

Multicentric study: statistical correlation between clinical data and instrumental findings in laryngopharyngeal reflux: proposal for a new ENT classification of reflux

Studio multicentrico: correlazione clinico-statistica tra dati clinici e rilievi strumentali nel reflusso laringofaringeo: proposta di un nuovo criterio di classificazione del reflusso in ORL

C.A. LEONE, F. MOSCA

Department of Otolaryngology, "Monaldi" Hospital, Naples, Italy

Key words

Laryngo-pharyngeal reflux • Classification • Diagnosis

Parole chiave

Reflusso faringolaringeo • Classificazione • Diagnosi

Summary

Clinical pictures of laryngopharyngeal reflux, described in the literature, often differ considerably and are described with wide severity. Some classifications employ a total score i.e., addition of the assigned scores to single aspects of video-laryngoscopy. These classifications have the disadvantage of being complex, not reproducible and, in part, subjective. In this study, an original video-laryngoscopic classification is proposed, based on a topographic criterion with distinction of anterior, from posterior and lateral, lesions and an anatomopathological criterion that assigns a marked severity to the granulomatous and erosive lesions, in comparison with the erythematous and oedematous lesions. Four classes are proposed or grades of patients (A, B, C, D). The study was multicentric on 178 patients. Results were considered estimating the clinical parameters and the symptoms, correlating them at the stages of the classification proposed. The data obtained indicate that our classification presents an indicative distribution as far as concerns severity and it seems acceptable for efficacy and simplicity: no significant correlation emerged between the single manifestations and the severity of the objective picture; in the majority of cases, the most constant symptomatological triad was globus, cough and dysphonia.

Riassunto

I quadri clinici descritti in letteratura del reflusso faringolaringeo sono spesso molto diversi e vengono descritti con gravità molto varie. Esistono alcune classificazioni che producono un punteggio complessivo costituito dalla somma di punteggi assegnato a singoli aspetti della videolaringoscopia. Queste classificazioni hanno lo svantaggio di essere complesse, non riproducibili ed in parte soggettive. In questo studio viene proposta una classificazione videolaringoscopica originale basata su un criterio topografico che distingue le lesioni anteriori da quelle posteriori e laterali e un criterio anatomopatologico che assegna maggiore gravità alle lesioni granulomatose ed erosive rispetto a quelle eritematose ed edematose. Vengono proposte quattro classi o gradi di pazienti (A, B, C, D). Lo studio è stato multicentrico su 178 pazienti. Sono stati considerati i risultati valutando i parametri clinici e i sintomi, correlandoli agli stadi della classificazione proposta. I dati emersi indicano che la nostra classificazione presenta una distribuzione indicativa di una progressione per gravità e sembra accettabile per efficacia e semplicità. Non emerge una correlazione significativa tra le singole manifestazioni e la gravità del quadro obiettivo e nella maggioranza dei casi del nostro campione la triade sintomatologica più costante è stata il globo, la tosse e la disfonia.

Introduction

The remarkable polymorphism that exists in the literature for symptoms and nosology of gastro-oesophageal reflux disease (GERD) and or laryngopharyngeal reflux (LFR) led us to propose a classification that would respond to simplicity but also reproducibility for use in the different diagnostic and research institutes.

Obviously, for the ENT specialist, the diagnostic hinge is represented by video-laryngo-fibrosocopy

and, therefore, the positivity of the reports with this method represent not only an important diagnostic criterion but also the possibility of evaluating, in an objective way, a variety of definable pictures with a growing gravity order.

In the literature, some classifications already exist, like that of the Reflux Finding Score^{1,2}.

In this classification, 8 video-laryngoscopic aspects are taken into consideration: subglottic oedema, ventricular obliteration, erythema-oedema, cordal oedema, widespread laryngeal oedema, hy-

peritrophy of the posterior commissure, granulomatous lesions.

The clinician assigns severity scores to these aspects which added together produce a score ranging between 0 and 26, thus quantifying the overall severity of the case.

Obviously, this kind of classification, which is useful from a scientific point of view for the evaluation of the effects of GERD treatments, presents the disadvantage of certain practical difficulties. Moreover, the relative weight of the scores of each single videolaryngoscopic aspect, in comparison with others and a certain subjectivity in the score assignments constitute other critical elements.

Taghavi et al.³ proposed other indices (the symptom association probability, the symptom index and the symptom sensitivity index) that have been used as predictable indices of a good response to proton pump inhibitors (PPI).

Park et al.⁴ did not check the reliability of the reflux finding score and of the reflux symptom index, as diagnostic indicators of the LFR. On the contrary, Wang et al.⁵ verified a good forecast of an index based only on gastrointestinal symptoms.

Materials and methods

We propose a classification that should be simple to use that is based on the following criteria:

- 1) topographic criterion: distinguishing anterior, from posterior and lateral, lesions (more proximal to the oesophagus);
- 2) clinical criterion: assigning a greater severity to granulomatous and erosive lesions than to those of an erythematous and oedematous nature.

Endoscopic mucosal lesions are defined as an area presenting an appreciable difference to the adjacent mucosa.

The topography that we have considered differentiates the followings districts in the front and back (and/or lateral) regions:

Front regions: 2/3 front aryepiglottic plicae;
2/3 front vocal cords, epiglottis.

Back regions: 1/3 back aryepiglottic plicae;
(and/or lateral) 1/3 back arytenoid vocal cords;
Arytenoids;
Interarytenoid mucosa;
Pyriform sinus.

Therefore, we have selected 4 stages that combine lesions presenting increasing histological and extension severity:

Grade A Erythema/Oedema
back and/or lateral regions;

Grade B Erythema/Oedema
back and/or lateral and front regions;

Grade C Erosion/Granulation
back and/or lateral regions;

Grade D Erosion/Granulation
back and/or lateral and front regions.

For examples, see Figures 2-7.

A file prepared *ad hoc* on which to collect the data was sent to the centres taking part in the study:

- Otorhinolaryngology Unit, “Monaldi” Hospital, Naples;
- Otorhinolaryngology Unit, “Fazzi” Hospital, Lecce;
- Otorhinolaryngology Clinic, Policlinico ICP, Milan.

A data file in excel (.xls) was prepared in which patients' personal data were reported.

As the diagnostic criteria, or LFR, differ considerably in the literature, in order to study clinical cases, without doubts concerning disorders or LFR, we have confirmed favourable therapy with proton pump inhibitors (PPI). Therefore, cases have been observed after 8 weeks' treatment with double dose of PPI and only those with a favourable response have been admitted in the study.

Absence, or improvement, of more than 50% of the major manifestations (subjective score 0/4), in addition to negative video-laryngoscopy or at least 50% reduction of the pathological mucosal areas were considered a favourable response.

Therefore, the cases admitted to the study have been selected with the following criteria:

- 1) Positive video-laryngoscopy, in the initial phase;
- 2) Favourable response to PPI treatment defined using the above-mentioned criteria.

This study group comprised 178 patients.

42 patients have been excluded from the study with highly indicative manifestations:

- 37 cases “non responder” to PPI treatment: 15 with indicative manifestations but without videolaryngoscopy signs (other aetiology dysphonia, allergy, vocal abuse, etc.) and 22 granulomas with mixed aetiopathogenesis (intubation, smoke, vocal abuse);
- 5 “responder” cases (reduction or absence of symptoms following PPI) but without videolaryngoscopy evidence.

The 178 cases have been divided into different groups as shown in Figure 1 (Grade A 38.2%, Grade B 39.3%, Grade C 19.1%, Grade D 3.4%).

If Group D proves to be that in which the pathology is presumed to be serious, it needs to be less represented. If, ideally, we join the peaks in the columns in Figure 1, we find an approximate curve as the middle of a Gaussian curve: this fact indicates a good dispersion of the sample and, therefore, reliability of the type of classification proposed. The statistical test used has been the corre-

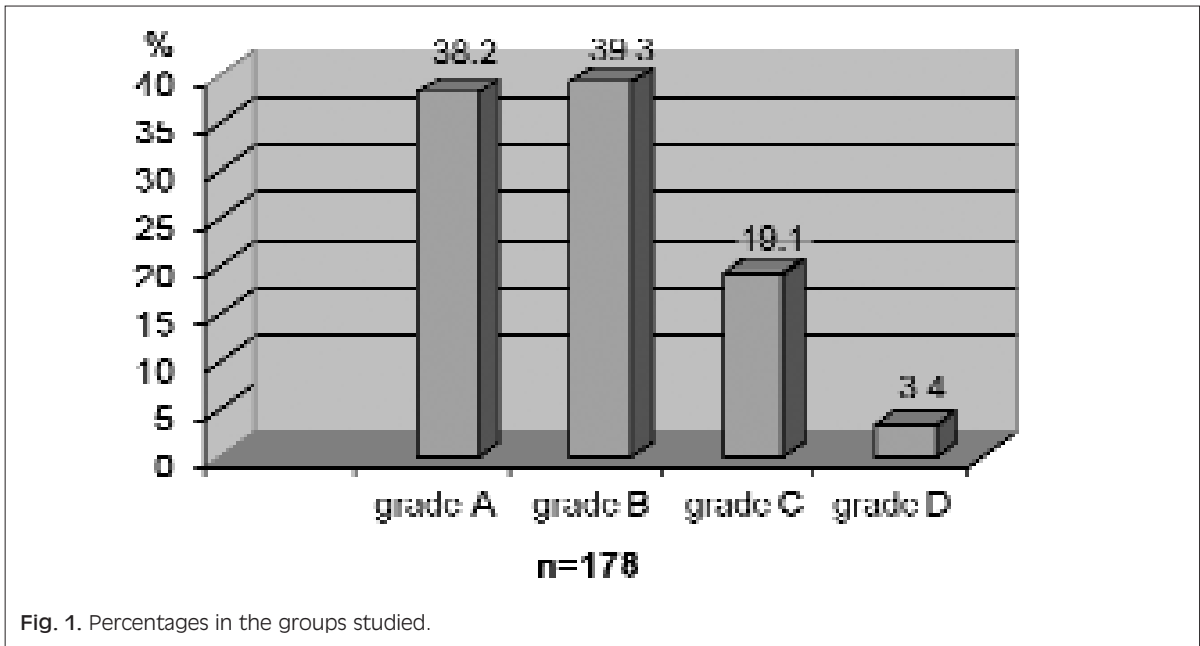


Fig. 1. Percentages in the groups studied.

lation that consents to measure the relation between two groups of data independent from the measure unity. Calculation of the correlation of population gives back the covariance of the two groups of data divided by the product of the respective standard deviations. It is possible to use the correlation test to determine whether the two gaps of data grow proportionally whether the high values of one group are associated with the high values of the

other (positive correlation), if the low values of one group are associated with the high values of the other (negative correlation) or if no correlation exists between the values of the two groups (next to zero correlation). We accepted the following values of significance:

- Not significant $n > 0.5$ $n < -0.5$ (*);
- Significant > 0.6 $n < -0.6$ (**);
- Highly significant $n > 0.7$ $n < -0.7$ (***)

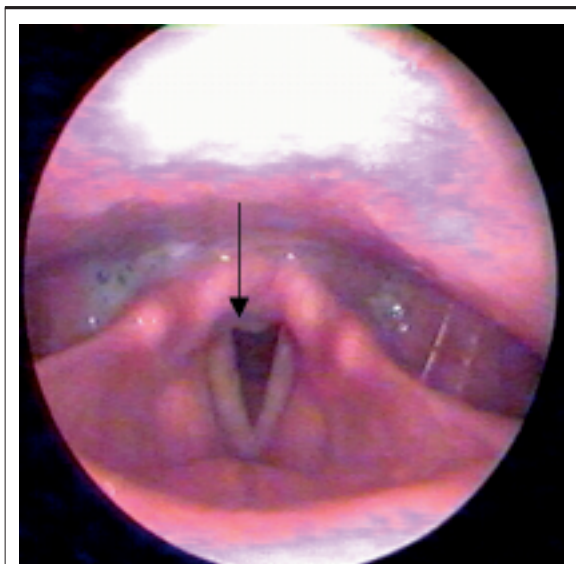


Fig. 2. Example of grade A: interarytenoid oedema with reflux in right pyriform sinus.

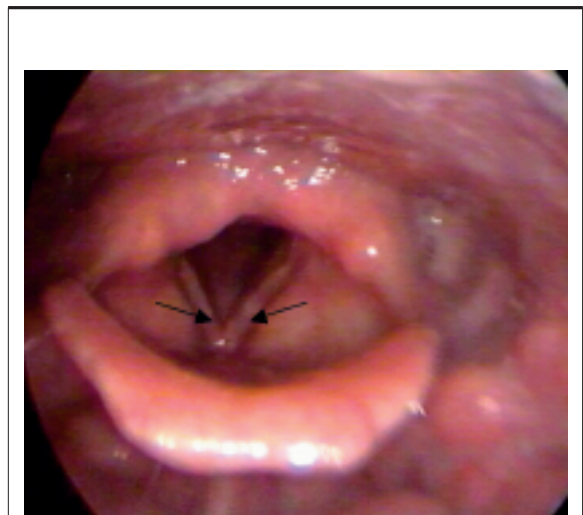


Fig. 3. Example of grade B: erythema in anterior regions.

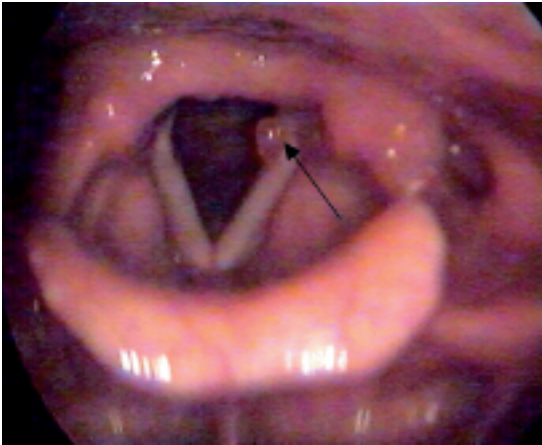


Fig. 4. Example of grade C: posterior granuloma.



Fig. 6. Same case in Figure 5 after PPI therapy.

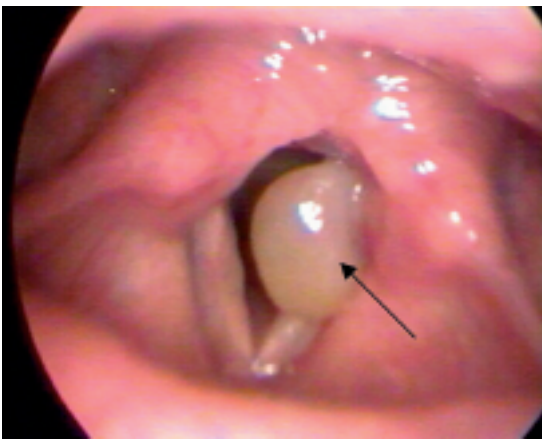


Fig. 5. Example of grade D: postero-anterior granuloma.

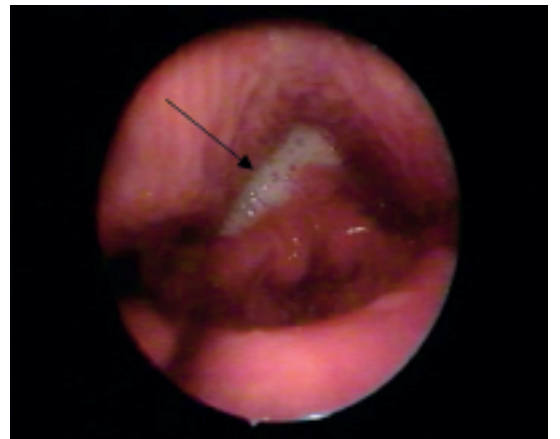


Fig. 7. A typical reflux from esophagus.

These values are lower in absolute values of than those commonly used ($n > 0.7$) as the data analyzed used only alpha-numerical terms 0 and 1.

The correlations between every parameter present in the file have been evaluated, from age to sex including the instrumental parameters, within every single group (A, B, C) of our classification.

Group D was not included as it comprised only $n = 4$ cases that did not allow us to reliably use the statistical tests.

The values expressed (Table II) did not reach significant values.

Percent appearance of the manifestations were calculated in the entire sample and each of the groups in our classification with the exception of Group D (Table III).

The first three in appearance of frequency have been defined as major manifestations and the other five have been defined as minor manifestations.

Combinations of the major and minor manifestations that could be present in the majority of patients, belonging to different groups have been evaluated.

The most significant data regard those patients belonging to group B in which the combination globus and dysphonia locates 100% of the cases of this group. The combination of 4 manifestations are sufficient to circumscribe the majority of cases. The most constant manifestations, in the total series of patients and in groups A and B, have been globus, cough and dysphonia. In group C, among the major manifestations, cough and dysphonia disappear and pyrosis and acid regurgitation appear (Table IV).

Table I. Data collected.

Grade A	Grade B	Grade C	Grade D	First diagnosis
Sex M	F			Relapse
Age (yrs) 0-44	45-55	> 55		
Globus	Dry throat	Cervical lateral pain	Cough	Dysphonia
Pharyngitis	Otalgia	Odynophagia	Haemophtoe	Halitosis
Laryngeal spasmus	Regurgitation	Back sternal pain	Gastritis	Asthma
Acid pyrosis	Hiatal hernia	Gastric ulcer	Impendenzometry	pH-metry
PPI treatment	Habitual, diet therapy	Other treatment		

Every item was assigned a score: 0 – absent or normal manifestation; 1 – present or pathological manifestations; this procedure was useful in the statistical elaboration of data.

Table II. Coefficients of correlation between manifestations and classification groups.

	Group A	Group B	Group C
First diagnosis	0.11	-0.1	0.15
Relapse	0.2	0.17	0.09
Sex M	-0.22	-22	0.06
Sex F	0.2	0.01	0.03
Age 0-44 yrs	0.12	0.24	-0.15
45-55	0.11	0.28	0.16
> 55	-0.26	0.04	-0.03
Globus	0.03	0.18	0.08
Cough	-0.17	0.27	0.01
Hoarsness	0.38	0.06	0.09
Otalgia	0.1	0	0.3
Pain on deglutition	0.1	0.02	0.16
Sialorrhea	0.01	0.13	0.06
Dry throat	0.01	0.37	0.07
Lat. cervical pain	0.29	0.09	0.08
Haemophtoe	0	0.02	0
Laryngeal spasm	0	0.02	0.04
Halitosis	-0.14	0.02	0.22
Epigastralgia	0.19	-0.16	-0.03
Heartburn	0.03	0.19	0.24
Hiccup	0	0	0
Regurgitation	0.1	0.14	0.06
Back sternal pain	0.03	0.19	0.24
Hiatal hernia	0.37	0.38	0.01
Gastric ulcer	0.15	0.39	0.01
Gastritis	0.09	-0.12	0.12
Asthma	0	0.02	0

Table III. Percent appearance of manifestations in different classification groups; those underlined and in bold script are the three most frequent (major manifestations), the underlined are the five successive in order of appearance (minor manifestations).

	Total	A	B	C
Globus	77	27	80	71
Cough	66	19	77	11
Dysphonia	81	21	94	15
Otalgia	5	1	2.9	1
Odynophagia	17	4	17	29
Sialorrhoea	3.4	1	2.9	6
Dry throat	18	8.2	11	24
Lateral cervical pain	23	13	2.9	29
Haemophthoe	0	0	0	0
Laryngospasm	9	8	6	12
Halitosis	3	0	3	12
Epigastralgia	33	15	23	29
Pyrosis	40	13	29	65
HICCUP	0	0	0	0
Acid reflux	40	16	31	47
Back sternal pain	17	5	20	18
Hiatal hernia	25	4	3	24
Gastric ulcer	7	1	3	6
Gastritis	6	1	6	12
Asthma	3	2	3	0

Table IV. Percentages of groups presenting a combination of major and minor manifestations.

Patients n = 178 92.3-95.5% of patients 2 major manifestations + 2 minor manifestations
Grade A n = 68 94.2-96.1% of patients 2 major manifestations + 1 minor manifestation
Grade B n = 70 94.3-100% of patients 2 major manifestations + 2 minor manifestations (100% if globus + dysphonia were chosen)
Grade C n = 34 83.7-89.3% of patients 2 major manifestations + 2 minor manifestations

All the patients included in the study have undergone pH-metry. A large majority (no. = 154) had a positive test, whereas it was negative in 24 (13.3%). Of these, the majority (54.3%) presented in group A. Surprisingly, in 24 cases with negative pH-metry, the most common symptomatological triad was the same as in the rest of the sample: globus, cough and dysphonia.

Conclusions

- 1) The proposed classification presents an indicative distribution of the progression of severity and would, therefore, appear to be acceptable as far as concerns efficiency and simplicity.
- 2) It seems not to emerge among all manifestations that one who is singularly considered is provided with the gravity in the objective picture⁶, on the contrary our classification seems to correlate to a group of symptoms or signs.
- 3) In the majority of cases in our sample, the most constant symptomatological triad was globus, cough and dysphonia (corresponding to the findings of Remacle)⁷. We refer to them as RISK "Reflux Infernal Serial Killers".
- 4) Changing the histological nature in erosion or granulation (group C) so called typical symptoms (or properly intestinal) pyrosis and regurgitation appear among the most frequent manifestations.
- 5) In the oedematous lesions or erythematous lesions extended beyond the posterior region (group B), the only symptoms, globus and dysphonia are present together in 100% of cases in this group, so they need particular clinical attention.
- 6) Among the subjects excluded from the study were 22 cases of granulomas with indicative manifestations but not responding to PPI: it is always

necessary, in these cases, to suspect aetiology not only referable to reflux.

- 7) Granulomas caused by reflux need prolonged medical therapy with PPI; in such lesions, surgery (both traditional and laser) must be critically evaluated since recurrence is very frequent.
- 8) Among the subjects excluded from the study, a

small group (n. 5) presenting characteristic symptoms, but without video-laryngoscopy signs, improved with proton pump inhibitor (PPI).

- 9) The pH-metry results did not seem to influence the onset of the most frequent symptoms (globus, cough, dysphonia), therefore it does not appear to be appropriate as a first level test.

References

- ¹ Belafsky PC, Postma GN, Koufman JA. *The validity and reliability of the reflux finding score (RFS)*. Laryngoscope 2001;111:1313-7.
- ² Belafsky PC, Postma GN, Koufman JA. *Laryngopharyngeal reflux symptoms improve before changes in physical findings*. Laryngoscope 2001;111:979-81.
- ³ Taghavi SA, Ghasedi M, Saberi-Firoozi M, Alizadeh-Naeni M, Bagheri-Lankarani K, Kaviani MJ, et al. *Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole*. Gut 2005;5:1067-71.
- ⁴ Park KH, Choi SM, Kwon SU, Yoon SW, Kim SU. *Diagnosis of laryngopharyngeal reflux among globus patients*. Otolaryngol Head Neck Surg 2006;134:81-5.
- ⁵ Wang JH, Luo JY, Dong L, Gong J, Zuo AL. *Composite score of reflux symptoms in diagnosis of gastroesophageal reflux disease*. World J Gastroenterol 2004;10:3332-5.
- ⁶ Ford CN. *Evaluation and management of laryngopharyngeal reflux*. JAMA 2005;28:1534-40.
- ⁷ Remacle M, Lawson G. *Diagnosis and management of laryngopharyngeal reflux disease*. Curr Opin Otolaryngol Head Neck Surg 2006;14:143-9.