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Retrograde cricopharyngeal dysfunction management with botulinum toxin A

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ABSTRACT

INTRODUCTION. Retrograde cricopharyngeal dysfunction (R-CPD) is the inability to belch due to impaired upper oesophageal sphincter relaxation. Botulinum toxin A injection shows promise, but standardised protocols are lacking. Objective: To evaluate the effect of botulinum toxin A for R-CPD in a Danish population.

METHODS. A retrospective case series study at Aarhus University Hospital included R-CPD patients treated from January 2021 to December 2024. The diagnosis was clinical, supported by otorhinolaryngological examination, modified barium swallow and oesophagoscopy. Under general anaesthesia, all patients received 50 IU of botulinum toxin A into the cricopharyngeal muscle. Symptom relief and adverse effects were assessed at follow-ups performed at two weeks and three months. Statistical analysis with Fisher's exact test compared treatment responses in patients aged 18-25 years versus those over 25 years.

RESULTS. Among 40 patients (22 males, 18 females, mean age 27.5 years), 35 experienced symptom relief within two weeks. Long-term follow-up (31 patients) showed that 18 continued to belch after three months. Thirteen patients required additional treatments with botulinum toxin A doses increased to 75-100 IU, 24 achieved satisfactory results, while nine await further procedures.

CONCLUSIONS. Botulinum toxin A is a safe, effective R-CPD treatment with minor side effects (transient dysphagia, mild sore throat, sour eructation) and no vocal fold or respiratory complications. Over half of the patients improved after 50 IU treatment, whereas one-third required dose escalation, suggesting that 100 IU may enhance outcomes.

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Retrograde cricopharyngeal dysfunction (R-CPD) is a relatively newly recognised disorder characterised by an inability to belch. Although the term 'R-CPD' was first formally introduced by Bastian et al. in 2019, case reports describing elements of this condition date back several decades [1, 2]. Patients with R-CPD typically present with a variety of symptoms, including abdominal bloating and discomfort, chest pain, socially disruptive gurgling noises, excessive flatulence, and, in some cases, difficulty vomiting [3]. These symptoms are considered to appear in adolescence or early adulthood and can impact quality of life considerably, leading to social inhibition, work-related difficulties and psychological distress [4].

The pathophysiology of R-CPD is not fully understood, but current evidence suggests that it results from failure of the cricopharyngeal muscle, the primary component of the upper oesophageal sphincter (UES), to relax in response to oesophageal gas reflux [1]. Unlike primary cricopharyngeal dysfunction, R-CPD patients exhibit normal deglutition, with dysfunction manifesting specifically in the context of oesophageal distension [5].

High-resolution pharyngeal manometry with impedance (HRPM-I) has been proposed as a diagnostic tool, showing absent or incomplete UES relaxation in response to oesophageal gas reflux [6]. However, R-CPD is

primarily a clinical diagnosis based on symptom recognition.

Treatment with botulinum toxin A injection into the cricopharyngeal muscle has emerged as an effective intervention, with most patients experiencing rapid symptom relief and restoration of the ability to belch. Early reports suggested that the effect of botulinum toxin A might extend beyond its pharmacological duration, potentially due to reconditioning of the belch reflex, as the afferent-efferent feedback to the brain initiates belching [1, 4]. While botulinum toxin A injection under general anaesthesia remains the most reported technique, recent studies have revealed alternative approaches, e.g., percutaneous botulinum toxin A injection under ultrasound or electromyographic guidance [7]. Partial cricopharyngeal myotomy has also been proposed as a treatment option for refractory cases [1].

Despite increasing awareness, R-CPD remains a new entity in clinical practice, and standardised diagnostic and treatment protocols are lacking. In this study, we present a series of cases from a Danish cohort, describing the demographic distribution, symptomatology and outcomes following botulinum toxin A injection under general anaesthesia. By consolidating current knowledge and contributing new clinical data, we aim to advance our understanding of R-CPD and inform future management strategies.

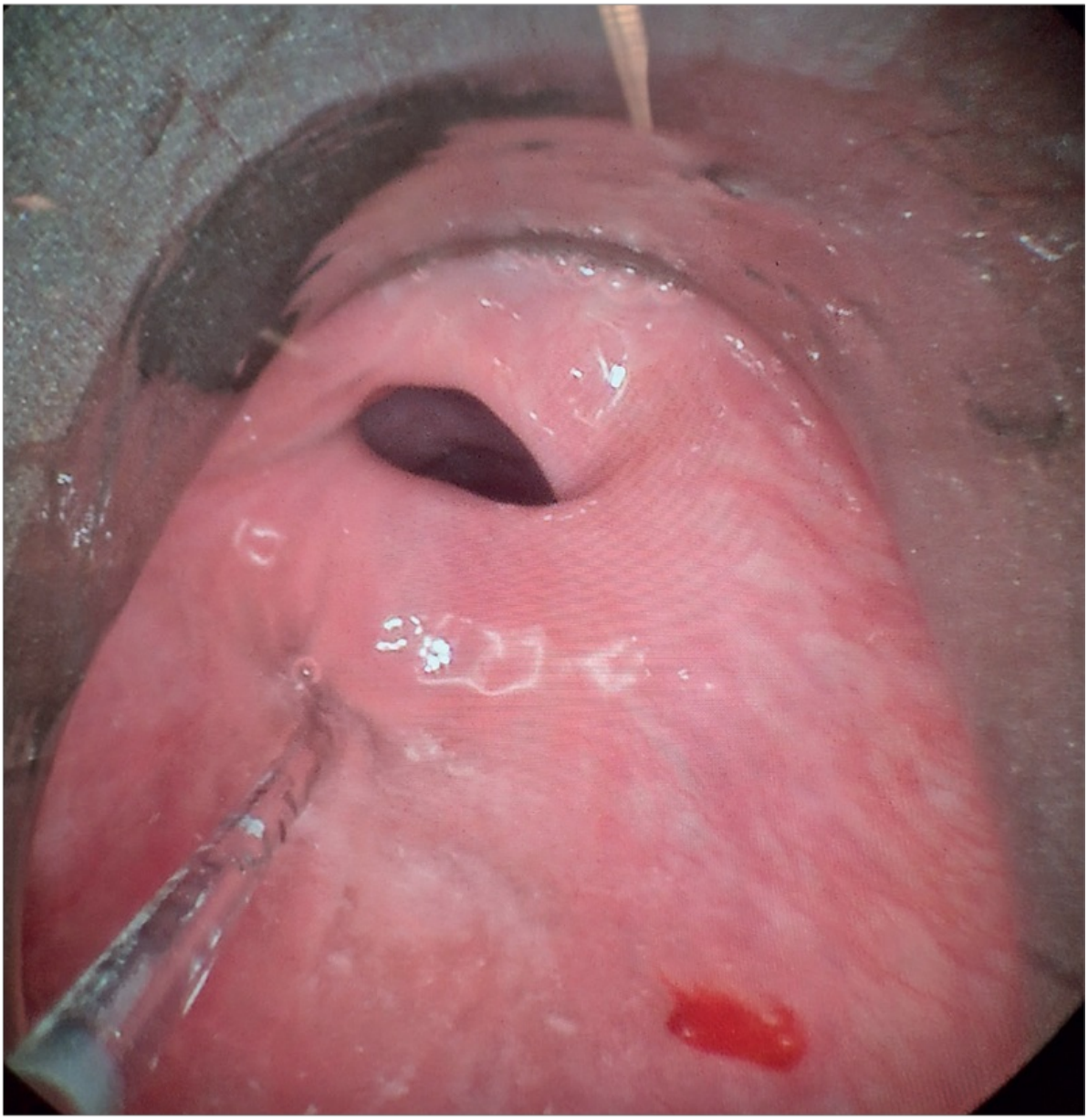
Methods

This was a retrospective qualitative case series study approved by the Quality and Education Department, Aarhus University Hospital, Denmark, and conducted at a single tertiary referral centre between 1 January 2021 and 31 December 2024. The study population consisted of patients diagnosed with R-CPD who underwent botulinum toxin A injection at our centre. Diagnosis was made clinically based on symptoms, including an inability to belch, bloating, gurgling noises, chest and abdominal discomfort and flatulence. In addition to the clinical presentation, all patients underwent a thorough otorhinolaryngological examination, fibreoptic laryngoscopy, modified barium swallow (MBS) and either a prior or newly performed oesophagoscopy to exclude other pathologies. Some patients underwent HRPM-I, but this was not consistent practice, and the findings were therefore not included in this study. Patients with competing disorders were excluded from the study.

Data were obtained retrospectively from electronic medical records and included patient age and sex, the presence of symptoms, the botulinum toxin A dose administered, procedural details, post-treatment follow-up data and any repeated procedures. Adverse effects were systematically documented, with specific attention to dysphagia, respiratory difficulties, voice changes, pain and other unexpected complications.

All patients were treated with botulinum toxin A at a total dose of 50 IU, divided into two injections. The procedure was performed under general anaesthesia using transoral direct laryngoscopy. Exposing the cricopharyngeal muscle, an injection was placed into the posterior aspect of the muscle as shown in **Figure 1**. Repeated injections were considered individually based on symptom recurrence.

FIGURE 1 Endoscopic exposure of cricopharyngeal muscle and botulinum toxin A injection placement.



Treatment outcomes were assessed based on subjective symptom relief reported by patients during telephone follow-ups conducted two weeks and three months after the procedure. Botulinum toxin A effect lasts from two weeks to three months, during which new neuromuscular junction re-establishes, although, in some cases, the effect lasts longer [8]. In cases where the initial botulinum toxin A treatment was insufficient, additional treatments were performed, extending follow-up to a maximum of 30 months. Patients were specifically asked about changes in their ability to belch and improvements in associated symptoms. Adverse effects were also assessed to ensure early detection of any complications.

Statistical analyses were performed using descriptive statistics, including mean, median, range and percentages.

To explore potential differences in response to treatment based on age, the cohort was divided into two groups: patients aged 18-25 years and those over 25 years. Fisher's exact test was used to compare categorical variables between the two age groups.

Trial registration: not relevant.

Results

The study included 40 patients, the characteristics of whom are summarised in **Table 1.** Referrals came from general practitioners, private otorhinolaryngologists and other departments of otorhinolaryngology across all regions of Denmark. At the time of analysis, nine patients had not yet reached long-term follow-up.

TABLE 1 Demographics of the Danish cohort with retrograde cricopharyngeal dysfunction, and symptoms.

Patients, n (%)	
Male	22 (55)
Female	18 (45)
Total	40 (100)
Age, yrs	
Mean	27,5
Median	25
Range	19-53
Symptoms, n (%)	
Inability to belch	40 (100)
Abdominal bloating	35 (86)
Gurgling noises	23 (58)
Chest or abdominal pain	11 (28)
Excessive flatulence	8 (20)

All patients underwent objective otorhinolaryngological examinations, including flexible laryngoscopy, and all 40 patients had MBS examination to exclude cricopharyngeal bar and assess swallowing function. Additionally, 36 patients underwent anterior-posterior radiographic examination of the oesophagus and stomach to evaluate excessive air accumulation before and after food and contrast-enhanced beverage consumption. No cases of cricopharyngeal bar were identified. Seven patients had excessive air in the gastric fundus before consuming food or beverages, whereas 27 patients exhibited excessive air in the stomach after ingestion, as examined with

MBS.

The standard initial botulinum toxin A dose was 50 IU for all patients; and in case of treatment failure, patients were offered a second injection of 75 or 100 IU. A few patients with unsatisfactory results received a third and fourth injection, and one procedure included proximal oesophageal balloon dilation. Response to treatment was defined as the ability to belch within 14 days (early effect) and after three months (long-term effect). Details regarding botulinum toxin A treatment, outcomes and adverse effects are summarised in **Table 2.** No patients reported respiratory difficulties or voice changes following the procedure.

TABLE 2 Botulinum toxin A dosage for retrograde crico-pharyngeal dysfunction treatment, effects and side effects.

	Patients, n/N (%)
1st injection	
50 IU of botulinum toxin A:	
Early effect after 14 days: belch	35/40 (88)
Early side effect after 14 days: transient dysphagia	30/40 (75)
Early side effect after 14 days: sore throat	9/40 (23)
Long-term effect after 3 mos.	18/31 (58)
Late side effect after 3 mos.: acid reflux	5/31 (16)
Subtotal	40 (100)
2nd injection	
75 IU of botulinum toxin A:	
Early effect after 14 days: belch	1/1 (100)
Early side effect after 14 days: transient dysphagia	1/1 (100)
Long-term effect after 3 mos.: belch	0/1 (0)
Subtotal	1 (100)
100 IU of botulinum toxin A:	
Early effect after 14 days: belch	10 (100)
Early side effect after 14 days: transient dysphagia	8 (80)
Long-term effect after 3 mos.: belch	5/7 (71)
Subtotal	10 (100)
3rd injection	
100 IU of botulinum toxin A:	
Early effect after 14 days: belch	2/2 (100)
Early side effect after 14 days: transient dysphagia	2/2 (100)
Long-term effect after 3 mos.: belch	1/2 (50)
Subtotal	2 (100)
4th injection	
100 IU of botulinum toxin A + balloon dilatation:	
Early effect after 14 days: belch	1/1 (100)
Early side effect after 14 days: transient dysphagia	1/1 (100)
Long-term effect after 3 mos.: belch	1/1 (100)
Subtotal	1 (100)
Long-term effect of min. and max dosage, total	
50 IU of botulinum toxin A	18/31 (58)
100 IU of botulinum toxin A	7/10 (70)

To explore potential predictors of treatment success, the cohort was divided into two age-based subgroups:

patients aged 18-25 years and those over 25 years. The younger group comprised 22 patients (12 males, ten females), whereas the older group included 18 patients (ten males, eight females). A statistical analysis was performed to determine whether age or sex influenced early response to 50 IU of botulinum toxin A. Among younger patients, 21 (95%) responded to the initial dose, compared to 14 (78%) of the older group. Fisher's exact test revealed a p value of 0.07, which was not statistically significant. No significant differences were found when comparing sex-based response rates within the younger group ($p = 1.0$) or the older group ($p = 0.6$). Overall, younger patients showed a trend towards a better early response to botulinum toxin A treatment, though this did not reach statistical significance. Sex did not appear to influence the treatment outcomes.

Discussion

This study is the first analysis of a Danish R-CPD cohort, with patients referred to the Department of Otorhinolaryngology, Head, and Neck Surgery, Aarhus University Hospital, from all regions of Denmark. The primary symptom among patients was the inability to belch, and many had undergone prior evaluations by general practitioners, gastroenterologists or abdominal surgeons, often without a definitive diagnosis. Some patients had received a diagnosis of irritable bowel syndrome (IBS), whereas others had been treated with anti-reflux medication without symptom relief.

The first patient to receive a botulinum toxin A injection for R-CPD at our institution actively sought treatment, contacting several departments of otorhinolaryngology via email in 2021 to inquire about the procedure. At that time, our department was the first in Denmark to offer this treatment. Since its initial description by Bastian et al. in 2019, R-CPD has remained a relatively new entity in the medical literature [1]. Our goal was to establish a structured diagnostic approach, following recommendations from previous studies. Diagnostic workup included a general otorhinolaryngological examination, flexible laryngoscopy, oesophagoscopy and MBS to exclude alternative diagnoses. In addition, we introduced a simple bedside test involving the ingestion of half a glass of carbonated water to assess the ability to burp [1, 4].

Initial studies on R-CPD found no pathological findings on MBS, though excessive gas accumulation in the oesophagus and stomach was commonly noted [1]. This often led to misdiagnosis, including gastro-oesophageal reflux disease, IBS or psychosomatic symptoms. Similarly, Karagama's study reported a few patients with gaseous distention in the oesophagus and stomach [4]. Our study revealed that 75% of patients who underwent MBS exhibited excessive air retention in the stomach following food or beverage consumption, though not in the oesophagus. This finding may serve as a useful objective diagnostic criterion for R-CPD.

The therapeutic effect of botulinum toxin A injection generally begins within three to ten days, peaking around two weeks after the procedure. Based on this timeline, we scheduled an early follow-up after two to three weeks to assess the initial treatment response. The pharmacologic effect of botulinum toxin A typically lasts for approximately three months in neuromuscular junctions, which served as the rationale for long-term follow-up timing [8]. While some might argue that a longer follow-up period is necessary, we consider three months sufficient to evaluate treatment efficacy [4, 8].

Previous studies have reported initial botulinum toxin A doses of 50 IU, with subsequent increases to 75 IU or 100 IU, depending on patient response [1, 4, 7, 9]. In our study, 50 IU resulted in long-term improvement in 58% of patients, whereas 100 IU produced symptom relief in 70% of patients with available long-term follow-up data in seven patients out of ten. Although we lack long-term follow-up for some patients treated with both 50 IU and 100 IU of botulinum toxin A, we consider our data comparable to those of other studies. These findings align with results from Bastian's study, as well as Hoesli's study, which reported a 79.9% long-term response rate, and Wajsberg's study, which found an 80% success rate after six months of follow-up [1, 7, 9]. In Karagama's study, a

100 IU botulinum toxin A dose yielded 100% long-term efficacy [4]. All previous studies concluded that a three-month follow-up period is sufficient to determine the long-term effects of R-CPD treatment [1, 4, 7, 9].

The age range of R-CPD patients in previous studies spans from 16 to 68 years, whereas our Danish cohort had a similar range of 19-53 years, with a predominance of younger individuals [1, 4]. Since R-CPD is still a relatively new condition, we did not offer this treatment to patients under 18 years of age. We hypothesise that younger patients are more likely to compare themselves to peers, especially regarding the consumption of carbonated beverages, and are more motivated to seek an explanation and treatment for their inability to belch. Many of the patients in our study became aware of the condition and available treatment options through internet searches and social media, particularly a dedicated Facebook group created by one of the first Danish patients to undergo botulinum toxin A treatment. This highlights the significant role of online communities in guiding patients towards specialised care.

Although R-CPD is primarily diagnosed based on clinical symptoms, HRPM-I has been proposed as a potential tool to assess UES dysfunction in these patients. Studies have demonstrated that patients with R-CPD exhibit abnormal UES relaxation and oesophageal air entrapment during HRPM-I evaluations, particularly following carbonated drink challenges [6]. Additionally, HRPM-I has been utilised to identify oesophageal motility disorders associated with R-CPD, offering valuable insights into the pathophysiology of the condition [10]. The integration of HRPM-I into the diagnostic process may enhance the accuracy of R-CPD diagnosis and inform more targeted treatment strategies.

Since the introduction of botulinum toxin A treatment for R-CPD at our institution, other departments of otorhinolaryngology in Denmark have started offering the procedure. We suggest that patients presenting with hallmark symptoms be referred directly from general practitioners or private otorhinolaryngologists to centres with experience in diagnosing and treating this condition.

Conclusions

Botulinum toxin A treatment is a safe and effective option for R-CPD patients, with minor side effects such as transient dysphagia, mild sore throat and acid reflux, but no reported vocal fold involvement or breathing difficulties. Our study demonstrates that more than half of the patients achieved satisfactory results after an initial 50 IU of botulinum toxin A injection, while one-third required an additional treatment with a higher dose. These findings suggest that the initial treatment dose could be safely increased to 100 IU to enhance efficacy from the first procedure. Additionally, we emphasise the importance of diagnostic tools such as MBS, carbonated beverage intake test and oesophagoscopy in establishing a correct diagnosis for R-CPD.

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