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ORIGINAL ARTICLE

Preliminary design and validation of the "6-K-scale" for bulbar symptoms evaluation in SBMA

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Abstract

Background Spinal and bulbar muscular atrophy (SBMA) is a late onset, X-linked neuromuscular disease. Bulbar symptoms are a main characteristic of the disease but a tool for their clinical evaluation still does not exist. The aim of this study was to design and test a new scale (6-K-scale) for evaluation of bulbar function in SBMA.

Methods We considered 60 genetically confirmed SBMA patients and built a scale to evaluate the V, VII, IX, X, and XII cranial nerves (CN) and the ansa cervicalis. Functional status was evaluated through the Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS), 6-min-walk-test (6MWT), Adult Myopathy Assessment Tool (AMAT) scale, and FVC%. Twenty patients underwent a re-test after 3 weeks, while 31 were tested longitudinally after 6 months. Validation of the scale included reliability assessment and factorial analysis. To evaluate convergent validity, correlations between the 6-K-scale and functional parameters were performed.

Results Internal consistency as measured by Cronbach's alpha was high (0.85) as was test–retest reliability. Principal component analysis yielded a six-factor solution accounting for 71.7% of the variance. The scale score was strongly correlated with the functional parameters.

Conclusion In conclusion, we designed and validated a new scale for bulbar evaluation in SBMA patients. This scale will be a useful tool in the clinical practice as well as a possible outcome measure in clinical trials.

Keywords SBMA · Bulbar symptoms · Functional scale · Outcome measures

Background

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare, X-linked, late onset neuromuscular disorder [1]. The disease is characterized by slowly progressive degeneration of lower motor neurons (LMN) in the brainstem and spinal cord leading to muscle dysfunction [2]. Predominant features of the disease are weakness and wasting mainly of the proximal limb muscles associated with bulbar involvement [3]. Respiratory failure is rare, but still possible [4]. The disease is caused by a CAG repeat expansion in the first exon of the androgen receptor gene encoding for a polyQ tract, with a number of CAG repeats higher than 38 considered pathogenic. It usually affects adult males and the CAG repeat size inversely correlates with the age of symptoms' onset but not with disease progression or severity [3, 5].

Bulbar symptoms are one of the key clinical features of SBMA, occurring in about 10–30% of patients at onset of the disease [3, 6, 7]. They are usually mild but generally worsen over time [8] and, in the late stages, they may lead to choking, aspiration, and *ab ingestis* pneumonia, which is considered a leading cause of death in SBMA patients [6].

Bulbar involvement in neurological diseases is classically evaluated by instrumental examinations such as videofluoroscopy and fiberoptic endoscopy [9], which accurately describe different stages of swallowing and allow the

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recognition of inhalation episodes. These techniques have been applied in SBMA patients, describing the presence of delayed oral and laryngeal phases of deglutition [9–11]. Nevertheless, instrumental examinations are invasive and do not allow comprehensive assessment of the bulbar functions nor individual evaluation of speech and phonation alterations [12]. A comprehensive clinical swallowing examination identifying patients with bulbar impairment who should undergo instrumental evaluation has been proposed [1] and, recently, a functional scale investigating the function of cranial nerves (CN) involved in bulbar function has been validated [13], showing good reliability in the identification of dysphagia. Such evaluation of single CN appears to be of great interest in SBMA patients, which are known for developing bulbar involvement at some point of the disease and would therefore benefit of regular monitoring in a routine clinical setting. Functional evaluation of CN could be also considered a biomarker of disease progression or an efficacy outcome in upcoming pharmacological clinical trials. In fact, even though several functional scales dedicated to SBMA have been developed in the context of trial readiness projects [14–16], they usually focus on motor abilities and much less on bulbar function [17]. Evaluation of tongue pressure has been proposed as a possible marker of bulbar involvement in SBMA patients [18], but a comprehensive tool considering global bulbar impairment does still not exist.

The aim of this study was to design and validate a functional scale called the 6-K-scale for the evaluation of bulbar dysfunction in SBMA.

Methods

Patients

The ethics committees of the Azienda Ospedaliera of Padova and of the University of Padova (Italy) approved the study. Sixty consecutive patients with genetically confirmed SBMA were recruited and signed informed consent to the study.

To test inter-rater reliability, at each evaluation, patients were assessed twice by two independent experienced evaluators (I.B. and L.M.). To assess intra-rater reliability (test–retest reproducibility), 20 randomly selected patients out of the 60 participants were assessed twice at an interval of 3 weeks. This period was considered short enough to avoid the effect of disease's progression on the evaluation.

Clinical history was collected for all the patients considering age and site of onset of muscle weakness and number of CAG repeats in the AR gene. We investigated also the presence of self-referred symptoms related to CN involvement such as voice's modifications and dysarthria, sialorrhea, laryngospasm, and dysphagia.

Finally, 30 patients were re-evaluated after 6 months to assess longitudinal reliability of the scale.

The bulbar scale for Kennedy's disease: *the 6-K-Scale*

The 6-K-Scale is derived from a validated scale for evaluation of neurogenic dysphagia [13]. In order to obtain a compact and easy applicable scale, we chose to evaluate six cranial nerves related to bulbar function which are known to be impaired in SBMA, comprising the assessment of the trigeminal (V CN), facial (VII CN), glossopharyngeal (IX CN), vagus (X CN), and hypoglossal nerve (XII CN). Moreover, movements related to the ansa cervicalis (XI CN-C1-C3 nerve roots) accounting for the neck's stabilization during swallowing were evaluated. Each nerve was assessed through a set of specific items, as summarized in Table 1. For each item of the scale, alternatives were designed to standardize the evaluation and to increase replicability of the test.

Each subscale relative to a CN is composed by several items aiming at the evaluation of specific motor and sensitive functions. For each subscale, a score is calculated. Summation of the single subscale scores gives a total final score which ranges from 0 to 61 (normal). The V and VII CN–related subscales contain four items, the IX CN–related subscale contains three items, the X CN–related subscale contains two items, and the XII CN–related subscale contains four items. The supplementary subscale dedicated to the function of the ansa cervicalis contains three items.

Scale's composition

Trigeminal nerve The V CN carries tactile sensations from the face and the oral cavity. Its motor efferent component innervates the muscles of mastication, the mylohyoid muscles, and the anterior bellies of the digastric muscles, which allows anterior elevation of the hyoid laryngeal complex during the swallowing reflex. Its afferent component collects the tactile sensory information of the anterior 2/3 of the tongue. To evaluate it, we created the following items: jaw opening against resistance, jaw lateralization, tactile sensitivity of the face, and tactile sensitivity of anterior portion of the tongue.

Facial nerve The VII CN innervates the facial muscles including the orbicularis oris and buccinator muscles, the posterior belly of the digastric and the stylohyoid muscles, and the submandibular and sublingual salivary glands. In addition, the sensory components of the VII CN convey taste sensations from the anterior two-thirds of the tongue and oral cavity. In addition, the contraction of the orbicularis oris and buccinator muscles prevents food/liquid spillage from the mouth. In the 6-K-scale, we evaluated the integrity of this nerve through the following tasks: eye closure, wrinkle eyebrows, smile, and kiss.

Table 1 Items composing the "6-K-scale": evaluation of single cranial nerves determining bulbar symptoms in SBMA

V-trigeminal nerve	Jaw open to resistance	Opening and strength are normal	3
		Opening is normal but strength is weak	2
		Opening is minimal and strength is absent	1
		Absence of jaw opening	0
	Jaw lateralization	Lateralization of both sides in normal	3
		Deficit of lateralization on one side	2
		Minimal lateralization attempts	1
		Absence of movement	0
	Tactile sensitivity of the face (eyebrows, cheeks, superior lips, inferior Lips)	Normal	3
		Mild reduction	2
		Moderate reduction	1
		Severe reduction	0
	Tactile sensitivity of 2/3 anterior portion of the tongue (right and left)	Normal reduction	3
		Mild reduction	2
		Moderate reduction	1
		Severe reduction	0
VII-facial nerve	Eye closure	Eye closure is possible on both sides	3
		One or both sides remain slightly open (less than ½ of eye-lid)	2
		One or both sides remain slightly open (more than ½ of eye-lid)	1
		Absence of eye closure	0
	Wrinkle eyebrows	Contraction is normal and symmetric	3
		Slightly asymmetric contraction	2
		Severe asymmetric contraction	1
		Absence of contraction	0
	Smile	Contraction is normal and symmetric	3
		Slightly asymmetric contraction	2
		Severe asymmetric contraction or slightly movements of the angles of the mouth	1
		Absence of contraction	0
	Kiss	Contraction is normal and symmetric	3
		Slightly asymmetric contraction	2
		Severe asymmetric contraction	1
		Absence of contraction	0
IX-glossopharyngeal nerve	Elevation of the soft palate	Contraction is normal and voice is not nasal	3
		Slightly weak contraction and/or nasal quality of speech	2
		Absence of contraction and/or hypernasality	1
	Tactile sensitivity of 1/3 posterior portion of the tongue (right and left)	Tactile sensitivity is present on both sides of the tongue	3
		Tactile sensitivity in reduced or is present only on one side of the tongue	2
		Absence of tactile sensitivity	1
	Gag reflex	Present	3
		Hypoactive	2
		Absence of reflex	1
X-vagus nerve	Voluntary cough	2 consecutive sound cough events	3
		1 consecutive sound cough event	2
		1 consecutive sound cough event and weak	1
		Absence of cough	0
	Vocal quality	No dysphonia	3
		Slight dysphonia	2
		Severe dysphonia	1
XII-hypoglossal nerve	Lingual protrusion	The patient protrudes 2/3 of the tongue out	3
		The patient protrudes 1/3 of the tongue out and/or there is slight lateralization of the tongue during protrusion	2
		The patient protrudes less than 1/3 of the tongue out and/or there is great lateralization of the tongue during protrusion	1
		Absence of protrusion	0
	Lingual lateralization	Lateralization in possible without difficulties at both sides of the mouth	3
		Lateralization is possible for one side of the mouth and is accomplished by using jaw movements	2
		Lateralization is limited at one or both sides of the mouth	1
		Absence of lateralization	0
	Sliding of the tongue	The movement is possible for the superior and inferior dental arch	3
		The movement is imprecise for the superior and inferior dental arch	2
		The movement is limited for one or both dental arches	1
		Absence of sliding of the tongue	0
	Click of tongue	The click is possible with sound	3
		The click is weak without the specific sound	2

Table 1 (continued)

		There is a hint of the click	1
		Absence of click	0
Ansa cervicalis (XI cranial nerve –C1–C3 spinal nerves)	Head control a) Up and down b) Rotation right–left c) Inclination right–left	The three movements (a, b, c) are possible without problems.	3
		2 out of the 3 movements are possible	2
		Only 1 movement is possible with difficulties in controlling head's position	1
		No head control	0

Glossopharyngeal nerve The IX CN supplies general sensation and taste from the posterior third of the tongue, soft palate, and pharynx and visceral sensation from the carotid body and sinus. The motor component of IX CN merges with the motor component of the X CN, forming the pharyngeal plexus. This was tested by the following items: elevation of soft palate, tactile sensitivity of the posterior third of the tongue, and gag reflex.

Vagus nerve The X CN carries visceral sensations from the lower pharynx, larynx, trachea, and esophagus. It is responsible for laryngeal adduction and for triggering cough, which prevent food/liquid inhalation into the airways. The vagus nerve was tested by the evaluation of voluntary cough, vocal quality, and wet voice.

Hypoglossal nerve The XII CN supplies the motor component of the intrinsic and extrinsic muscles of the tongue which are fundamental for the articulation of phonemes and for the preparatory phase of swallowing as well as for tongue's shaping and trophism. Tongue movements were assessed by these tasks: lingual protrusion, lingual elevation, lingual lateralization, sliding of the tongue, and click of the tongue.

Ansa cervicalis The ansa cervicalis is composed of fibers coming from the C1 and C3 nerve roots which do not belong to the cervical plexus. Together with fibers coming from the accessory nerve (XI CN), they are responsible of head position control during swallowing. We evaluated its function by the following items: head control up–down, rotation of the head right–left, and inclination of the head right–left.

Clinical variables

A neurologist blinded by the result of the 6-K-scale assessed clinical parameters.

The Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS) [14] was used to assess global functional status of the patients and its subscales were applied to describe the bulbar, limbs, truncal, and respiratory function.

Each patient underwent the 6-min-walk test (6MWT) [19] and Adult Myopathy Assessment Tool (AMAT) scale [17] as well. These two tests are retained to be reliable in the description of muscle deficit in SBMA, considering both the presence of weakness and fatigability of the muscle. In addition, pulmonary function was evaluated by measuring the forced vital capacity (FVC) as percentage of the predicted value. Patients' weight and BMI were collected as well.

Table 2 Clinical and functional scores (described as mean value ± standard deviation) and frequency of bulbar symptoms in the studied population

Parameter	Mean value (± st dev)	Range
Age at examination (years)	59 ± 10	42–80
Age at onset (years)	43 ± 11	20–71
Disease duration at evaluation (years)	17 ± 13	1–45
CAG repeat length	46 ± 3	40–55
SBMAFRS total score	44 ± 6	26–55
SBMAFRS bulbar score	16 ± 2	10–19
AMAT total score	27 ± 11	1–44
6MWT (meters)	244 ± 189	0–560
FVC%	98 ± 23	60–164
Weight (Kg)	79 ± 11	51–107
BMI	26 ± 3	17–33
Bulbar symptoms	Proportion	Percentage (%)
Laryngospasm	28/60	46%
Speech modifications	45/60	75%
Sialorrhea	21/60	35%
Dysphagia (self-reported)	32/60	53%

Table 3 Cronbach's alpha for the total "6-K-scale" and for its single items

	Raw Cronbach's alpha	Std Cronbach's alpha
Total score	0.85	0.87
V-NC subscale	0.83	0.88
Jaw open to resistance	0.84	0.88
Jaw lateralization	0.83	0.88
Tactile sensitivity of the face	0.84	0.88
Tactile sensitivity of 2/3 anterior portion of the tongue	0.84	0.88
VII-NC subscale	0.82	0.87
Eye closure	0.84	0.89
Wrinkle eyebrows	0.83	0.88
Smile	0.83	0.88
Kiss	0.83	0.88
IX-NC subscale	0.83	0.88
Elevation of the soft palate	0.83	0.88
Tactile sensitivity of 1/3 posterior portion of the tongue	0.84	0.87
Gag reflex	0.84	0.88
X-NC subscale	0.83	0.88
Voluntary cough	0.84	0.89
Vocal quality	0.83	0.88
XII-NC subscale	0.81	0.87
Lingual Protrusion	0.82	0.88
Lingual lateralization	0.83	0.88
Sliding tongue	0.83	0.87
Click of tongue	0.83	0.88
Cervical ansa subscale	0.84	0.89

The clinical protocol was repeated after 6 months in a subgroup of 31 patients.

Statistical analysis

Statistical analysis was performed using JMP13.

Descriptive statistics such as mean and standard deviation were used to summarize continuous quantitative measures, while percentage was used to describe ordinal variables. Normality was assessed using the Shapiro–Wilk test. Group comparisons of normally distributed variables were performed using the Student t test. The significance level was set at $p < 0.05$. In non-normally distributed data, the two-tailed unpaired Mann–Whitney U test was used at a significance level of 5%.

Validity of the scale was evaluated considering internal consistency as described by Cronbach's alpha.

Acceptability (distribution of the subscales and total score) and reliability of the scale (test–retest reliability) were applied. For test–retest reliability, Spearman's rank order correlation coefficient (Spearman's rho) was carried out on total score and subscore level. In addition, the percentage of perfect agreement was calculated to measure the level of agreement on item level.

To detect the structure in the relationships between items, factor analysis using principal component analysis with varimax rotation and an eigenvalue of 1 was performed.

Convergent validation was calculated by comparing the scores achieved in the items of the 6-K-scale with the corresponding ones of the SBMAFRS (where possible), with AMAT score, 6MWT, and with respiratory function using Spearman's rank order correlation coefficient.

Table 4 Spearman's rho for the "6-K-scale" subscales

	Spearman's rho
Total score	0.71
V NC subscale	0.70
VII NC subscale	0.74
IX NC subscale	0.80
X NC subscale	0.80
XII NC subscale	0.76
Cervical ansa subscale	0.69

Results

Study population

Sixty SBMA patients were considered in the study. Mean age of the patients was 59 ± 10 years (range 42–80). Mean age at onset was 43 ± 11 years (range 20–71) and mean disease duration was 17 ± 13 years (range 1–45). Seven patients out of 60 claimed bulbar onset of the symptoms (11%), while all other patients reported spinal onset. All patients reported the presence of bulbar symptoms at the moment of examination, mainly consisting of nasal speech or dysarthria and/or swallowing difficulties of variable degree. Forty-six percent of the patients reported laryngospasm episodes.

Mean total score of the 6-K-scale was 47 ± 5 (max score = 61). Clinical data and functional scores are reported in Table 2.

According to the scores obtained in the subscales for each cranial nerve, 36.6% of the patients showed an involvement of the V CN (22/60), 91.6% of the VII CN function (51/60), 58.3% (35/60) of the IX CN, 75% (45/60) of the X, and 58.3% (35/60) of the XII CN. We did not detect any alteration in the subscore relative to the cervical ansa subscale. Mean values for single subscales were the following: 11 ± 1 for V CN (maximal possible score = 12, 8.3% reduction), 9 ± 2 for VII CN (maximal possible score = 12, 25% reduction), 5 ± 1 for IX CN (maximal possible score = 6, 16.7% reduction), 7 ± 1 for X CN (maximal possible score = 9, 22.3% reduction), and 12 ± 3 for XII CN (max score possible = 15, 20% reduction). These results support the main involvement of the VII CN as a major contributor of bulbar symptoms in SBMA patients followed by the impairment of the X and IX CN.

Scale validation

Validity assessment

Internal validity of the scale was evaluated by Cronbach's alpha coefficient as shown in Table 3 and resulted adequate (total raw alpha 0.85; total standardized alpha 0.87). Cronbach's alpha for single items ranged between 0.81 and 0.89, confirming high internal consistency (Table 3).

Inter-rater reliability and test–retest reliability

Spearman's rank order correlation coefficients for test–retest reliability at baseline and after 3 weeks showed strong positive

Table 5 Factor analysis of the "6-K-scale"

Subscale	Component 1	Component 2	Component 3	Component 4	Component 5	Component 6
V NC subscale	0.51	0.09	0.72	−0.13	0.11	−0.03
Jaw open to resistance	0.28	0.12	0.51	−0.15	−0.01	0.29
Jaw lateralization	0.53	0.09	0.72	−0.13	0.11	−0.24
Tactile sensitivity of the face	0.06	0.03	0.85	0.26	0.00	−0.07
Tactile sensitivity of 2/3 anterior portion of the tongue	0.10	−0.09	0.71	0.02	−0.12	0.27
VII NC subscale	0.17	0.76	0.28	0.14	0.39	0.05
Eye closure	−0.14	0.11	0.64	0.12	0.04	−0.09
Wrinkle eyebrows	0.19	0.27	0.12	0.06	0.78	−0.19
Smile	0.18	0.68	0.12	0.06	0.78	−0.20
Kiss	0.14	0.75	0.22	0.17	0.09	0.11
IX NC subscale	0.18	0.23	0.19	0.80	0.20	0.27
Elevation of the soft palate	0.13	0.24	0.10	0.67	0.32	0.18
Tactile sensitivity of 1/3 posterior portion of the tongue	0.10	−0.02	0.04	−0.05	−0.07	0.82
Gag reflex	0.12	0.12	0.25	0.70	−0.07	−0.22
X NC subscale	0.10	0.79	−0.21	0.32	−0.23	−0.21
Voluntary cough	0.17	0.73	0.01	0.04	0.07	−0.10
Vocal quality	0.16	0.08	−0.21	0.66	−0.15	−0.13
XII NC subscale	0.95	0.15	0.09	0.16	−0.03	0.04
Lingual protrusion	0.81	0.00	0.13	0.09	−0.14	0.25
Lingual lateralization	0.78	0.22	0.28	0.24	−0.05	−0.08
Sliding tongue	0.89	0.07	−0.04	−0.00	0.04	0.21
Click of tongue	0.73	0.20	−0.04	0.15	0.05	−0.17
Cervical ansa subscale	−0.10	−0.04	−0.11	0.02	0.66	0.01
Variance explained by each factor	21.2%	36.7%	49.3%	59.2%	66.0%	71.7%

Table 6 Convergence analysis' correlations of the "6-K-scale"

	Age (years)	Disease duration (ys)	Weight (Kg)	6MWT (meters)	AMAT score	SBMAFRS total score	SBMAFRS bulbar subscore	SBMAFRS upper limbs subscore	SBMAFRS trunk subscore	SBMAFRS lower limbs subscore	SBMAFRS respiratory subscore	FVC%
Total CN scale	$r = -0.41$	$r = -0.20$	$r = 0.06$	$r = 0.36$	$r = 0.48$	$r = 0.58$	$r = 0.53$	$r = 0.26$	$r = 0.46$	$r = 0.40$	$r = 0.04$	$r = 0.34$
	$p = 0.01$	$p = 0.22$	$p = 0.68$	$p = 0.02$	$p = 0.01$	$p = 0.00$	$p = 0.02$	$p = 0.12$	$p = 0.02$	$p = 0.01$	$p = 0.70$	$p = 0.02$
V CN subscale	$r = 0.09$	$r = 0–13$	$r = -0.41$	$r = 0.20$	$r = 0.16$	$r = 0.24$	$r = 0.18$	$r = 0.23$	$r = 0.23$	$r = 0.15$	$r = 0.02$	$r = 0.11$
	$p = 0.56$	$p = 0.44$	$p = 0.01$	$p = 021$	$p = 0.32$	$p = 0.14$	$p = 0.27$	$p = 0.16$	$p = 16$	$p = 0.37$	$p = 0.63$	$p = 0.53$
VII CN subscale	$r = 0.34$	$r = -0.03$	$r = 0.20$	$r = 0.34$	$r = 0.40$	$r = 0.49$	$r = 0.36$	$r = 0.22$	$r = 0.47$	$r = 0.32$	$r = 0.10$	$r = 0.17$
	$p = 0.03$	$p = 0.85$	$p = 0.21$	$p = 0.03$	$p = 0.01$	$p = 0.00$	$p = 0.02$	$p = 0.17$	$p = 0.00$	$p = 0.03$	$p = 0.42$	$p = 0.53$
IX CN subscale	$r = -0.17$	$r = -0.04$	$r = -0.09$	$r = 0.19$	$r = 0.33$	$r = 0.32$	$r = 0.27$	$r = -0.03$	$r = 0.36$	$r = 0.12$	$r = 0.12$	$r = 0.43$
	$p = 0.29$	$p = 0.79$	$p = 0.58$	$p = 0.25$	$p = 0.03$	$p = 0.03$	$p = 0.10$	$p = 0.85$	$p = 0.02$	$p = 0.44$	$p = 0.37$	$p = 0.00$
X CN subscale	$r = -0.35$	$r = 0.10$	$r = -0.06$	$r = 0.16$	$r = 0.29$	$r = 0.38$	$r = 0.33$	$r = 0.23$	$r = 0.25$	$r = 0.26$	$r = 0.15$	$r = 0.16$
	$p = 0.02$	$p = 0.54$	$p = 0.67$	$p = 0.32$	$p = 0.07$	$p = 0.01$	$p = 0.03$	$p = 0.16$	$p = 0.12$	$p = 0.10$	$p = 0.30$	$p = 0.33$
XII CN subscale	$r = -0.22$	$r = -0.20$	$r = 0.01$	$r = 0.24$	$r = 0.31$	$r = 0.36$	$r = 0.39$	$r = 0.12$	$r = 0.24$	$r = 0.12$	$r = 0.04$	$r = 0.25$
	$p = 0.17$	$p = 0.07$	$p = 0.92$	$p = 0.14$	$p = 0.04$	$p = 0.02$	$p = 0.01$	$p = 0.45$	$p = 0.14$	$p = 0.10$	$p = 0.81$	$p = 0.14$
Cervical ansa subscale	$r = -0.14$	$r = 0.02$	$r = 0.01$	$r = -0.03$	$r = 0.03$	$r = 0.36$	$r = 0.09$	$r = -0.11$	$r = 0.13$	$r = 0.06$	$r = 0.12$	$r = 0.17$
	$p = 0.38$	$p = 0.85$	$p = 0.92$	$p = 0.85$	$p = 0.83$	$p = 0.02$	$p = 0.56$	$p = 0.49$	$p = 0.44$	$p = 0.68$	$p = 0.45$	$p = 0.32$

correlations which were statistically significant both for single subscores and for the total scale. Results are shown in Table 4.

Perfect agreement between test and retest on a subscale level showed high test–retest reliability (84% for the V CN–related subscale, 80% for the VII CN–related subscale, 83% for the IX CN–related subscale, 82% for X CN–related subscale, 86% for XII CN–related subscale, and 81% for the cervical ansa subscale). The perfect agreement between test and retest for the total score was 78%.

Factor analysis

Factor analysis of the 6-K-scale yielded a six-factor solution, which accounted for 71.7% of the variance. Such result describes the presence of six main domains building the structure of the scale, confirming the presence of six subscales constituting the final total score (Table 5).

Convergence analysis

Significant correlation as measured by Spearman's rho was demonstrated between the scale's total score and the 6MWT and with the total score and subscores of the SBMAFRS ($p < 0.05$). Significant correlations were found also between the total score and the AMAT value and with respiratory function expressed by FVC%. 6-K-scale's total score was not correlated with disease duration or with weight and BMI. Complete results and correlations for the single subscales are reported in Table 6.

No correlation was found between CAG's repeat size and CN involvement.

Longitudinal evaluation

Thirty-one patients underwent longitudinal evaluation after 6 months. No significant difference was found at the two time points for the 6MWT, the AMAT score, and the SBMAFRS scores ($p > 0.05$). We observed a significant decrease in the global score of the 6-K-scale ($p = 0.004$). A significant decrease was observed also in the subscore for the VII CN ($p = 0.031$), while no difference was found when considering longitudinal data between the baseline and the 6 months' evaluation for others CN.

Conclusions

In this study, we propose and validate a functional scale to assess bulbar functions in patients affected by SBMA. The scale has shown high internal consistency and validity, and its scores correlate with other recognized functional outcomes of the disease. Moreover, inter-rater and test–retest reliability is satisfactory, depicting good applicability of the scale in a clinical setting.

Bulbar evaluations proposed in the literature are often focused on neurogenic swallowing dysfunction [11–13, 20]. Nevertheless, bulbar involvement in SBMA patients is due to progressive degeneration of LMN in the whole brainstem and is characterized by global flaccid paralysis of muscles innervated by the V, VII, IX, X, and XII CN. Inherently, dysarthria is a frequent symptom (75% of the patients in our population) and is usually characterized by hypernasality related to incomplete soft palate elevation. Frequently, it is also associated with a decreased range of pitch and loudness of the voice [10]. Such symptoms can evolve in overt articulation's impairment with reduced intelligibility in the late stages of the disease. Similarly, LMN degeneration determines slowing of the oropharyngeal phase of swallowing associated with bilateral paralysis of the muscles of the pharynx and larynx with reduced pharyngeal peristalsis and elevated risk of inhalation and penetration of the bolus in the upper airways [9]. Degeneration of bulbar motor neurons in SBMA is responsible as well of impairment of tongue's movements, which are associated with tongue's fasciculation and atrophy [18, 21]. Facial weakness and asymmetry, head tremor [22], perioral fasciculation, acoustic impairment, and jaw drop related to masseter's muscle weakness are observed as well [23]. Moreover, laryngospasm has been described in a high percentage of patients (up to 47%) [24] and might be present at the onset of the disease [7] with variables severity, frequency, and duration. Its origin is not completely clear but it has been related to the presence of gastroesophageal reflux and to the dysfunction of the X CN [25]. Interestingly, in our study, we demonstrate altered function of the X CN in 58.5% of the patients, with a score's reduction of 22.3%. This could explain the high incidence of laryngospasm episodes in SBMA patients and open the way to more complete studies of this frequent but still not completely known phenomenon. We also demonstrate the presence of the relevant involvement of the VII CN, determining facial weakness and asymmetry, which are present in 75% of the patients. Facial weakness accounts for difficulties in bolus management in the oral cavity and in liquid assumption, which are the main components of dysphagia in SBMA. Finally, we identified a frequent involvement of the IX CN (75% of the patients), which is reasonably responsible for the presence of dysphonia in SBMA patients.

Altogether, we propose a scale for bulbar function evaluation which can be quickly applied in a routine clinical setting and allows identification of specific impairment of CN involved in SBMA. The results of our study sustain known bulbar presentation in SBMA and seem therefore to be a good detector of bulbar symptoms. Statistical validation of the scale demonstrates good applicability and internal reliability, while longitudinal evaluation evidences a significant decrease over time, suggesting it could be a good biomarker of disease progression. Further studies including comparison with instrumental examinations will also confirm efficacy of the 6-K-scale in the identification of dysphagia and in the selection of patients who could present higher risk of

inhalation and of aspiration pneumonia and as a longitudinal biomarker in upcoming clinical trials.

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Compliance with ethical standards

The ethics committees of the Azienda Ospedaliera of Padova and of the University of Padova (Italy) approved the study.

Conflict of interest The authors declare that they have no conflict of interest.

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