analyses between with and without subjective dysphagia.

	SBMA		
Characteristic	With subjective dysphagia (N = 53)	Without subjective dysphagia (N = 58)	P
Pharyngeal residue after initial swallowing (%)	17.3 ± 19.0 (0–70)	11.0 ± 17.0 (0–75)	0.07
Oral residue after initial swallowing (%)	6.7 ± 5.6 (0–30)	3.9 ± 3.3 (0–15)	**0.002**
Piecemeal deglutition (number of multiple swallowing sessions)	1.7 ± 0.8 (1–4)	1.2 ± 0.6 (1–4)	**0.001**
Penetration–aspiration scale	1.3 ± 0.7 (1–5)	1.5 ± 0.9 (1–6)	0.22

Values represent means ± SD; ranges are in parentheses. P-values in bold indicate significant differences between with and without subjective dysphagia.

Clinical outcome measure

In this SBMA patient cohort, we speculated that there was less of a genetic and phenotypic heterogeneity burden than in an ALS patient cohort, which is one of the main hindrances to therapeutic development. SBMA is a slowly progressive disease[1,4]; thus, long-term clinical trials are necessary to assess whether certain drugs alter the natural disease progression or not by targeting clinical endpoints such as the occurrence of aspiration pneumonia or becoming wheelchair bound. Suitable surrogate endpoints, which reflect the pathogenesis and severity of SBMA are essential to assess the therapeutic efficacy in drug trials.

We previously reported that tongue pressure may serve as a marker of swallowing function at an early stage of SBMA.[29] VFSS enables visualization of the swallowing movement, while tongue pressure assesses a part of the swallowing function. In this study, compared with controls, SBMA patients had significantly more *pharyngeal residue after initial swallowing,* more *oral residue after initial swallowing,* more *piecemeal deglutition* (multiple swallowing sessions), and higher *penetration–*

aspiration scale scores. Significantly more *oral residue after initial swallowing* and frequent *piecemeal deglutition* were found in SBMA patients with subjective dysphagia, which was essentially irrelevant to laryngeal penetration. At this point in our current study, the amount of *pharyngeal residue after initial swallowing* and the *penetration–aspiration scale* might be candidates for outcome measures, even though longitudinal changes in the disease course of these measures need to be clarified, and a ceiling effect of the penetration–aspiration scale has been reported.[30]

The amounts of pharyngeal barium residue have also been shown to correlate with the incidence of aspiration and quantitative scintigraphy data.[31,32] Pharyngeal residue has also been reported to be the most important VFSS variable in reflecting pharyngeal pressure measurements in both diseased and healthy participants.[33] To measure pharyngeal residue more precisely, the Normalized Residue Ratio Scale, using image analysis software, was recently proposed.[34] We trained evaluators to keep high concordance rate, but an automated measurement system may become a better option in the future to minimize subjective measurement. Previous studies have shown

high intra- and interrater reliabilities, although not much is known about the reproducibility of this parameter.[35]

We also evaluated temporal parameters, which did not significantly reflect dysphagia severity in this cohort. In our study, a longer duration of cricopharyngeal opening (DCPO) – in other words, a longer upper esophageal sphincter opening duration – was related to smaller amounts of pharyngeal and oral residues in healthy controls, whereas comparable relationships were not found in the SBMA group (data not shown). Variabilities in the compensatory mechanisms of SBMA patients may have contributed to the lack of significant relationships between pharyngeal residues and DCPO in SBMA, and also the lack of a significant difference in DCPO between the SBMA group and controls.

**Table 4.** Relationship between subjective dysphagia and laryngeal penetration.

	Subjective dysphagia		
	+	−	Total
Laryngeal penetration			
+	10	19	29
−	43	39	82
Total	53	58	111

Values represent numbers of patients. McNemar test was significant. ($P < 0.001$).

Strengths and limitations

Among several modalities, VFSS is a superior method to assess the severity of dysphagia in terms of visualizing the characteristics of penetration and aspiration. In this study, SBMA patients with subjective dysphagia had oral-phase VFSS abnormalities. We also found that the risk of laryngeal penetration is not related to the presence of a subjective dysphagia in the SBMA group. Possibly, this paradoxical finding can be explained by the speculation that patients with subjective dysphagia tend to swallow carefully (slowly or with multiple sessions of swallowing), leading to a low incidence of laryngeal penetration. VFSS is also useful to evaluate the effects of adaptive swallowing methods, such as the chin-tuck maneuver, the supraglottic swallow, and the effortful swallow. Given that the presence of pharyngeal residue is the most common finding in SBMA patients and a laryngeal penetration risk exists even in those without subjective dysphagia, we recommend the chin-tuck maneuver and the effortful swallow as safe methods of swallowing for all SBMA patients with dysphagia.[36,37] We also reported that a 6-week head lift exercise may improve swallowing dysfunction as measured by tongue pressure.[38] Reinforcement of compensatory swallowing mechanisms may lead to effective rehabilitation in dysphagia patients.

The limitations of VFSS include poor reproducibility and radiation exposure. Longitudinal changes in VFSS
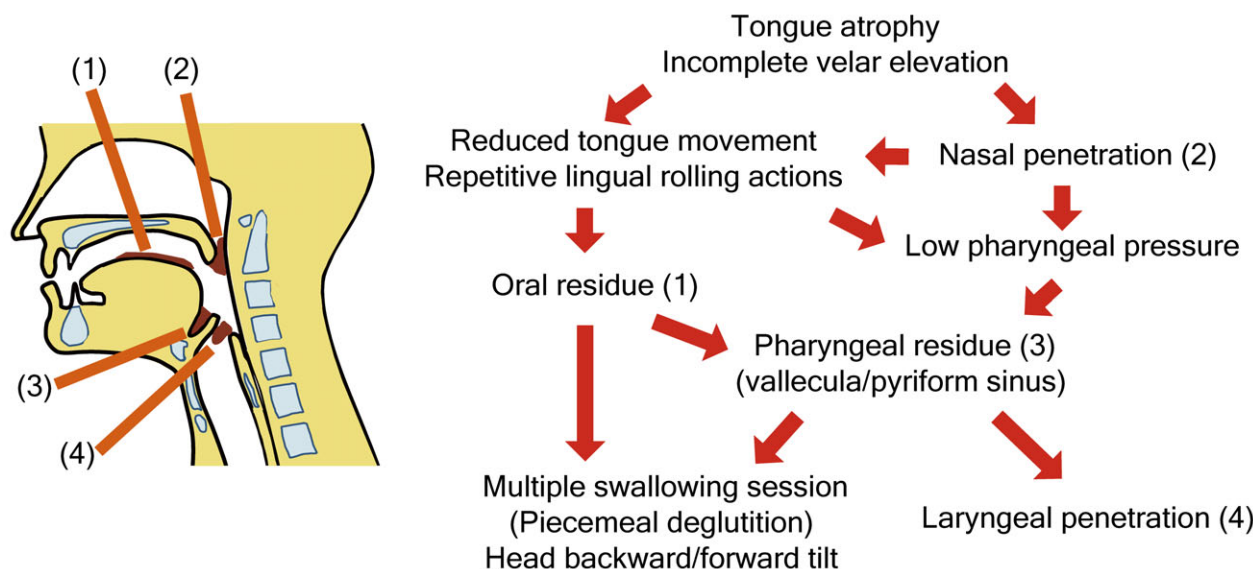
Figure 2. Putative scheme of dysphagia in SBMA patients. Dysphagia in SBMA stems from tongue atrophy and incomplete velar elevation, both of which cause dysfunctional tongue movement. Tongue movement dysfunction leads to oral and pharyngeal residues, both of which eventually result in multiple swallowing sessions (piecemeal deglutition) and laryngeal penetration. Incomplete velar elevation/tongue atrophy also lead to nasal penetration, inevitably causing reduced tongue movement to compensate and low pharyngeal pressure, which leads to pharyngeal residue (residue in the vallecula and pyriform sinuses), and finally laryngeal penetration.

findings, especially in the presence of pharyngeal residue in SBMA patients, is another major limitation, partly caused by poor reproducibility of VFSS findings.[23] In this study, we found that reproducibility of quantitative markers could be improved by measuring multiple swallows and using the average values of three swallows. This method appears to overcome the weakness of quantitative VFSS analysis, especially when the initial swallowing was exaggerated by a chance finding. It is possible, however, that the degree of dysphagia may be underestimated by a "practice effect" in the averaged analysis. In addition, averaged data may also be difficult to interpret when the barium residue is carried over, even after washout. Therefore, quantitative analysis should be performed in consideration of the initial swallowing as well as the average of multiple swallows. Comparisons between control and diseased/treatment groups are crucial for establishing valid VFSS markers, but due to radiation problems we limited the number of healthy controls compared with the number of SBMA patients. More recently, real-time MRI was reported to display dysphagia equally as well as VFSS.[39] Our study results will help select quantitative measures for real-time MRI evaluations. Another limitation is the presence of abnormal radiographic findings in healthy controls, which can be caused both by aging and by variable swallowing habits of individuals. We could not analyze direct relationships between VFSS findings and pneumonia, as only one of the participants had dysphagia severe enough to experience pneumonia, partly because our cohort was focused on ambulatory patients. Because swallowing is composed of serial motions of various bulbar musculatures, multiple modalities, including VFSS, tongue pressure, patient-reported outcomes, and other devices, are informative for assessing dysphagia in SBMA patients. Noninvasive, portable devices that can continuously measure pharyngeal residue would be ideal.

According to our VFSS findings, SBMA patients are qualitatively characterized by increased oral and pharyngeal barium residues and laryngeal penetration, resulting from tongue and pharyngeal weakness, as well as compensative responses including repetitive swallows. Among quantitative indices, both pharyngeal residue after initial swallowing and penetration–aspiration scale might reflect the major features of dysphagia in SBMA. These findings will help to understand the mechanism of dysphagia and can be applied to future clinical studies of pharmacological and physical interventions.

Acknowledgments

Author Contributions

HB, MK, and GS participated in conception and design of the studies. HB participated in statistical analyses and drafting the manuscript. MK and GS participated in final editing of the manuscript. All authors contributed to the acquisition and analysis of data.

Conflict of Interest

Nothing to declare.

References

1. Kennedy WR, Alter M, Sung JH. Progressive proximal spinal and bulbar muscular atrophy of late onset A sex-linked recessive trait. Neurology 1968;18:671–680.

2. Sperfeld AD, Karitzky J, Brummer D, et al. X-linked bulbospinal neuronopathy: kennedy disease. Arch Neurol 2002;59:1921–1926.

3. Sobue G, Adachi H, Katsuno M. Spinal and Bulbar Muscular Atrophy (SBMA). In: Dickinson D, Weller RO, eds. Neurodegeneration: the molecular pathology of dementia and movement disorders, 2nd ed. New York: Wiley-Blackwell, 2011:307–314.

4. Atsuta N, Watanabe H, Ito M, et al. Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. Brain 2006;129:1446–1455.

5. La Spada AR, Wilson EM, Lubahn DB, et al. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 1991;352:77–79.

6. Sobue G, Hashizume Y, Mukai E, et al. X-linked recessive bulbospinal neuronopathy. A clinicopathological study. Brain 1989;112:209–232.

7. Adachi H, Katsuno M, Minamiyama M, et al. Widespread nuclear and cytoplasmic accumulation of mutant androgen receptor in SBMA patients. Brain 2005;128:659–670.

8. Banno H, Katsuno M, Suzuki K, et al. Pathogenesis and molecular targeted therapy of spinal and bulbar muscular atrophy (SBMA). Cell Tissue Res 2012;349:313–320.

9. Katsuno M, Adachi H, Doyu M, et al. Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy. Nat Med 2003;9:768–773.

10. Banno H, Katsuno M, Suzuki K, et al. Phase 2 trial of leuprorelin in patients with spinal and bulbar muscular atrophy. Ann Neurol 2009;65:140–150.

11. Katsuno M, Banno H, Suzuki K, et al. Efficacy and safety of leuprorelin in patients with spinal and bulbar muscular atrophy (JASMITT study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:875–884.

12. Logemann JA, Kahrilas PJ, Kobara M, Vakil NB. The benefit of head rotation on pharyngoesophageal dysphagia. Arch Phys Med Rehabil 1989;70:767–771.

13. Logemann JA, Pauloski BR, Rademaker AW, et al. Temporal and biomechanical characteristics of oropharyngeal swallow in younger and older men. J Speech Lang Hear Res 2000;43:1264–1274.

14. Logemann JA. Evaluation and treatment of swallowing disorders, 2nd ed. Austin: PRO-ED Inc, 1998.

15. Rosenbek JC, Robbins J, Roecker EV, et al. A penetration-aspiration scale. Dysphagia 1996;11:93–98.

16. Cedarbaum JM. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169:13–21.

17. Ohashi Y, Tashiro K, Itoyama Y, et al. Study of functional rating scale for amyotrophic lateral sclerosis: revised ALSFRS (ALSFRS-R) Japanese version. No To Shinkei 2001;53:346–355.

18. Hashizume A, Katsuno M, Suzuki K, et al. A functional scale for spinal and bulbar muscular atrophy: cross-sectional and longitudinal study. Neuromuscul Disord 2015;25:554–562.

19. McHorney CA, Robbins J, Lomax K, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. Dysphagia 2002;17:97–114.

20. Wada M, Hoshino Y, Okudaira N. Assessment of quality of life for people with dysphagia: use of the SF-36 and trial use of the SWAL-QOL and SWAL-CARE outcomes tool in Japan. Jpn J Dysphagia Rehabil 2003;7:109–116.

21. Manor Y, Giladi N, Cohen A, et al. Validation of a swallowing disturbance questionnaire for detecting dysphagia in patients with Parkinson's disease. Mov Disord 2007;22:1917–1921.

22. Yamamoto T, Ikeda K, Usui H, et al. Validation of the Japanese translation of the Swallowing Disturbance Questionnaire in Parkinson's disease patients. Qual Life Res 2012;21:1299–1303.

23. Hashizume A, Katsuno M, Banno H, et al. Longitudinal changes of outcome measures in spinal and bulbar muscular atrophy. Brain 2012;135:2838–2848.

24. Fernández-Rhodes LE, Kokkinis AD, White MJ, et al. Efficacy and safety of dutasteride in patients with spinal and bulbar muscular atrophy: a randomised placebo-controlled trial. Lancet Neurol 2011;10:140–147.

25. Robbins J, Hamilton JW, Lof GL, Kempster GB. Oropharyngeal swallowing in normal adults of different ages. Gastroenterology 1992;103:823–829.

26. Daggett A, Logemann J, Rademaker A, Pauloski B. Laryngeal penetration during deglutition in normal subjects of various ages. Dysphagia 2006;21:270–274.

27. Pikus L, Levine MS, Yang YX, et al. Videofluoroscopic studies of swallowing dysfunction and the relative risk of pneumonia. AJR Am J Roentgenol 2003;180:1613–1616.

28. Warnecke T, Oelenberg S, Teismann I, et al. Dysphagia in X-linked bulbospinal muscular atrophy (Kennedy disease). Neuromuscul Disord 2009;19:704–708.

29. Mano T, Katsuno M, Banno H, et al. Tongue pressure as a novel biomarker of spinal and bulbar muscular atrophy. Neurology 2014;82:255–262.

30. Ludlow CL, Humbert I, Saxon K, et al. Effects of surface electrical stimulation both at rest and during swallowing in chronic pharyngeal Dysphagia. Dysphagia 2007;22:1–10.

31. Eisenhuber E, Schima W, Schober E, et al. Videofluoroscopic assessment of patients with dysphagia: pharyngeal retention is a predictive factor for aspiration. AJR Am J Roentgenol 2002;178:393–398.

32. Logemann JA, Williams RB, Rademaker A, et al. The relationship between observations and measures of oral and pharyngeal residue from videofluorography and scintigraphy. Dysphagia 2005;20:226–231.

33. Pauloski BR, Rademaker AW, Lazarus C, et al. Relationship between manometric and videofluoroscopic measures of swallow function in healthy adults and patients treated for head and neck cancer with various modalities. Dysphagia 2009;24:196–203.

34. Pearson WG Jr, Molfenter SM, Smith ZM, Steele CM. Image-based measurement of post-swallow residue: the normalized residue ratio scale. Dysphagia 2013;28:167–177.

35. Kuhlemeier KV, Yates P, Palmer JB. Intra- and inter-rater variation in the evaluation of videofluorographic swallowing studies. Dysphagia 1998;13:142–147.

36. Wheeler-Hegland K, Ashford J, Frymark T, et al. Evidence-based systematic review: oropharyngeal dysphagia behavioral treatments. Part II—impact of dysphagia treatment on normal swallow function. J Rehabil Res Dev 2009;46:185–194.

37. Leigh JH, Oh BM, Seo HG, et al. Influence of the chin-down and chin-tuck maneuver on the swallowing kinematics of healthy adults. Dysphagia 2015;30:89–98.

38. Mano T, Katsuno M, Banno H, et al. Headlift exercise improves swallowing dysfunction in spinal and bulbar muscular atrophy. Eur Neurol 2015;74:251–258.

39. Olthoff A, Carstens PO, Zhang S, et al. Evaluation of dysphagia by novel real-time MRI. Neurology 2016;87:2132–2138.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Data S1. Supplemental tables and methods.