JAMA Otolaryngology–Head & Neck Surgery | Brief Report

Origin and In-Office Treatment of Retrograde Cricopharyngeus Dysfunction

Marie Mailly, MD; Robin Baudouin, MD, MS; Claire Thibault, MD; Stephane Hans, MD, PhD, MS; Jerome R. Lechien, MD, PhD, MS

IMPORTANCE Retrograde cricopharyngeus dysfunction (R-CPD) is an emerging disorder associated with disabling symptoms. The origin of R-CPD remains unknown.

OBJECTIVE To investigate the development of symptoms, diagnosis approach, and therapeutic outcomes of R-CPD in patients treated with in-office botulinum toxin injection (BTI) into the cricopharyngeus.

DESIGN, SETTING, AND PARTICIPANTS This was a case series including patients with R-CPD who were consecutively and prospectively recruited from April 2022 to May 2024 in an academic hospital. Semistructured interviews were conducted to collect and analyze data on each patient's clinical history, potential causes or factors associated with R-CPD development, diagnostic approaches, and symptom presentation.

INTERVENTION Clinic-based (in-office) BTI into the cricopharyngeus.

OUTCOMES AND MEASURES Associations with laryngopharyngeal reflux disease, patients' Reflux Symptom Score-12 (RSS-12), and BTI effectiveness, revisions, and complications were evaluated.

RESULTS The case series comprised 106 patients with R-CPD treated with BTI (52 females [49.1%] and 54 males [51.9%]). Their mean (SD) age at symptom onset was 13.6 (7.7) years, and at diagnosis, 30.4 (6.4) years. Sixty-eight patients (64.2%) had potential congenital R-CPD, according to the parents' testimonies. A family history was reported in 18 of 62 cases (29.0%). In 105 cases (99.1%), patients made the diagnosis themselves despite medical consultations (n = 162), empirical treatments (n = 113), and additional examinations (n = 92). The cumulative success rate of BTI was 90.6% (96 of 106 patients). In 26 cases (24.5%), additional injections were administered to address the symptoms. Family history of R-CPD was a negative predictor of single-BTI success. Dysphagia was the primary adverse effect occurring after 89 of 126 BTIs (70.6%) and lasted a mean (SD) of 16.3 (12.0) days. In 10 cases, operating-room BTI was administered after primary in-office BTI.

CONCLUSIONS AND RELEVANCE R-CPD is an emerging and poorly known disorder associated with high rates of ineffective consultations, additional examinations, and self-diagnosis by patients. In-office BTI was associated with a high rate of partial or total symptom relief and long-term effectiveness.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jerome R. Lechien, MD, PhD, MS, Department of Surgery, Research Institute for Health Sciences and Technology, University of Mons, Avenue Maistriau, 7000 Mons, Belgium (jerome.lechien@umons.ac.be).

JAMA Otolaryngol Head Neck Surg. 2025;151(4):396-400. doi:10.1001/jamaoto.2024.5046
Published online January 30, 2025.

Retrograde cricopharyngeal dysfunction (R-CPD) can be defined as a disorder with absent or incomplete upper esophageal sphincter (UES) relaxation in response to abrupt esophageal distention by gastroesophageal gas reflux.[1] R-CPD is an emerging condition with the first case series published in 2019 by Bastian and Smithson.[2] The gaseous esophageal distension related to R-CPD leads to disabling symptoms, ie, inability to burp, bloating, gurgling noise, excessive flatulence, and chest pain.[1] To date, the condition remains underappreciated by clinicians despite an emerging literature of retrospective case series.[1] The development of symptoms, related comorbidities, effectiveness, and postoperative outcomes of in-office botulinum toxin injection (BTI) in the UES is poorly investigated.

This case series aimed to report the etiological factors, clinical presentation, and therapeutic outcomes of patients with R-CPD treated with in-office BTI.

Key Points

Question What are the origin, clinical presentation, and treatment outcomes of retrograde cricopharyngeus dysfunction (R-CPD)?

Findings This case series comprising 106 participants with a mean age of 13.6 years at R-CPD symptom onset and 30.4 years at diagnosis found that in-office injection of botulinum toxin into the cricopharyngeus was associated with a 90.6% success rate.

Meaning Although R-CPD remains underdiagnosed by clinicians and its origin is unknown, in-office injection of botulinum toxin is a safe and effective treatment for R-CPD.

Methods

Patients and Setting

Patients were consecutively recruited from an academic hospital (Foch Hospital, Paris, France) from April 2022 to May 2024. The diagnosis was based on the Bastian and Smithson criteria,[2] which include 4 major symptoms: inability to burp, chest pain/bloating, excessive flatulence, and gurgling noises. Patients with a history of esophageal surgery or radiation, another esophageal dysmotility condition (eg, aperistalsis, achalasia), or severe psychiatric illness were excluded. This study adhered to the principles of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Institutional review board approval was not required for retrospective analysis of prospective data.

Semistructured Interviews

The first author (M.M.) conducted semistructured interviews of patients with R-CPD to investigate the following outcomes: pattern of symptom development, ability to burp during childhood, unsuccessful investigations/consultations/treatments before making the diagnosis, the method of diagnosis, and the distance between hospital and home (highlighting the potential unawareness of local practitioners). The impact of symptoms on quality of life (QoL) was evaluated with a 10-point Likert scale. The reflux symptoms were investigated with the Reflux Symptom Score-12 (RSS-12).[3]

In-Office Botulinum Toxin Injection

The treatment consisted of in-office unilateral injection of incobotulinum toxin A (dilution of 100 units/0.45 mL) with electromyographic (EMG) guidance (Natus Dantec Keypoint, Focus). Patients were placed in a neutral supine position. Briefly, the posterior left side of the cricoid cartilage was used to find the UES through the EMG needle. The needle tip position was confirmed on EMG with swallowing (loss of signal with UES relaxation followed by motor unit recruitment with post-swallow contraction), sustained vowel /i/ (to avoid the injection in the thyrocricoid muscle), and a sniffing maneuver (to avoid the injection into the posterior cricoarytenoid muscle). The clinicians injected 75 units of botulinum toxin.

Postoperative Outcomes

The following postoperative outcomes were collected: doses, duration, and complications of primary and additional (revision) BTI, effectiveness of BTI on the ability to burp, and number and time of recurrence(s).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, version 30.0; IBM Corp). The association between demographics, RSS-12, and posttreatment outcomes was investigated with bivariate analysis.

Results

Patients and Settings

In all, 106 patients (52 females [49.1%] and 54 males [50.9%]) completed the evaluations. Demographic information and diagnoses findings are reported in **Table 1**. The mean (SD) age was 30.4 (6.4) years. The mean (SD) duration of symptoms was 15.6 (10.4) years. Sixty-eight patients (64.2%) had no comorbidity. Gastroesophageal reflux disease (GERD) and mental health diseases were found in 7 (6.6%) and 6 patients (5.7%), respectively (eAppendix in Supplement 1). The mean (SD) age at R-CPD onset was 13.6 (7.7) years (Table 1). However, parents confirmed the inability to burp during childhood in 68 cases (64.2%) (Table 1). Family interview data were available for 62 (58.5%) patients. Among these, 18 patients (29.0%) reported having a family member with R-CPD (first-degree relative), with only 1 case with symptom-related QoL impairment.

Diagnosis Approaches

The patients initially performed the diagnosis themselves in 105 of 106 cases (99.1%) through online forums and searches (Table 1). Ninety-two additional examinations had been performed without providing a diagnosis before the otolaryngologist diagnosis in 46 patients (43.4%). Gastrointestinal endoscopy was carried out in 45 patients (42.5%) without suggesting the diagnosis. Overall, patients had 162

Table 1. Characteristics of 106 Patients With Retrograde Cricopharyngeus Dysfunction (R-CPD)

Characteristic	No. (%)
Age, mean (SD), y	30.4 (6.4)
Sex	
Female	52 (49.1)
Male	54 (50.9)
Body mass index,[a] mean (SD)	22.0 (3.2)
R-CPD symptom duration, mean (SD), y	15.6 (10.4)
Symptoms onset	
Birth to 10 y	24 (22.6)
11-19 y	59 (55.7)
20-29 y	18 (17.0)
>29 y	2 (1.9)
No response	3 (2.8)
Symptom worsening during adolescence	74 (69.8)
Parent interview of R-CPD in patient's childhood	
Confirmation of ability to burp	28 (26.4)
Confirmation of inability to burp	68 (64.2)
No parent interview	10 (9.4)
Diagnosis approaches	
Self-diagnosis (internet search/forum)	105 (99.1)
Primary care diagnosis	1 (0.9)
Type of investigations before diagnosis, No. (%) of 92 patients	
Gastrointestinal endoscopy	45 (42.4)[b]
Blood test	7 (6.6)
Urea breath test	6 (5.7)
Videofluoroscopy	6 (5.7)
High-resolution manometry	5 (4.7)
Abdominal tomodensitometry	5 (4.7)
pH monitoring	3 (2.8)
Abdominal ultrasonography	3 (2.8)
Other	12 (11.3)
Type of treatments before the diagnosis, No. (%) of 113 patients	
Proton pump inhibitors/alginate	45 (42.5)
Active carbon	17 (16.0)
Probiotics	11 (10.4)
Antispasmodic	9 (8.5)
Homeopathy	8 (7.5)
Gluten/lactose-free diet	7 (6.6)
Gastroprokinetic	6 (5.7)
Antiemetics	6 (5.7)
Antibiotics	4 (3.8)

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Of 45 gastrointestinal endoscopy procedures, 12 had positive results for gastroesophageal reflux disease. Gastrointestinal endoscopy was performed 2 and 3 times in 3 and 1 cases, respectively.

unsuccessful medical consultations before making the diagnosis (mean [SD], 1.64 [1.40] per patient). Proton pump inhibitors or alginate, active carbon, and probiotics were the most common empirical treatments prescribed to patients (Table 1).

Table 2. Clinical Findings in 106 Patients With Retrograde Cricopharyngeus Dysfunction (R-CPD)

Symptom	No. (%)
Inability to burp	106 (100)
Chest pain	85 (80.2)
Bloating	100 (94.3)
Gurgling noises	99 (93.4)
Excessive flatulence	96 (90.6)
Nausea	53 (50.0)
Heartburn	55 (51.9)
Globus sensation	96 (90.6)
Oropharyngeal dysphagia	97 (91.5)
Vomiting inability	54 (50.9)
Weight loss due to R-CPD	12 (11.3)
Symptom relief in supine position	86 (81.1)
Reflux Symptom Score-12, mean (SD)[a]	35.0 (8.5)
Reflux Symptom Score-12 QoL, mean (SD)[a]	13.7 (8.3)

Abbreviation: QoL, quality of life.

[a] Reflux Symptom Score-12 was completed by 35 patients because it was introduced during the study conduction.

Clinical Findings

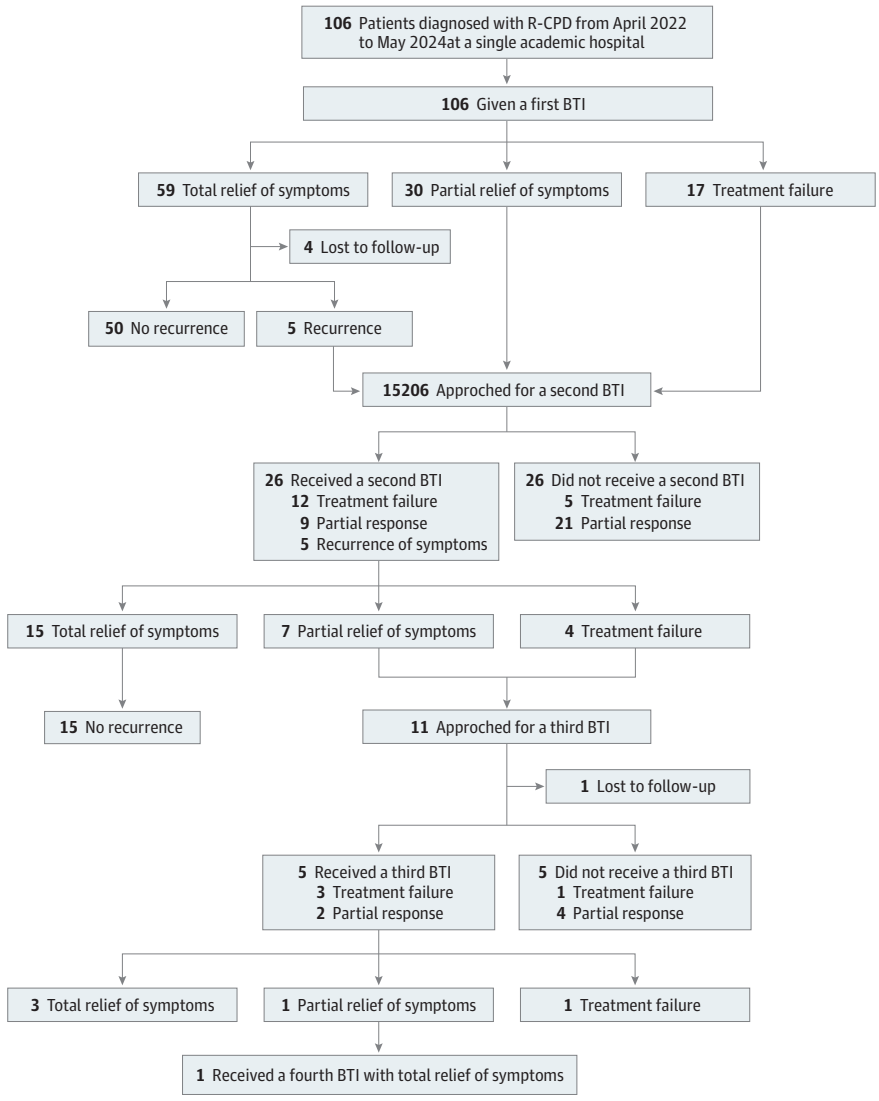
The prevalence of symptoms is reported in **Table 2.** In addition to the 4 primary symptoms, patients commonly had Globus sensation, oropharyngeal dysphagia, heartburn, and nausea. The supine position was associated with partial symptom relief in 86 cases (81.1%). Symptoms worsened during adolescence in 74 patients (69.8%). The mean (SD) RSS-12 and RSS-12 QoL index scores were 35.0 (8.50) and 13.7 (8.4), respectively. Only 2 patients did not reach the RSS-12 thresholds for suggesting the laryngopharyngeal reflux disease (LPRD) diagnosis.

Therapeutic Outcomes

The therapeutic outcomes are summarized in the **Figure.** The median (range) follow-up was 285 (17-886) days. The overall mean (SD) rate of BTI success in symptom relief was achieved at 2.5 (2.1) days. Symptoms improved after the first BTI in 89 patients (84.0%), including 59 (55.7%) with total symptom relief and 30 (28.3%) with partial symptom relief (Figure). The second and third BTIs reported success in 15 of 26 patients (84.6%) and 4 of 5 patients (80.0%), respectively. The 1 patient receiving a fourth BTI was free of symptoms after the injection. Considering patients with partial or total relief of symptoms, the cumulative success rate of BTI was 96 of 106 patients (90.6%). Among the patients with recalcitrant disease, 10 (38.5%) were performed in the operating room due to the patient's wish related to poor satisfaction with the in-office injection (pain, fear of needle). Considering the operating room injection as a failure of the in-office BTI, 79 patients (74.2%) reported success of in-office BTI.

The adverse effects data were available for 126 BTIs. Dysphagia was the primary adverse effect, occurring in 89 cases (70.6%) and lasting a mean (SD) of 16.3 (12.0) days. Transient dysphonia and regurgitations occurred in 24 (19.0%) and 27

Figure. Flow Diagram of Study Patients With Retrograde Cricopharyngeus Dysfunction (R-CPD) Receiving Botulinum Toxin Injection (BTI)



Lost to follow-up were patients who came from other countries. Partial response consisted of improvement of R-CPD symptoms and related quality of life without total resolution. Some participants did not require second/third BTI to achieve the quality of life improvement. Among patients without response and no additional BTI, the following reasons were reported: pain during the BTI, fear of needles, and distance from their home to the hospital.

cases (21.4%), respectively. Recurrence occurred in 5 patients (4.7%) after a mean (SD) of 6 (2) months postinjection. The second BTI was successful in this group of patients without additional recurrence.

Considering the 62 patients with a complete family history investigation, the success rate of a single BTI was higher in patients without a family history (37 of 43 [86.0%]) compared with those with a family history of R-CPD (13 of 19 [68.4%]; difference; 17.6%; 95% CI, −3.4% to 41.2%).

Discussion

The present investigation provides important knowledge related to the causes, development, and therapeutic outcomes of R-CPD. The significant proportion of congenital cases and family history can support a genetic origin, with symptoms developing at birth or in the first 3 decades of life. However, a parent's recall bias cannot be excluded regarding the retrospective collection of this information.

A recent systematic review supports the potential role of GERD in the development of R-CPD. A considerable number of patients with R-CPD have reported common LPRD symptoms, reaching the RSS-12 threshold for suggesting the diagnosis. Reflux disease can be suspected as a contributing factor of R-CPD, with a reflux disease influenced by the diet habits of the patient and their family. Importantly, GERD has been known for a long time to worsen the motility disorders of the esophagus,[4,5] which can support its potential role regarding the UES dysfunction in R-CPD. However, to date, the relationship between LPRD and R-CPD is not known. Although these 2 disorders are commonly presented together, they could be associated or causal, with R-CPD as a cause of reflux disease or vice versa. This point and

the evaluation of post-BTI development of LPRD require future prospective studies.

The high rates of ineffective medical consultations, additional examinations, and self-diagnosis by patients make the diagnosis a challenging point for future studies. The importance of detecting and diagnosing R-CPD is strengthened by the effectiveness of BTI, which is widely performed in operating rooms,[1,2] while the procedure can be performed in-office with EMG guidance.[1]

Limitations

The findings of this case series study include some limitations. Regarding the findings presented in this study, the in-office BTI procedure may be a cost-effective option for managing R-CPD; however, being a case series report, these results must be viewed with caution. It is important to note that some patients fear needles and experience pain during the procedure or live far from the hospital, all of which impede follow-up and the acceptation of a second in-office injection. Moreover, the rate of recurrence reported in the present study may be underestimated because, at the time of the study conclusion, some patients had been followed up for 6 months and some of may have experienced recurrence after evaluation. The long-term effectiveness of single BTI needs to be better understood regarding the limited duration of BTI in patients with laryngeal neuromuscular disorder.[6] Despite evidence about the effectiveness of in-office and operating-room BTI, there is no standardization of recommended BTI doses. Moreover, the short follow-up of some patients and the study design (case series) can limit the drawing of a definitive conclusion about the effectiveness of BTI. Also, the lack of RSS-12 score data post-BTI is another limitation that can be addressed in future studies.

Conclusions

The findings of this case series study suggest that R-CPD is an emerging and poorly known disorder associated with high rates of ineffective consultations, additional examinations, and self-diagnosis by patients. The potential congenital development of R-CPD needs to be investigated in future pediatric investigations. In-office BTI may lead to a high rate of partial or total symptom relief, and an effective long-term treatment.

ARTICLE INFORMATION

Accepted for Publication: December 2, 2024.

Published Online: January 30, 2025. doi:10.1001/jamaoto.2024.5046

Author Affiliations: Department of Otolaryngology–Head and Neck Surgery, Foch Hospital, School of Medicine, Paris Saclay University, Paris, France (Mailly, Baudouin, Hans, Lechien); Department of Otolaryngology–Head and Neck Surgery, Centre Hospitalier Universitaire (CHU) de Strasbourg, Strasbourg, France (Thibault); Department of Surgery, Research Institute for Health Sciences and Technology, University of Mons, Mons, Belgium (Lechien); Division of Laryngology and Broncho-esophagology, Department of Otolaryngology–Head Neck Surgery, EpiCURA Hospital, Baudour, Belgium (Lechien); Department of Otolaryngology, Elsan Polyclinic de l'Atlantique, Poitiers, France (Lechien); Department of Otolaryngology–Head and Neck Surgery, CHU Saint-Pierre, Brussels, Belgium (Lechien).

Author Contributions: Drs Mailly and Lechien had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lechien and Hans contributed equally as co-senior authors.

Concept and design: Mailly, Thibault, Hans, Lechien.
Acquisition, analysis, or interpretation of data: Mailly, Baudouin, Hans, Lechien.
Drafting of the manuscript: Hans, Lechien.
Critical review of the manuscript for important intellectual content: Mailly, Baudouin, Thibault, Lechien.
Obtained funding: Mailly, Hans.
Administrative, technical, or material support: Thibault.
Supervision: Mailly, Hans, Lechien.

Conflict of Interest Disclosures: None reported.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank B. Johnson, MS for proofreading the manuscript; this individual was not compensated.

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