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Original Article

Retrograde Cricopharyngeus Dysfunction, a New Motility Disorder: Single Center Case Series and Treatment Results

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Background/Aims
Retrograde cricopharyngeus dysfunction (R-CPD) is a new clinical entity characterized by inability to belch and associated symptoms of loud gurgling noises, chest and/or abdominal pressure, abdominal bloating, and excessive flatulence. R-CPD can be treated with botulinum toxin (BT) injection in the upper esophageal sphincter. We hereby report patient demographics, symptomatology, and treatment results of a series of consecutive patients who presented at our center.

Methods
Data on 50 consecutive patients presenting with R-CPD were prospectively collected using a standardized questionnaire prior to, 1 month after treatment and at the end of follow-up. All patients were diagnosed using a set of clinical symptoms.

Results
Fifty patients (26 females) were included, median age was 27.5 years (range, 17-65). Median body mass index was 22.7 kg/m^2 (range, 16.6-37.5). Inability to belch was present in all patients, > 90% of patients experienced gurgling noises and abdominal/chest discomfort as result of their condition. One month after injection of BT, 40.8% of patients experienced complete relief of symptoms, 24.5% good symptom improvement, 24.5% some symptom improvement and 10.2% no improvement. At median follow-up of 29 months (range, 3-50) post-treatment, 51.3% (n = 20/39) of patients reported persistent complete relief of symptoms, 12.8% good improvement of symptoms (n = 5/39), in 15.4% some improvement (6/39) and 20.5% loss of or no response (n = 8/39). Only minor and transient side effects were reported.

Conclusions
Our case series of 50 patients with R-CPD shows very good short-term and good long-term improvement of symptoms after injection of BT. These results are in line with previous studies.
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Key Words
Botulinum toxins; Esophageal sphincter, upper; Manometry

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Introduction

Recently, a new clinical entity of retrograde cricopharyngeus dysfunction (R-CPD) is described by Bastian and Smithson.[1] Patients with this syndrome, also called inability to belch, typically present with symptoms of bloating, abdominal and retrosternal or chest pain/discomfort, gurgling noise in the chest, and excessive flatulence.[2] It is hypothesized that dysfunction of the cricopharyngeus muscle, which functions as upper esophageal sphincter (UES), leads to failure to evacuate air through the upper sphincter. The cricopharyngeus muscle is usually in a state of contraction and only relaxes after swallowing to allow passage of food down or during belching/burping when a high pressure builds up below the UES.[2] The belching reflex induces relaxation of the UES to allow an adequate belch.[3,4] According to Bastian and Smithson, R-CPD is a clinical diagnosis that can be validated by relief of symptoms after botulinum toxin (BT) injection.[1]

As only 3 case series have been reported, the condition and results of the treatment are poorly understood.[2,5,6] We hereby report a prospectively collected consecutive case series involving 50 patients who presented at a single center with a clinical syndrome of R-CPD/inability to burp. Our aim is to report patient demographics, symptomatology, and short- and long-term post-treatment results of BT in patients presenting with R-CPD.

Materials and Methods

Patients

Data on a series of consecutive patients diagnosed with R-CPD based on typical symptoms and treated with BT were prospectively collected (from August 2018 until January 2023). The setting of this study was a referral laryngology practice. Most patients were self-referred (after diagnosing themselves) through an internet post (n = 33). Diagnosis was confirmed in all patients using the clinical symptoms proposed by Bastian and Smithson.[1] All patients were screened in the outpatient clinic of gastroenterology and otolaryngology to rule out alternative diagnoses. All patients filled out a questionnaire including patient characteristics and symptoms at baseline. One month after treatment and at longer term follow-up questionnaires were sent by e-mail to collect information on the short-term and long-term outcome of the procedure.

Procedure

All BT injection procedures were performed under general anesthesia in ambulatory settings. Initially, the injection technique consisted of injection of an equal dose (37.5 units of BT dissolved in 1.5 mL NaCl 0.9%) of BT bilaterally posterior in the cricopharyngeus muscle (superficial and deep) by rigid upper esophagoscopy by the laryngologist. After the first 25 patients the technique was adapted to a combined technique of bilateral superficial BT injection (2 injections of 18.75 units BT each dissolved in 0.75 mL NaCl 0.9%) by flexible upper endoscopy and bilateral deep injection (2 injections of 18.75 units BT each dissolved in 0.75 mL NaCl 0.9%) by rigid upper esophagoscopy using a rigid direct laryngoscope (8661 CN; Karl Storz, Tuttlingen, Germany) or Hollinger-Weerda rigid laryngoscope (12068A; Karl Storz) in cases with difficult exposure of the cricopharyngeal muscle bar. The total dose of BT in all patients was 75 units or 100 units (in case of failure or loss of response after the first procedure). The manufacturer of the BT vials was Abbvie Inc (Chicago, IL, USA).

Some patients were referred for a standard high-resolution impedance esophageal manometry (HRIM) to detect underlying motility disorders. At the time of treating these patients, there were no data regarding HRIM in patients with R-CPD. Later, the protocol was modified to include 200 mL (or until symptoms were provoked) of sparkling water at the end of the standard manometry. The impedance manometry responses to the sparkling water was analyzed qualitatively.

Statistical Methods

Descriptive statistics were used to report on demographic features and results.

Ethics

All patients gave consent to collect their data. This retrospective study was approved by the Ethical committee (EC number B1172023000018).

Results

Patient Demographics

Our population consisted of 50 patients, of which 24 (48.0%) were male and 26 (52.0%) were female (Table 1). Median age at diagnosis was 27.5 years (range, 17-65 years) (Fig. 1). Twenty-nine patients (58.0%) were younger than 10 years old at onset of symp-

Table 1. Patient Demographics

	All patients	Male patients	Female patients
Number of patients (n)	50	24	26
Age category at onset of symptoms (n)			
< 10 years old	29	13	16
10-19 years old	10	65	4
20-29 years old	7	3	4
30-39 years old	3	1	2
> 40 years old	0	0	0
Missing	1	1	0
Age at diagnosis (yr)			
Median	27.5	27.0	28.5
Minimum	17.0	20.0	17.0
Maximum	65.0	44.0	65.0
Age category at diagnosis (n)			
< 20 years old	1	0	1
20-29 years old	27	14	13
30-39 years old	19	9	10
40-49 years old	2	1	1
> 50 years old	1	0	1
Self-referral/self-diagnosis through internet (n)	33	14	19
BMI at diagnosis (kg/m^2)			
Median (range, 16.6-37.5)	22.7	23.1	21.6
Medical history (n)			
No medical history	37	21	16
Intestinal atony	4	0	4
Connective tissue disease	3	2	1
Ehlers-Danlos syndrome	2	2	0
Marfan syndrome	1	0	1

BMI, body mass index.

toms, 10 patients between 10-19 years old, 7 patients between 20-29 years old, and 3 patients between 30-39 years old. Median body mass index (BMI) at diagnosis was 22.7 kg/m^2 (range, 16.6-37.5 kg/m^2). All patients reported inability to belch, 34 patients (68.0%) had never been able to belch (Table 2). Other typical symptoms such as gurgling noises (n = 49; 98.0%), abdominal/chest pain (n = 48; 96.0%), excessive flatulence (n = 45; 90.0%), and abdominal distension (n = 43; 86.0%) were present in most of the patients. Seventy-eight percent of the patients experienced an important feeling of social inhibition because of their symptomatology. Forty-one patients reported an unremarkable medical history, 3 patients were known with a connective tissue disorder (Ehlers-Danlos and Marfan syndrome), 3 patients with eczema, 1 patient with asthma, and 1 patient underwent obesity surgery (gastric sleeve). In this patient, symptomatology of R-CPD was already present prior to obesity surgery.

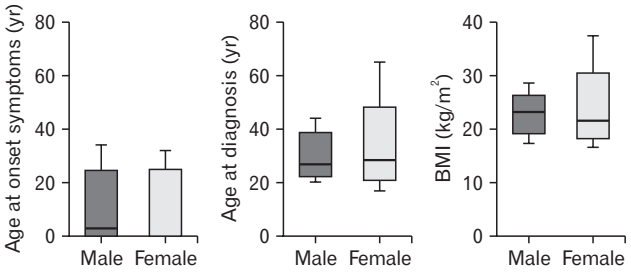

Figure 1. Patient demographics. BMI, body mass index.

Table 2. Patient Symptomatology

	Number of patients (n)	Percentage of all patients (%)
Inability to belch		
Inability to belch as long as can be recalled	29	58.0
Inability to belch since years	21	42.0
Gurgling noises, present	49	98.0
Abdominal/chest pain or discomfort, present	48	96.0
Abdominal bloating, present	43	86.0
Social inhibition, present	39	78.0
Excessive flatulence, present	45	90.0
Heartburn, present	25	50.0
Constipation, present	11	22.0

High-resolution Impedance Manometry Findings

Since HRIM was not systematically performed in all patients in this cohort, in patients with typical symptoms where HRIM was performed, and a belch provocation test was added to the protocol, qualitative analysis revealed characteristic abnormalities as previously described.[5,7,8] These include absence of UES relaxation upon gastro-esophageal gas reflux, air entrapment, and secondary peristalsis to clear the air from the esophagus. (Fig. 2 and 3).

Procedural Characteristics

In 42 patients (84.0%) the procedure was performed by the laryngologist in combination with the gastroenterologist. Total dose of BT injection was 75 units diluted in 3 mL NaCl 0.9%. Five patients experienced improvement that disappeared in time, in those patients a second procedure was performed with a median interval of 6 months. All those second procedures were combined procedures of the laryngologist and the gastroenterologist and the injected dose of BT was 100 units diluted in 3 mL NaCl 0.9%.

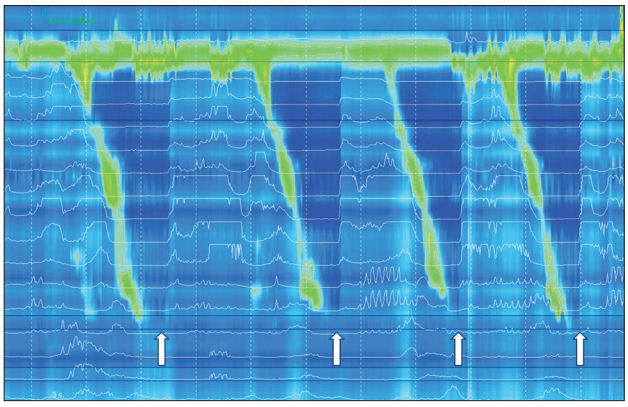

Figure 2. Retrograde cricopharyngeus dysfunction patient: gas reflux events (arrows) not triggering upper esophageal sphincter relaxation and followed by secondary peristalsis.

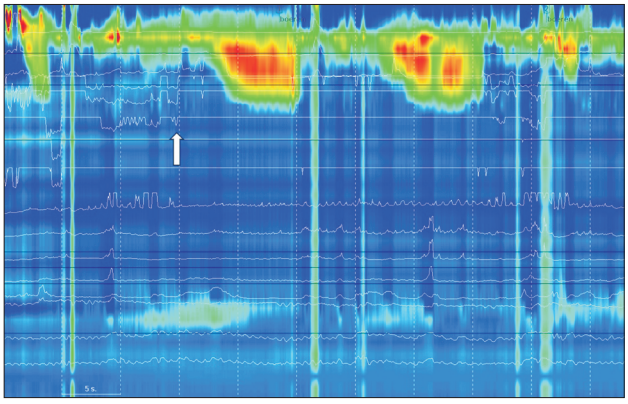

Figure 3. Retrograde cricopharyngeus dysfunction patient: increase in upper esophageal sphincter pressure upon arrival of air in the proximal esophagus, seen as a rise in impedance (arrow).

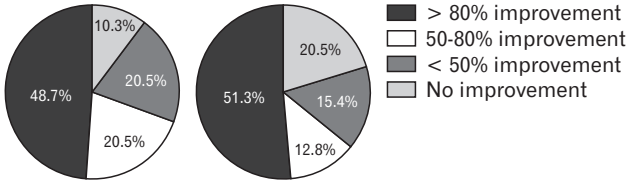

Figure 4. Global symptom improvement 1-month post-treatment and at median follow-up of 29 months after last botulinum toxin injection (n = 39 patients: 36 patients after first injection; 3 patients after second injection).

Post-treatment Results

One-month post-treatment, 40.8% (n = 20) of patients experienced complete relief of symptoms, 24.5% (n = 12) more than 50% symptom improvement, 24.5% (n = 12) less than 50% improvement, and 10.2% (n = 5) no improvement (Fig. 4 and Table 3). Twenty-four patients (48.0%) had temporary swallowing problems lasting from a few days to a few weeks, 11 patients (22.0%) had painful throat post-treatment lasting maximally 72 hours, 9 patients (18.0%) mentioned reflux. No major adverse events were

Table 3. Post-treatment Results (1 Month)

	Number of patients (n)	Percentage of patients (%)
Global symptom improvement (n = 49[a])		
80-100%	20	40.8
50-80%	12	24.5
< 50%	12	24.5
No improvement	5	10.2
Inability to belch (n = 45)		
Complete improvement	26	67.8
Partial improvement	8	17.8
Little improvement	9	20.0
No improvement	2	4.4
Gurgling noises (n = 45)		
Complete improvement	28	62.2
Partial improvement	10	22.2
Little improvement	4	8.9
No improvement	3	6.7
Chest/abdominal pain and discomfort (n = 45)	34	75.6
Complete improvement	7	15.6
Partial improvement	3	6.7
Little improvement	1	2.2
No improvement		
Abdominal bloating (n = 44)		
Complete improvement	27	61.4
Partial improvement	9	20.5
Little improvement	5	11.4
No improvement	3	6.8
Heartburn (n = 45)		
Complete improvement	28	62.2
Partial improvement	10	22.2
Little improvement	4	8.9
No improvement	3	6.7
Nausea (n = 45)		
Complete improvement	38	84.4
Partial improvement	4	8.9
Little improvement	2	4.4
No improvement	1	2.2
Duration to improvement (n = 43)		
< 24 hours	11	25.6
< 1 week	20	46.5
< 2 weeks	4	9.3
< 1 month	5	11.6
No improvement	3	7.0

[a]Not all patients answered all questions.

reported.

Thirty-nine patients had a minimum follow-up of 3 months. Long-term follow-up was collected at a median follow-up of 29 months (range, 3-50 months) after the last BT injection. At long-term follow-up 51.3% of those patients (n = 20/39) still experienced complete relief of symptoms, 12.8% (n = 5/39) more than 50% symptom improvement, 15.4% (n = 6/39) less than 50% improvement, and 20.5% (n = 8/39) no improvement (Fig. 4). All long-term responders had early response at well.

Five patients underwent a second procedure. Two patients experienced complete relief of symptoms after the second procedure, 2 other patients more than 50% symptom improvement, and 1 patient less than 50% symptom improvement.

Discussion

With this patient cohort we describe the presence of R-CPD in a European population and we show good results of BT injection. Hitherto only 3 case series have been reported describing the syndrome of R-CPD. More than 50% of patients in our cohort made an appointment in our clinic by self-referral/self-diagnosis through the internet (through an American social news site called "Reddit"). Most patients were experiencing symptoms for many years and without diagnosis despite several diagnostic tests including upper endoscopy, 24-hour pH/impedance monitoring and high-resolution esophageal manometry. With this report we hope to shift attention of primary care physicians, gastroenterologists, and laryngologists towards this entity. The entity of R-CPD is still insufficiently known among gastroenterologists where the patient will most likely present.

The patient population presenting with this syndrome has several unique characteristics. Interestingly, most of the patients report onset of symptomatology in their childhood and only 1 patient was older than 50 years at diagnosis. Karagama[2] reported similar findings of young age at diagnosis. A possible explanation could be the decline of sympathetic and parasympathetic responses with older age.[9] The cricopharyngeus muscle is supplied by the pharyngeal plexus of the vagus nerve and could lose some of its resting tone with age. Easier access to the internet (and Reddit) for younger people could also explain this young age at diagnosis. Median BMI was 22.7 kg/m^2, reflecting a patient group with only a few overweight patients. Oude Nijhuis et al[5] enrolled prospectively 8 patients with inability to belch, median BMI in this cohort was 26.0 kg/m^2. This normal BMI likely reflects a maintained nutritional status despite major symptomatology and social inhibition to go out for eating. Patients could adapt drinking habits by excluding gas-rich beverages. As this patient population is young at diagnosis, medical history is rather limited. However, 3 patients were known with a connective tissue disorder (Ehlers-Danlos and Marfan syndrome). Given the combined diagnosed prevalence of 1 patient with Ehlers-Danlos syndrome or hypermobility spectrum disorder in 500 people in a national cohort study in Wales, the prevalence of those connective tissue disorders in our R-CPD population is clearly higher.[10] Patients with hypermobility spectrum disorders may possibly look up more information about their disease on the internet and diagnose themselves easier with R-CPD. It is also known that patients with hypermobility spectrum disorders have higher occurrence of autonomic dysfunction.[11] Given the rather small patient population in this study, it is difficult to draw conclusions, however it remains a remarkable observation.

Our good short-term and long-term improvement of symptoms after injection of 75 units or 100 units of BT confirms earlier results reported by Karagama.[2] In that study, 72 patients had undergone injection of 100 units of botulinum toxin. All of them were able to burp again within 4 weeks, with persistent effect in 96% of patients after 3 months. Bastian et al[6] reported a total of 200 consecutive patients with R-CPD that underwent treatment by injecting 50 units or 75 units of BT. The dose of BT was increased by 25 units when performing a second injection, and 99.0% of patients experienced relief of cardinal symptoms and 79.9% experienced lasting relief of their symptoms. Our results are somewhat less favorable, but this may be partly due to a subjective interpretation of the patient as the results were collected through e-mail (and not during an on-site visit). BT inhibits release of acetylcholine in all parasympathetic and cholinergic postganglionic sympathetic neurons resulting in a decrease of cricopharyngeus muscle tone.[12] Typically, the effect of botulinum lasts for 8-12 weeks, however in our population 79.5% of patients still experienced improvement of symptoms at a median follow-up of 29 months. Bastian and Smithson[1] hypothesized that this may be the result of "retraining" of the cricopharyngeus muscle. Patients could be able to learn to belch again and maintain this maneuver. Recovery of cricopharyngeus muscle tone may be insufficient to hold back this trained maneuver.

A second procedure was performed in 5 patients (3 failures and 2 recurrence of symptoms). We were unable to find predictors for recurrence/failure of the BT injections. In an attempt to enhance the response we injected 100 units in those who underwent a second treatment. However it is unsure whether the increase of dose from 75 units to 100 units is of any benefit. Since all procedures were performed by the same physician (K.D.) the success rate cannot be

operator dependent.

In this population, BT was initially injected by rigid laryngoscopy and later in combination with flexible upper endoscopy to better target the UES and inject both superficial and deep. Temporary swallowing difficulty lasting maximally a few weeks was the most common reported side effect. Karagama[2] also described effortful swallowing during 1-2 weeks after the procedure in most of the patients. Other procedures such as electromyography-guided percutaneous injection have been described. Xie et al[13] performed electromyographic-guided injection preceded by insertion of a balloon catheter to optimize cricopharyngeus muscle visualization. All 18 patients undergoing this procedure gained the ability to burp with improvement of the associated symptoms. However, 7 patients experienced noisy breathing after this procedure, indicating the risk of laryngospasm after diffusion of BT in the posterior cricoarytenoid muscle, the adductor of the vocal folds.[14]

Functional dyspepsia is a more common functional gastrointestinal disorder with a prevalence of 7.2%.[15,16] Symptomatology of those patients includes epigastric pain or burning, early satiation, and postprandial fullness/bloating. Inability to belch and gurgling noises are not reported as symptoms in patients with functional dyspepsia. Since R-CPD can induce symptomatology of bloating and epigastric pain, it should be added to the differential diagnosis of functional dyspepsia.

In these 50 (consecutive) patients, diagnosis was made upon clinical symptoms suggested by Bastian and Smithson.[1] Although these good post-treatment results are in line with results of previous studies, the need for randomized sham-controlled therapeutic trials and objective diagnostic tests is obvious. Our study has some weaknesses: the analysis was done retrospectively but the data were collected prospectively. Hitherto, the diagnosis of R-CPD is based on symptoms only. Standard HRIM does not show abnormalities, but a provocation test with 200 mL of sparkling water can show oscillations, however this provocation test lacks normal values as it has not yet been standardized in healthy controls. Furthermore a repeat examination in cases of failure of treatment could potentially guide physicians on how to manage these patients. Oude Nijhuis et al[5] showed in 8 prospectively selected patients that basal UES pressure significantly lowered after BT injection and restored belching capacity in all patients. Further research using HRIM with belch provocation test is ongoing in our research group.

In conclusion, our case series of 50 patients with R-CPD shows good short-term and long-term results after BT injection. These results are in line with previous studies. However, we need randomized sham-controlled therapeutic trials and objective diagnostic tests.

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