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Botulinum toxin alleviates dysphagia of patients with inclusion body myositis

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ABSTRACT

Objectives: Oropharyngeal dysphagia is a disabling and undertreated symptom that often occurs in patients with sporadic inclusion body myositis (s-IBM). In this study, we examined the effect of botulinum neurotoxin A (BoNT-A) injections to the cricopharyngeus muscle (CPM) of patients with s-IBM and dysphagia.
Patients, materials and methods: A single-center retrospective study involving 40 biopsy-proven s-IBM-patients treated in the District of Southwest Finland from 2000 to 2013. The incidence of dysphagia, rate of aspirations, rate of aspiration pneumonias and treatment results of dysphagia were analyzed. Patients treated for dysphagia were evaluated before and after surgery by video-fluoroscopy and/or using a questionnaire.
Results: Twenty-five of the 40 s-IBM patients (62.5%) experienced dysphagia. BoNT-A was injected a median of 2 times (range 1–7) in 12 patients with dysphagia. Before the injections 7 patients reported aspiration, none afterwards. The corresponding figures for aspiration pneumonia were 3 and 0. All of these patients had normal swallowing function 12 months (median, range 2–60) after the last injection.
Conclusion: BoNT-A injections to the CPM alleviate the dysphagia of s-IBM patients reversibly and appear to reduce the rate of aspiration effectively.

1. Introduction

Although sporadic inclusion body myositis (s-IBM) is a rare disease, it is the most common inflammatory myopathy in people over 50 years of age [1–2]. s-IBM has a male predominance and a reported overall prevalence of 1–71 per million inhabitants, depending upon the population, with a zenith of 139 per million inhabitants among people over 50 years [1–10]. The cause of s-IBM is unclear and it is refractory to immunosuppressive treatments [11–13].

Dysphagia is common among s-IBM patients: 40–86% of the patients report dysphagia [14–15]. The prevalence of dysphagia at least weekly in the healthy western population is 3% [16]. Presenting symptoms of s-IBM vary, sometimes dysphagia heralds the disease [12]. Dysphagia is probably underreported by the vast majority of s-IBM patients, because often experienced as an embarrassing symptom by the patients [17]. Nevertheless, dysphagia can be reliably diagnosed by asking the patient two simple questions: "Does food get stuck in your throat?" and "Do you have to swallow repeatedly to get rid of food?" [14,17–18]. There is no effective treatment to cure the disease, but there are various ways to alleviate the symptoms.

For decades, our department of otorhinolaryngology (ORL) has used cricopharyngeal myotomy and BoNT-A injections to treat cricopharyngeal dysphagia [19]. BoNT-A was introduced in 1989 by Schneider et al. [20] for patients with spasticity, hypertonia, or delayed relaxation of the upper esophageal sphincter (UES). In our experience, BoNT-A injections to the cricopharyngeus muscle (CPM) alleviate effectively the dysphagia symptoms, especially in s-IBM patients. Since there are only sparse case-studies reported on this treatment [21–25], we have summarized our promising results in this report.

2. Patients, materials and methods

The Ethics Committee of the Hospital District of Southwest Finland approved the study. In order to record all s-IBM patients within the Hospital District of Southwest Finland for evaluation and treatment of dysphagia, s-IBM patients were identified by a computer search of the electronic patient records in the Hospital District of Southwest Finland. The search terms "inclusion body", "IBM" and "inclusion body myositis", as well as the ICD-10 codes M60.8, M60.9 and G72.4 were used and the run was made by the Auria Biobank of the University of Turku, Finland. All patient records of patients treated between January 1, 2000 and December 31, 2013, who came up with these words, parts of these words, or the ICD-10 diagnosis codes were analyzed. The charts of these patients were evaluated for incidence of dysphagia and aspiration as

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well as aspiration pneumonia. The patients treated for dysphagia with BoNT-A injections were analyzed as a subgroup.

IBM diagnosis was always confirmed with a muscle biopsy. The histological biopsy for the diagnosis of IBM was routinely taken from the vastus lateralis muscle (n = 37), and the muscle biopsy findings were compatible with IBM according to the Griggs' or ENMC criteria [26–27]. The histological features for the diagnosis of IBM have been reported earlier [18]. If the vastus lateralis muscle was too atrophic, other muscle, such as anterior tibial or deltoid muscle was used (n = 3).

The s-IBM patients were referred to the ORL department for evaluation of dysphagia. They were examined by videofluoroscopic swallow study (VFSS, n = 10) and by endoscopy (n = 12). The inclusion criteria for BoNT-A-injection were age 18 years or more, biopsy-proven s-IBM, dysphagia, and CPM dysfunction documented by a videofluoroscopic swallow study (VFSS) or a tight CPM verified by rigid endoscopy. The diagnostic criteria of cricopharyngeal muscle dysfunction (CPD) by VFSS vary somewhat in the literature and range from the presence of a horizontal bar at the level of the cricoid cartilage in the posterior aspect of the barium column [28–29] to a cricopharyngeal bar that obstructs ≥50% of the lumen throughout the swallow (which is said to indicate defective opening of the UES) [29–30]. We used the latter as a criterion for CPD by VFSS. For VFSS, the patients were positioned upright for a lateral and anteroposterior view. Thin liquid barium and barium paste were administered three times at each of three volumes—3, 5 and 10 mL—as tolerated by the patient. All studies were recorded digitally for later review by a radiologist and the presence and the level of CPD was recorded.

Information on dysphagia was obtained either from a Deglutition Handicap Index (DHI) questionnaire [31] before and after treatments (filled in by 5/12 patients receiving BoNT-A injections), or from patient interviews during routine out-patient control visits or patient charts, in cases were DHI questionnaires were not available. In addition, each patient receiving the BoNT-A injection, was interviewed by telephone approximately 3 months after each treatment by the same physician who had administered the BoNT-A. If the patient had not returned the DHI questionnaire, the same questions or at least the two most important questions were asked verbally: “Does food get stuck in your throat” and “Do you have to swallow repeatedly in order to get rid of food” [14,17–18]. In addition, the patient was invited to contact the treating physician again when the symptoms of dysphagia returned and the patient had to change the diet from solid to liquid. To avoid unnecessary radiation burden, VFSS studies were repeated postoperatively only if the dysphagia persisted.

2.1. Botulinum toxin A (BoNT-A) injection

BoNT-A was obtained from Botox (onabotulinumtoxin-A, Botox/Vistabel, Allergan Inc., Irvine, CA, USA) as a freeze-dried lyophilized preparation. For clinical use, BoNT-A activity is defined in units, 1 unit representing the estimated median lethal dose for mice. Shortly before use, the 100 IU BoNT-A toxin was dissolved with 2 mL of 0.9% sterile saline solution (without preservative), then drawn into a 1 mL syringe with a dose equivalent to 50 IU/mL. Under general anesthesia and direct laryngoscopic guidance, the bulk of the cricopharyngeal muscle was identified dorsally (Fig. 1). The needle used for the BoNT-A injection is manipulated through a rigid endoscope (usually 300 × 12 × 16 mm in size). To avoid too superficial injection, a length of 20 mm of the tip of the needle was inserted in the cricopharyngeus muscle. If the injection is not intramuscular, BoNT-A may spread too widely, causing diffusion into adjacent pharyngeal musculature. If this happens, hoarseness or swallowing problems may ensue [32]. Botulinum toxin 0.4–0.5 mL, containing an equivalent dose of 20–25 IU of Botox per site, was injected into the left and right lateral sides and sometimes into the dorsomedial part of the muscle at an average total dose of 50 IU (Table 1, Figs. 1–3) [21].

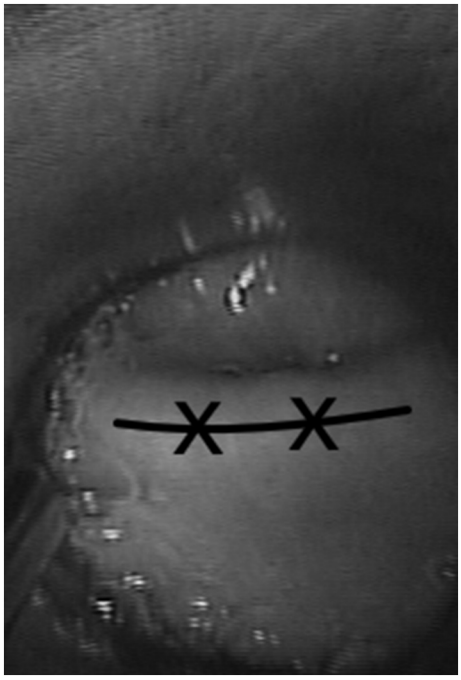

Fig. 1. Tight cricopharyngeus muscle (black curved line) seen through a rigid esophagoscope. The typical points of BoNT-A injection (black crosses) on the cricopharyngeus muscle.

3. Statistical methods

Data are expressed as mean and standard deviation, or median and range. The data was analyzed using the non-parametric Mann–Whitney *U* test because the variables were not normally divided. Values of $p < 0.05$ were considered statistically significant and are reported for the correlations; exact *p* values are reported unless $p < 0.001$. All analyses were conducted in IBM SPSS v. 23.0 software.

Table 1
The effect of botulinum toxin in the treatment of dysphagia in sporadic inclusion body myositis patients. The duration of time in months of the patient satisfaction to the dysphagia treatment was analyzed from the patient charts.

Gender	Age (years)	Aspiration pre	Dose (IU)	Aspiration post	Duration (months)
M	88	yes	50	no	8
F	83	yes	50	no	3
M	82	no	50	no	14
M	84	yes	50	no	8
F	75	no	50	no	6
F	76	yes	50	no	60
M	79	yes*	45	no	12
F	85	yes*	60	no	12
F	76	yes	50	no	12
F	89	no	50	no	14
F	93	no	40	no	2
M	99	yes*	55	no	6
Mean	84		50		14
Median	82		50		12
SD	7		5		15

M = male; F = female; aspiration pre = reported aspiration before Botox injection; yes = patient-reported aspiration; yes* = aspiration pneumonia reported/recorded in medical records; dose (IU) = the amount of botulinum toxin A (Botox, IU) injected to the cricopharyngeus muscle; aspiration post = reported aspiration after Botox injection; duration (months) = the number of months the patient was satisfied with the treatment of dysphagia; SD = standard deviation.

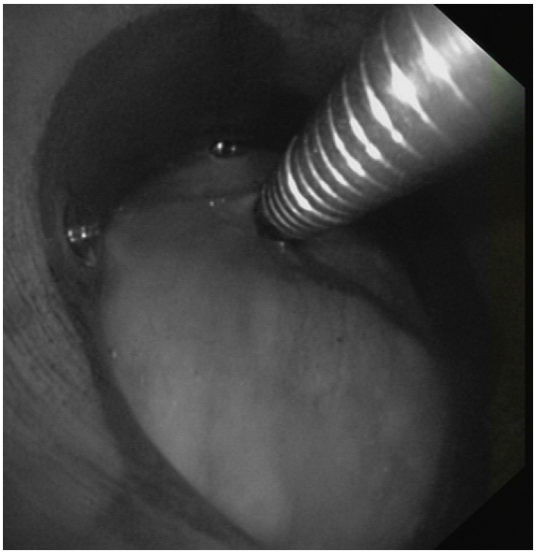

Fig. 2. Botox is injected into the cricopharyngeus muscle with a needle. We use the Karl Storz 10436 Transbronchial Aspiration Biopsy Needle 1.6 mm × 47 cm, Storz®, with a 20 mm needle at the tip of the device.

4. Results

The initial search in the patient data registry of the hospital district resulted in 229 patients, 40 of whom were found to fulfill the diagnostic criteria for s-IBM [33] and all of whom attended for a visit for evaluation at the neurological clinic. Twenty-five of the 40 patients (62.5%) had dysphagia. Overall, the majority (62.5%) of the patients was male, but there was a slight female preponderance (52%) of patients with dysphagia, but this difference was not statistically significant. Age at diagnosis of s-IBM was 68.0 years (median 69, range 43–87) and the mean duration of symptoms was 91.6 months (median 90, range 12–300). The patients with dysphagia were on average older than the patients without dysphagia (80.3 and 74.1 years, respectively; $p = 0.04$) and the patients with dysphagia had had IBM-related neurological symptoms significantly longer than the patients without dysphagia (146.9 vs. 74.4 months, $p = 0.02$). Preoperative BMI-values were similar between groups. Information on postoperative BMI-values was not available from the patient charts (Table 2).

Twelve patients were treated for dysphagia with cricopharyngeal BoNT-A-injections at the ORL department. The median number of injections was 2 (range 1–7). No complications were recorded. Each one of the 12 patients (100%) treated with BoNT-A experienced a better swallowing function postoperatively (Fig. 4), based on VFSS (5 patients), questionnaire (5 patients), or interviews. Patients were interviewed by telephone approximately 3 months after each treatment by the same physician who had administered the BoNT-A. All patients reported subjective improvement in oral feeding at the three-month interview. The median duration of the effect was 12 months (range 2–60). Before the treatments seven patients (58%) had experienced aspiration and three had had frank aspiration pneumonias (25%). After the BoNT-A treatments, none of the patients experienced aspiration or aspiration pneumonias for at least six months (Table 1).

Fifteen of the 25 patients with dysphagia were referred to the ORL clinic. Ten of these 15 patients underwent VFSS demonstrating an obvious CPD, i.e., either obstruction to thick or solid barium at the UES or a cricopharyngeal bar that obstructs 50% or more of the lumen throughout the swallow, and were thus treated with BoNT-A injection to the CPM. Another two patients with the anamnesis of dysphagia and clinical finding of CPD at endoscopy, were also treated with BoNT-A. The remaining three patients, who underwent endoscopy in the ORL clinic, did not fill the inclusion criteria for BoNT-A injection. One of these patients had normal findings at endoscopy, whereas one had scar formation of the CPM probably from prior surgical myotomy more than a decade earlier, and the third one declined endoscopy despite CPD at VFSS (Table 3).

Although only 12/40 of the s-IBM patients (30%) were treated with cricopharyngeal BoNT-A-injection, we were retrospectively able to identify dysphagia in as many as 25 of the 40 s-IBM patients (62.5%). Ten s-IBM patients with dysphagia were never referred to the clinic of otorhinolaryngology for assessment (Table 4). Three of these s-IBM patients with dysphagia were evaluated in another clinic with fiberoptic esophagoscopy or clinical examination. One patient was diagnosed with a Schatzki ring in the lower third of the esophagus. The second patient underwent fiberoptic esophagoscopy and percutaneous gastrostomy (PEG) in another clinic due to repeated aspiration pneumonias. He had had a tight upper esophageal sphincter through which the endoscope passed with a snapping sound. Fiberoptic esophagoscopy may not allow proper visualization of the CPM [34]. The third patient had also repeated pneumonias, but was not referred for endoscopy evaluation because of a stroke. Further seven s-IBM patients with dysphagia were found in the retrospective analysis, which were never treated for dysphagia.

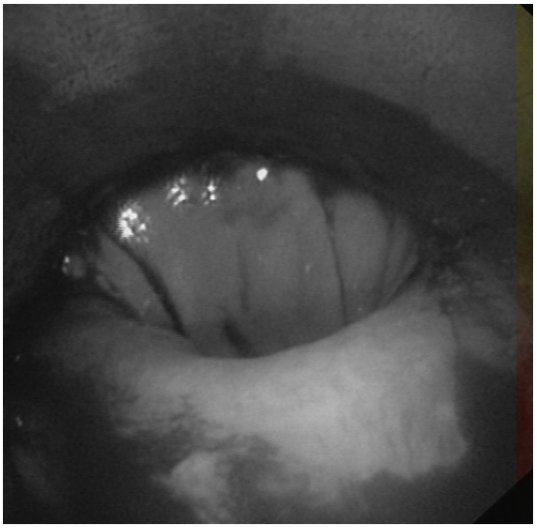

Fig. 3. Cricopharyngeus muscle immediately after Botox-injection. A few minutes after the injection a 12 × 16 mm rigid esophagoscope is usually easily forwarded through the upper esophageal sphincter.

Table 2
Characteristics of sporadic inclusion body myositis patients with and without dysphagia.

	With dysphagia	Without-dysphagia	*p*
	(n = 25)	(n = 15)	
Male/female	13/12	12/3	
Age (years)	80.4 (8.3)	74.1 (10.3)	0.04[a]
Weight (kg)	72.2 (18.6)	80.7 (15.8)	0.17
Height (m)	1.70 (0.8)	1.75 (0.08)	0.10
BMI (kg/m^2)	24.7 (5.9)	26.4 (3.8)	0.38
Age at dg (IBM)	68.1 (7.3)	67.9 (10.1)	0.93
Duration of neurological symptoms (months)	146.9 (72.4)	74.4 (57.2)	0.002[a]
Smoking (yes/no)	2/25	2/15	0.66
Reflux (yes/no)	11/25	5/15	0.52
Aspiration (yes/no)	11/25	0/15	0.14

Data are given as means (standard deviations). BMI = body mass index; IBM = inclusion body myositis.
[a] Statistically significant.

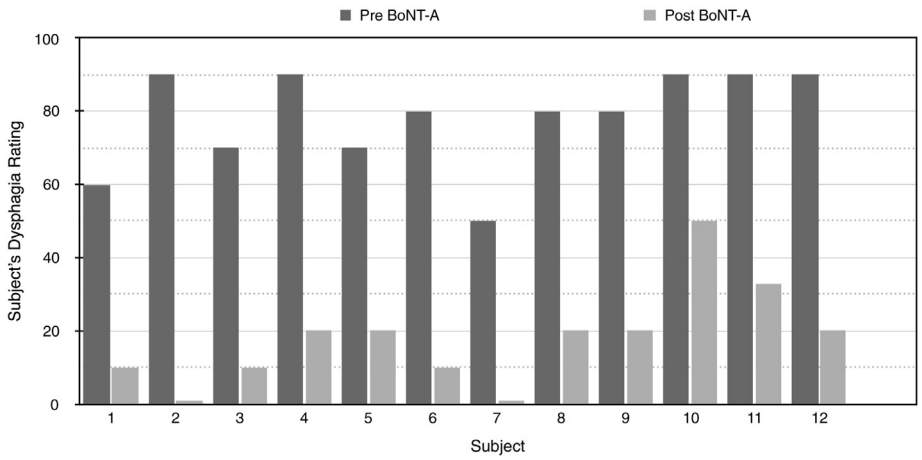

Fig. 4. Pre- and postinjection ratings of dysphagia severity with a scale from 1 to 100, where 100 stands for total obstruction and 1 stands for normal swallowing and no visible signs of obstruction (dark grey = preinjection, light grey = postinjection).

5. Discussion

The reported prevalence of s-IBM in Finland in 1996 was 0.9 per million population [4]. The catchment area of the Hospital District of Southwest Finland is approximately 470.000 residents. We found 40 patients with s-IBM, which yields a prevalence of 8.5 patients per million population a decade later. Needham et al. reported also an increase in the prevalence of s-IBM in Western Australia from 2000 to 2007. This increase was interpreted as probably being due to improved referral and diagnosis [1]. Prevalence figures vary by country and time, and this might be due to circumstances like referral patterns in different countries, lack of patient awareness that the symptoms could be related to s-IBM rather, than "normal aging", and difficulties in taking and interpreting muscle biopsies, especially in the early phase of the disease [1].

A male preponderance was found in s-IBM patients (25 out of 40, 62.5%), which is in line with the previous data presented in the literature [16–25,28]. The incidence of dysphagia in s-IBM patients was, however, slightly higher among female patients (10 out of 25, 52%), which is also in line with previous studies. In our cohort, all 12 patients with s-IBM and dysphagia experienced long-lasting (median 12 months, range 2–60) benefit from BoNT-A injection to the CPM. This is a surprising result, as typically the effect of BoNT-A wears off in three months. We cannot entirely explain the observed long-lasting effect in this particular indication, but similarly long-lasting results have been described by Shaw et al. [32]. We can only hypothesize that the long duration of the effect might be associated with the primary nature of the disease. The IBM patients suffer from widespread muscle pathology, and a plausible explanation for a botulinum toxin-responsive cricothyroideus dysfunction might be a compensatory overactivity of this muscle leading to secondary dysphagia (despite of no indication of any other muscle overactivity). Due to the primary muscle weakness, the botulinum toxin effect might then be longer than expected. Liu et al. reported two IBM patients who experienced beneficial effects on dysphagia with durations of 6.4 and 8 months [25]. Oh et al. reported two IBM patients for whom botulinum toxin injection to the UES was ineffective, but the doses and the injection technique were not reported [21].

An important observation in our study was that dysphagia was either ignored or not recognized and therefore not treated in seven of the 25 s-IBM patients (28%) who did report dysphagia. In three of the 25 patients who reported dysphagia, only fiberoptic esophagoscopy was carried out in another clinic, which may not be sufficient for examination of the cricopharyngeal or upper esophageal sphincter. Another three patients underwent rigid esophagoscopy without an indication to BoNT-A treatment. Altogether ten patients with dysphagia not referred to our clinic might have benefited from BoNT-A-injections.

Patients with cricopharyngeal dysphagia have been treated with a range of methods and variable results [35–43]. In our cohort, all s-IBM patients treated with BoNT-A benefited from the treatment, although re-injections were needed. However, after multiple BoNT-A injections the duration of the effect appears to be shorter, which could be caused by weakening of the pharyngeal muscles [39], or fibrosis or scarring of the CPM due to multiple interventions [40]. Myotomy can always be recommended to patients experiencing good alleviation of dysphagia symptoms by botulinum toxin injections.

The effect of cricopharyngeal relaxation becomes apparent almost immediately after the injection of BoNT-A, and has been documented by electromyographic studies by Shaw et al. [32] and manometric studies by Schneider et al. [41]. After the injection, a 300 × 12 × 16 mm rigid esophagoscope is usually easily passed through the cricopharyngeal sphincter, which is impossible before the injection. This effect of relaxation is not evident after a saline injection (our unpublished observation).

Table 3
Videofluoroscopic studies (VFSS) and endoscopy results of the 12 s-IBM patients with dysphagia. All patients with cricopharyngeal dysfunction (CPD) underwent endoscopy and administration of botulinum toxin A by injection (BoNT-A) to the cricopharyngeus muscle.

Case	Age (years)	Gender	VFSS Obst Pre/Post	VFSS Aspir	Endoscopy	BoNT-A
1	88	M	60	yes	yes/CPD	yes
2	83	F	90/0	yes	yes/CPD	yes
3	82	M	70	no	yes/CPD	yes
4	84	M	n/a	n/a	yes/CPD	yes
5	75	F	70	no	yes/CPD	yes
6	76	F	80	no*	yes/CPD	yes
7	79	M	50/0	no*	yes/CPD	yes
8	85	F	80/20	yes	yes/CPD	yes
9	76	F	n/a	n/a	yes/CPD	yes
10	89	F	90/50	yes	yes/CPD	yes
11	93	F	90/33	no	yes/CPD	yes
12	99	M	90	yes	yes/CPD	yes

M = male; F = female; VFSS Obst Pre/Post = severity of cricopharyngeal obstruction i.e. % of cricopharyngeal bar from the maximal diameter of the totally relaxed upper esophageal sphincter in VFSS prior to any procedures, and after the procedure where applicable; no* = no aspiration seen by VFSS, but had a history of aspiration and aspiration pneumonias; CPD = cricopharyngeal dysfunction; BoNT-A = botulinum toxin A injection to the cricopharyngeus muscle; n/a = data not availabale.

Table 4
The varying treatment of dysphagia in s-IBM patients.

	N	(%)
s-IBM	40	(100)
Females	15	(37.5)
Males	25	(62.5)
Dysphagia	25	(62.5)
Females	13	(32.5)
Males	12	(30)
Treatment of dysphagia		
ORL	15	(37.5)
BoNT-A	12	(30)
Other[a]	3	(7.5)
Treated elsewhere	3	(7.5)
No treatment	7	(17.5)

s-IBM = sporadic inclusion body myositis; ORL = department of otorhinolaryngology; BoNT-A = botulinum neurotoxin A injection to the cricopharyngeus muscle.
[a] BoNT-A injection not indicated.

The dosage of BoNT in previous studies has varied remarkably with Botox (4–100 IU) as well as with Dysport (2.5–360 IU) [21,42]. Clearly, a randomized, double-blinded dose-finding study of botulinum toxin injections for cricopharyngeal dysphagia is in order for s-IBM patients. We administered an average dose of Botox of 50 IU in one session; clinically this has proved to be effective. Similar doses have successfully been used by Shaw et al. with long-lasting results [32]. The physician doing the injections administered between 40 and 60 IU depending on subjective evaluation related to the severity of the symptoms and the size of the bulk of the visible cricopharyngeal muscle at rigid endoscopy.

Surgical CP myotomy is usually an effective, albeit non-reversible method to treat CP dysphagia, while BoNT-A-injection treatment is a reversible procedure. Thus, a step-wise protocol of treating patients with dysphagia with less terminal procedures, such as BoNT-A-injection, should be considered for primary treatment. However, although BoNT-A injection is a simple procedure in experienced hands, there have been reports of complications usually secondary to diffusion of botulinum toxin to the adjacent proximal pharynx [32]. In our experience, s-IBM patients react to BoNT-A injections to the CPM particularly well, and hence we have chosen to treat these patients repeatedly with BoNT-A [38,42–43].

Our study is limited in that it was not placebo-controlled. This precludes an in-depth discussion of the true benefits of this procedure. Patient selection was not prospective and therefore the results in our cohort may not be generalized to the s-IBM population as a whole. The addition of postoperative weight, if available, could have possibly brought important information about the nutrition changes after BoNT-A injection. Selection bias is possible, since only 12/25 of s-IBM patients were treated with BoNT-A. Still, the size of our patient cohort is the largest thus far published and provides valuable clues to the clinical management of dysphagia in patients with IBM.

6. Conclusion

Our study demonstrates that although s-IBM is incurable, some of the invalidating symptoms associated with the disease can be treated with good results. BoNT-A-injections to the cricopharyngeus muscle are in experienced hands an effective, safe, and rather simple procedure for the treatment of s-IBM patients with CPM-related dysphagia. Physicians caring for s-IBM patients must remember to proactively ask the s-IBM patients for symptoms of dysphagia, since this symptom is clearly under-reported. BoNT-A may prove to be an effective treatment for the cases where CPD is a contributing factor to dysphagia. A randomized prospective study is warranted to clarify the usefulness of this treatment.

Conflict of interest and funding

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