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RESEARCH SUBMISSIONS

Enlarging the spectrum of cluster headache: Extracranial autonomic involvement revealed by voice analysis

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Abstract

Background: People with cluster headache (CH) are frequently burdened by misdiagnosis or diagnostic delay. The peculiar somatic and behavioral changes characterizing patients with CH are not useful to improve diagnostic accuracy. In our clinical experience, we noticed a typical voice quality with low and croaking tone in patients with CH. In this cross-sectional study, we evaluated, by digital voice analysis, whether it is possible to identify typical voice quality characterizing patients with CH compared with healthy controls (HCs). Furthermore, to investigate whether putative differences in voice characteristics could be underpinned by constitutional aspects or pathological processes of vocal cords, subjects underwent a videolaryngostroboscopy. Smoking habits and alcohol consumption were specifically investigated.

Methods: After conducting digital recording of the voices from both patients with CH and HCs in a soundproof insulated cabin in the laboratory of the Audiology Department, a set of voice parameters was analyzed. We included the measures of fundamental frequency, calculations of jitter and shimmer, and noise-to-harmonics ratios as well as quantities related to the spectral tilt (i.e., H1–H2, H1–A1, H1–A2, and H1–A3) in 20 patients with CH and in 13 HCs. A videolaryngostroboscopy was performed in all subjects.

Results: Patients with CH, explored during the cluster bout period, showed significantly lower second harmonic (H1–H2) values compared with HCs (−6.9 ± 7.6 vs. 2.1 ± 6.7, $p = 0.002$), usually characterizing the so-called creaky voice. By using a laryngoscopy investigation, a significantly higher prevalence of mild to moderate vocal cord edema and laryngopharyngeal reflux signs were found in patients with CH (100% of patients with CH vs. 15% of HC, $p < 0.001$).

Conclusion: Creaky phonation is a "physiological mode of laryngeal operation" usually underpinned by shortened and thickened vocal folds. Creaky voice phonation can be due to a vocal fold's reduced capability to become slack or flaccid secondary to vocal

Abbreviations: apq, amplitude perturbation quotient; CGRP, calcitonin gene-related peptide; CH, cluster headache; HC, healthy controls; HNR, harmonics-to-noise ratio; IQR, interquartile range; loc, local; NHR, noise-to-harmonics ratio; NPY, neuropeptide Y; ppq, period perturbation quotient; rap, relative average perturbation; SD, standard deviation; VIP, vasoactive intestinal polypeptide.

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cord edema underpinned by laryngopharyngeal reflux affecting the phonatory mechanisms in patients with CH. The laryngopharyngeal reflux may represent a dysautonomic sign related to the increased parasympathetic tone during in-bout period, reinforcing the hypothesis of an extracranial autonomic dysfunction as part of CH clinical picture.

KEYWORDS
cluster headache, creaky voice, extracranial autonomic symptoms, laryngoscopy, vocal cord edema, voice analysis

INTRODUCTION

Cluster headache (CH) is a primary headache featuring attacks of excruciating, strictly unilateral and usually sharp, stabbing, or throbbing headache, associated with cranial ipsilateral autonomic symptoms and restlessness.[1,2] Although its clinical phenotype is well characterized, CH is frequently misdiagnosed with other primary headaches, especially migraine and hypnic headache, with a considerable diagnostic delay and consequent burden on patients' life.[3,4] Unfortunately, no structural or functional CH biomarkers are available to improve diagnostic accuracy to date.

In the 1970s, Graham suggested valorizing skull and soft tissue features constituting the so-called "leonine face" in patients with CH to support clinical diagnosis. These somatic characteristics have been subsequently explored by means of clinical inspections, craniometric measurements or, more recently, by neuroradiological investigations with conflicting results.[5–7] In contrast, the impression that patients with CH could be characterized by peculiar physical and behavioral traits is a common experience for clinicians dealing with headaches. Among these, in our clinical experience with patients with CH, we noticed a peculiar voice quality with a sort of low and croaking tone.

Although voice analysis has been widely used in many neurological and nonneurological disorders,[8–10] to the best of our knowledge, no studies have been conducted to elucidate these features in patients with CH.

In the present study, we evaluated, by means of an accurate, reproducible, and feasible digital voice analysis, whether it is possible to identify voice alterations characterizing patients with CH compared with healthy controls (HCs). Furthermore, to investigate whether putative differences in voice characteristics may be underpinned by constitutional aspects or pathological processes of the vocal cords, patients underwent a videolaryngostroboscopy, and smoking habits and alcohol consumption were specifically investigated.

We hypothesized that typical voice features may characterize patients with CH enriching the clinical CH profile and represent a putatively diagnostic clue in these patients.

METHODS

Study population and study design

In the present cross-sectional study, 20 Caucasian male patients with a diagnosis of episodic CH [3.1] according to the International Headache Society criteria (Headache Classification Subcommittee of the International Headache Society 2018)[11] were prospectively recruited between 2018 and 2020 from the CH population referring to the Headache Center of the Department of Neurology at the University of Campania "Luigi Vanvitelli." Demographic data as well as the following clinical features were obtained from patients: disease duration, frequency of CH attacks (attacks/day) and CH bouts (bouts/year), and average of pain intensity of CH attacks (assessed using a numerical rating scale). All patients with CH and HCs underwent the Epworth Sleepiness Scale (ESS). Information regarding smoking habits and alcohol consumption as well as previous traumatic head injuries was recorded. All patients were investigated contextually at the first outpatient visit, during the cluster bout period (outside CH attacks) before starting preventive CH treatment as well as the corticosteroid "bridge therapy."

Male individuals belonging to the same age range, with lifestyle habits that can be superimposed on patients with CH and in the absence of relevant pathologies were recruited as control group subjects. All controls were recruited among personnel of the Audiology section, Department of Neuroscience Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy. Thirteen Caucasian subjects with no family history of CH as well as other neurological or psychiatric disorders, with fewer than a few spontaneous nonthrobbing headaches per year, were recruited as HCs. The HCs were recruited exclusively for this study and, therefore, no elements of their data have been previously published.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli," and written informed consent was obtained from all subjects in accordance with the principles of the Declaration of Helsinki.

Voice analysis

A Shure 545SD Unidyme III microphone (owned by the Department of Modern Philology) with firm support was used for the recording procedure. The instrument was placed at a distance of about 8 cm from the speaker and was used in conjunction with Audacity, a

multitrack, cross-platform audio editing and recording software, distributed under the GNU General Public License. It is a program that also allows the editing of stored audios and their mixing, with the possibility of adjusting volume, speed, pitch, normalization, and file format. The criterion adopted for the volume is that, during recording, a red band should not appear on the sound wave, as this would indicate sound saturation. The "mono" mode is set, and the resulting file is saved in .wav format. The duration of the collected audios is on average 4 min and 45 s for the 20 patients and 5 min and 48 s for the 13 controls. Regarding the acquisition modalities, a partially soundproofed insulated cabin in the Audiology Department of the Nuovo Policlinico (Azienda Ospedaliera Universitaria Federico II) in Naples was used. During the recording, there were two operators together with the interviewee. Maximum silence was observed and electronic devices were not allowed because their waves could interfere with the acoustic recording operations. A set of voice measures were studied using the traditional measures of fundamental frequency, calculations of jitter and shimmer, and noise-to-harmonics ratios as well as quantities related to the spectral tilt, that is, H1–H2, H1–A1, H1–A2, H1–A3 (see Supporting Information 1). These measures were calculated based on the production of stressed vowels extracted from digitally recorded reading tasks. To have more reliable data, several vowel productions—2 or 11 to have at least 5 (but in most cases 12 or 11) valid measures for each subject–parameter pair (see Supporting Information)—were measured for each subject and the mean values used. Voice analysis was performed by means of the software PRAAT.[12,13] As for spectral measures, an adapted version of Mayer's (2014) Praat script was used.[14] The parameters f0, sd f0, jitter, shimmer, NHR, and HNR are the main parameters used in the literature for qualitative voice analyses and, specifically, to explore the link between vocal acoustic properties and specific disorders such as the stuttering observed during childhood and Parkinson's disease.[15,16] The parameters H1–H2, H1–A1, H1–A2, and H1–A3 were calculated considering the central steady-state portion of a stressed [a] vowel. Although acoustic parameters were calculated by recording sustained production of vowel sounds in numerous speech analysis studies, analysis of the central steady-state portion of vowels produced during continuous speech yielded statistically significant results.[17–19]

Laryngoscopy

Laryngostroboscopic evaluation was performed during the articulation of vowel /i/. The instrumentation consisted of a rigid endoscope, microlaryngoscope 70°/4 mm; LED stroboscopic system with an analysis frequency from 60 to 1000 Hz, phase range variation from 0o to 400o, and LED illumination. Stroboscopy is an essential diagnostic tool in the assessment of the vocal folds during phonation. Stroboscopy focused on morphostructural characteristics of the larynx and on the symmetry, periodicity, glottic closure, amplitudes, waveforms, and nonvibrating segments.

Statistical analysis

No statistical power calculation was conducted prior to the study, and the sample size was based on the available data. All demographic and clinical data were checked for normality using the Shapiro–Wilk test. Categorical data were reported as number and percentage, whereas continuous data were reported as mean ± standard deviation (SD), and scale scores were reported as median and interquartile range (IQR). We used the chi-squared test to compare categorical variables and the independent sample *t*-test to compare continuous variables, whereas the nonparametric, two-sided, Wilcoxon rank sum test was used for data not conforming to normal distribution. Statistical significance was set at $p < 0.05$, and the Bonferroni correction was applied to account for the 13 comparisons reported in Table 2 (i.e., 0.05/13 = 0.004). We used Quade's rank analysis of covariance to substantiate the between-group differences controlling for the potential confounding effect of age and differences in smoking status. Statistical analyses were preplanned, and the data were primarily collected for verifying our study hypotheses via SPSS software for Windows (version 22.0; SPSS, Chicago, IL, USA).

RESULTS

Patients with CH and HC

Descriptive demographic and clinical statistics of patients with CH and HCs are shown in Table 1. The sample of patients with CH displayed an average age of 42 ± 8.7 years and included only male patients. Patients reported a mean CH disease history of 9 years, with a median of one cluster bout per year characterized by a median two CH attacks per day. No significant differences were found between the CH group and HC in age, smoking habits, and in alcohol consumption. Among the study population, only one patient with CH had an ESS score indicative of daytime sleepiness (e.g., greater than 10).

Voice analysis

The voice analysis demonstrated that patients with CH showed a significantly lower difference between the amplitude of the first harmonic and the amplitude of the second harmonic (H1–H2) compared with HC (−6.9 ± 7.6 vs. 2.1 ± 6.7, $p = 0.002$) (see Table 2 and Supporting Information 1). Because patients with CH slightly differed from HC in age and smoking status, we also ran a Quade's rank analysis of covariance with H1–H2 as dependent variable and age and smoking status as covariates, which confirmed the pattern above, Quade's test = 7.84, $p \leq 0.001$. There were no missing data.[20]

TABLE 1 Demographic and clinical characteristics of CH patients and HC

Variable	CH patients ($N = 20$) Median (IQR) or count (%)	HC ($N = 13$) Median (IQR) or count (%)	*p*-value
Age (years)	40 (36–43.5)	38 (36–39)	0.210
Disease history (years)	9 (7–11.3)	—	
CH attacks/day	2 (1–2.3)	—	
CH bout/year	1 (1–2)	—	
Smoker (>15 cigarettes/day)	15 (75%)	13 (100%)	0.233
Alcohol user	4 (20%)	3 (23%)	0.881

Abbreviations: CH, cluster headache; HC, healthy control; IQR, interquartile range.

TABLE 2 Voice measures

Measures	Mean CH	SD CH	Mean HC	SD HC	*p* (Wilcox.)
f0 (Hz)	111.8	18.2	113.2	16.0	0.730
sd f0 (Hz)	9.2	5.5	9.2	5.9	0.842
jitter loc (%)	1.8	0.8	1.5	0.6	0.265
jitter rap (%)	0.5	0.3	0.5	0.9	0.730
jitter ppq5 (%)	0.6	0.3	0.6	0.3	0.941
shimmer loc (%)	10.2	3.4	11.9	2.5	0.110
shimmer apq3 (%)	4.2	1.5	4.9	1.4	0.194
NHR	0.3	0.1	0.3	0.2	0.785
HNR (dB)	8.6	3.1	8.6	3.1	0.842
H1–H2 (dB)	−6.9	7.6	2.1	6.7	***0.002***
H1–A1 (dB)	−10.2	5.1	−7.2	10.4	0.298
H1–A2 (dB)	−1.6	8.9	0.8	11.5	0.842
H1–A3 (dB)	11.9	8.9	11.9	12.2	0.813

Abbreviations: apq, amplitude perturbation quotient; CH, cluster headache patient group; HC, healthy control group; HNR, harmonics-to-noise ratio; loc, local; NHR, noise-to-harmonics ratio; ppq, period perturbation quotient; rap, relative average perturbation; SD, standard deviation.

The bold italic value indicates statistically significant findings.

Laryngoscopy findings

Laryngoscopic examinations showed a significantly higher prevalence of chordal edema (100% of patients with CH vs. 15% of HC, $p < 0.001$). Indeed, among patients with CH, 14 showed a marked bilateral chordal edema and six showed a mild bilateral chordal edema. All patients show marked signs of laryngopharyngeal reflux. Furthermore, one patient also showed an asymmetrical chordal vibration and insufficient chordal adduction. Conversely, among the HC group, 10 subjects showed a normal laryngeal picture, two subjects showed mild bilateral chordal edema, and one subject has been excluded due to the poor quality of the laryngoscopic examination. Only two HCs showed moderate signs of laryngopharyngeal reflux (Table 3, Figure 1 and Supporting Information 2).

DISCUSSION

In the present study we found, for the first time by means of an accurate, reproducible and feasible digital analysis, a peculiar voice quality characterized by low values of H1–H2 in a cohort of patients with CH studied during the cluster bout period in comparison with HCs. Our results support the hypothesis of a relationship between CH and a "creaky voice," generally associated with glottal constriction. Furthermore, laryngoscopy investigations demonstrated bilateral chordal edema—in a range from mild to marked—underpinned by signs of laryngopharyngeal reflux in patients with CH.

It is noteworthy that CH is a primary trigeminal autonomic headache characterized by attacks of severe strictly unilateral pain, usually sharp, stabbing, or throbbing, commonly localized in the orbital, supraorbital, and/or temporal regions. The headache episodes are characteristically accompanied by cranial ipsilateral autonomic features such as lacrimation (tearing), conjunctival injection (redness of the sclera), nasal congestion or rhinorrhea, hemifacial hyperhidrosis (excessive sweating), eyelid edema, miosis with or without ptosis, and a concomitant sense of restlessness or agitation.[21] CH can be subclassified as episodic or chronic (the latter when fewer than 3 months per year are headache free).

Although the clinical features of CH attacks are so peculiar, the possible presence of confounding features—often enriching the CH clinical picture—such as migrainous symptoms during attacks (e.g., nausea, vomiting, photophobia, or phonophobia), pain radiating to other cranial areas and rare alternating attack sides, may justify the notable diagnostic delay (from 2.6 to 6.9 years) and a high prevalence of misdiagnosis as demonstrated by several studies.[3,4] Therefore, being CH a very disabling and excruciating headache (so atrocious that female patients would describe attacks as worse than the experience of childbirth), overcoming the diagnostic challenges in clinical scenario seems to be ever more necessary.

Before the IHS criteria for CH diagnosis were published, these patients were considered characterized by a thick and coarse facial skin, sometimes almost a "peau d'orange" appearance, and a marked wrinkling of the forehead and face, with deep furrows configuring in the so-called "leonine face" as described by Graham.[5–7] However, these observations should be considered only of historical interest

TABLE 3 Morphological characteristics detected on laryngostroboscopic examination

Supraglottic structures' attitude	Normal	False chordal hypertonus		Reduced AP Ø	Reduced LL Ø		
CH	17	3		0	0		
HC	12	1		0	0		
Morphology vocal cords	**Normal**	**Reinke's edema***		**Nodule**	**Corditis**	**Polypus**	**Cyst**
		Mild	**Severe**				
CH	0	6	14	0	0	1	1
HC	11	2	0	0	0	0	0
Motility vocal cords	**Normal**	**Hypomobile**		**Fixed**			
CH	20	0		0			
HC	13	0		0			
Chordal vibration	**Symmetrical**	**Asymmetrical**					
CH	19	1					
HC	13	0					
Glottal closure	**Complete**	**Adductor insufficiency**					
CH	19	1					
HC	13	0					

Abbreviations: AL Ø, latero-lateral diameter; AP Ø, anteroposterior diameter; CH, cluster headache; HC, healthy control.
*Statistically higher prevalence of Reinke's edema in patients with CH compared with HCs ($p < 0.001$).

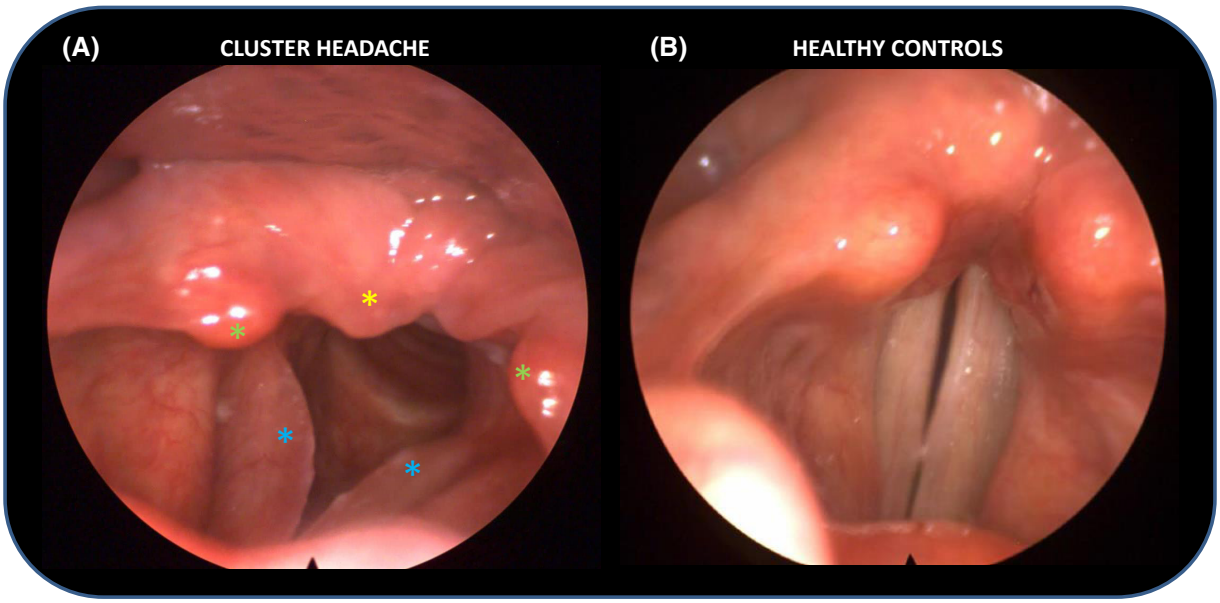

FIGURE 1 (A) Laryngoscopic image showing signs of laryngeal irritation associated with reflux: Interarytenoid bar is identified by the yellow asterisk; Arytenoid medial wall erythema/edema is identified by the green asterisks; Reinke's edema is identified by the blue asterisks. (B) Normotrophic true vocal folds in the absence of signs of laryngeal inflammation [Color figure can be viewed at wileyonlinelibrary.com]

but not diagnostically informative because they have been not supported by ensuing clinical inspections, craniometric measurements, and neuroradiological investigations.[22–24]

In the present study, patients with CH were characterized by a "creaky" quality of voice with low values of H1–A1 and were generally associated with glottal constriction compared with HCs. Creaky phonation (also known as creaky voice, vocal fry, laryngealization, or glottalization) is a "physiological normal mode of laryngeal operation" usually caused by shortened and thickened vocal folds that vibrate at a low and quasi-regular fundamental frequency with a long period of damping.[25] The measures of fundamental frequency, calculations of jitter and shimmer, and noise-to-harmonics ratios, mainly related to the regularity of the vibration and to the ratio between noise and harmonics, have been investigated in patients with neurological

disorders such as Parkinson disease and Down syndrome.[9–11] Spectral measures, mainly concerning the slope described by the decrease in the intensity as the value of frequency rises along the spectrum, have been recognized as valid tools for assessing voice quality—which, from the articulatory point of view, is considered as normally related to the parameters of muscular tension at the laryngeal level[26]—both concerning pathological and nonpathological voice quality description from a purely phonetic point of view[27,28] and in studies aiming to describe languages exploiting voice quality features such as breathiness and creakiness to differentiate sounds.[29–31]

Interestingly, creaky phonation in patients with CH is associated with a significantly higher prevalence of vocal cord edema from mild to moderate, affecting the phonatory mechanisms by a reduction in the capability of the vocal folds to become slack or flaccid and leading to the creaky voice.[32] Moreover, all patients with CH showed marked signs of laryngopharyngeal reflux, one of the most frequent causes of vocal cord edema. Laryngopharyngeal reflux is an inflammatory disease of the upper aerodigestive tract tissues related to direct and indirect effects of gastric content reflux, able to induce morphological changes in the upper aerodigestive tract.[33] In other terms, laryngopharyngeal reflux is an extraesophageal variant of gastroesophageal reflux frequently associated with chronic cough, hoarseness, dysphonia, recurrent throat clearing, and globus pharyngeus. It is well known that a smoking habit and alcoholic consumption as well as dysfunction of the autonomic nervous system should be invoked in laryngopharyngeal reflux mechanisms.[34] However, because no differences have been observed in smoking and alcohol intake between the two groups under examination, the observed laryngopharyngeal reflux can be independent from lifestyle factors and more probably related to the dysfunction of the autonomic nervous system.[35] Specifically, because the vagus nerve provides parasympathetic control of the gastrointestinal tract, a disturbed autonomic regulation causing a decreased vagal nerve activity could allow a functional failure with relaxation of the lower esophageal sphincter leading to laryngopharyngeal reflux. In other terms, voice characteristics and underlying laryngopharyngeal reflux may represent a specific autonomic feature of patients with CH. Accordingly, the autonomic and peptidergic innervations of the human larynx have been specifically investigated and immunoreactivities for a variety of regulatory peptides such as vasoactive intestinal polypeptide, neuropeptide Y, calcitonin gene-related peptide, substance P, and neurokinin A have been detected and proposed as possible mediators in laryngeal edema.[36,37] Nonetheless, these neuropeptides are widely known to be involved in CH pathophysiology as witnessed by the higher calcitonin gene-related peptide plasma levels found during CH attacks and, more generally, during the cluster bout period.[38–41] Nevertheless, the autonomic involvement can be observed beyond the cranial areas and outside the duration of CH attacks, as demonstrated by subclinical cardiac dysfunctions observed in a large cohort of patients with CH.[42]

Therefore, it could be inferred that laryngopharyngeal reflux could represent a neglected extracranial dysautonomic symptom in patients with CH, which needs attention in the general evaluation of the whole clinical picture. Furthermore, laryngeal morphological changes can lead to a creaky phonation, a feature that adds to and enriches the clinical spectrum of patients experiencing CH.

We are aware that our study is not exempt from some limitations as well. First, the present study includes a small sample size, which increases the probability of type II error and causes the underestimation of minimal clinically relevant differences. However, this is an exploratory study, and future studies on larger cohorts of patients are needed to validate our results. Second, we cannot exclude that the higher prevalence of laryngopharyngeal reflux in CH group could be related to the administration of sumatriptan, which is able to reduce—even so very rarely—the tone of the lower esophageal sphincter promoting, in turn, the gastroesophageal reflux, known to be one of the possible causes of laryngopharyngeal reflux. Otherwise, it should be underpinned that no patients referred symptoms consistent with gastroesophageal reflux. Further studies with a larger sample size are needed to better clarify these preliminary findings and to detect smaller effect size differences in voice measures. Moreover, our sample consisted of all male and Caucasian patients with CH; hence, the lack of a diverse sample population limits the generalizability of the results. Future studies are also needed to evaluate whether the observed voice features can discriminate patients with CH during in-bout periods from patients with CH during out-bout periods as well as from patients with other primary headache disorders to perform a differential diagnosis with, for example, migraine or hypnic headache as well as other primary trigeminal headaches. Finally, we cannot exclude that laryngopharyngeal reflux can be linked to sleep apnea syndrome. Therefore, patients with CH had undergone the ESS to screen for the presence of daytime sleepiness and, consequently, for sleep apnea syndrome. Only one of the patients in our group had an ESS score indicative of daytime sleepiness (e.g., greater than 10). We, therefore, believe that, in our sample of patients with CH, the influence of sleep apnea syndrome in the determination of our main findings is unlikely.

CONCLUSION

In conclusion, patients with CH can be characterized by a creaky voice phonation associated with vocal cord edema underlined by laryngopharyngeal reflux. These findings reinforce the hypothesis of extracranial autonomic dysfunctions as part of the CH syndrome presenting with laryngopharyngeal reflux and highlight the need to explore the presence of vocal cord edema in these patients.

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CONFLICT OF INTEREST

The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Silvestro has received speaker honoraria from Lilly, Novartis, and Teva. Professor Russo has received speaker honoraria from Allergan, Lilly, Novartis, and Teva and serves as an associate editor of *Frontiers in Neurology* (Headache Medicine and Facial Pain session). Professor Tessitore has received speaker honoraria from Novartis, Schwarz Pharma/UCB, Lundbeck, Abbvie, and Glaxo. Professor Tedeschi has received speaker honoraria from Sanofi Aventis, Merck Serono, Bayer Schering Pharma, Novartis, Biogen-Dompe´ AG, Teva, and Lilly; has received funding for travel from Bayer Schering Pharma, Biogen-Dompe´ AG, Merck Serono, Novartis, and Sanofi Aventis; and serves as an associate editor of *Neurological Sciences*. The other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Literature review, experimental design, image data analysis, results interpretation, statistical analysis, manuscript drafting: Marcello Silvestro. *Literature review, experimental design, image data analysis, results interpretation, manuscript drafting*: Francesca M. Dovetto and Antonio Russo. *Data acquisition, image data analysis, statistical analysis and results interpretation*: Virginia Corvino and Pasqualina Apisa. *Data acquisition and results interpretation*: Rita Malesci. *Data analysis and results interpretation*: Alessandro Tessitore. *Data analysis, statistical analysis, results interpretation, manuscript drafting*: Paolo Milizia. *Image data analysis, statistical analysis and results interpretation*: Gioacchino Tedeschi. *Literature review, results interpretation, manuscript drafting*: Elio Marciano.

INSTITUTIONAL REVIEW BOARD APPROVAL

Institutional Review Board approval was granted by the Ethics Committee of the University of Campania "Luigi Vanvitelli."

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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