LETTER TO THE EDITOR

Diagnosis and grading of laryngopharyngeal reflux disease with narrow band imaging: preliminary study

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To the Editor,

Laryngopharyngeal reflux (LPR) disease is a common problem in ear, nose and throat practice and involves about 4-10% of the general population. Symptomatology is characterized by dysphonia, chronic cough, sore throat, throat mucus and pharyngeal globous (1). LPR signs include mucosal modification, mucus dryness, epithelium thickening and occasional evidence of granuloma, contact between the epiglottis and hypertrophied lingual tonsil and oropharyngeal posterior wall (2).

The gold standard in LPR diagnosis is pH-metry. This is an invasive and expensive method that presents a poor reproducibility and lacks a clear pH cut-off level. In order to avoid this exam, two questionnaires are used in clinical practice for LPR diagnosis: the reflux symptoms index (RSI) and reflux findings score (RFS). In particular, the RFS is based on endoscopic evaluation and catalogues the various reflux lesions that may be present.

In recent years, some studies have proposed narrow band imaging (NBI) laryngoscopy as a useful method for diagnosing LPR, to quantitatively evaluate the signs of LPR observed (3). The aim of this preliminary study was to evaluate the potential use of NBI for the diagnosis of LPR. It is based on the research for a lowly invasive method that can help to improve the visualization of LPR signs, currently conducted with white light. Moreover, the NBI score was introduced as a possible grading system of LPR disease.

MATERIALS AND METHODS

This study was performed at the Department of Sense Organs of "Sapienza" University of Rome. Fifty-two patients (47 males, 5 females; 24-76 years of age, average 57 years) were enrolled between November 2019 and January 2020. All patients gave their written consent for all the tests and for their enrolment in the study. This research was performed in accordance with the principle of the Declaration of Helsinki and approved by the local Ethics Committee of "Sapienza" University of Rome.

The exclusion criteria applied were age <18 years, presence of oral disease, presence of laryngeal cancer, use of pump inhibitors or other drugs for LPR treatment at the time of and three months prior to the study.

All patients completed the Reflux Symptom index (RSI) questionnaire and white light laryngoscope evaluation calculating Reflux Findings Score (RFS) (Table I) (4-5). RSI is a self- conducted questionnaire based on nine questions with a maximum of 5 points for each answer that give a total maximum score of 45 points. A high suspicion of LPR is considered with a score ≥ 13. RFS considers 8 findings with a scale that goes from 0 to 26, gives a diagnosis of LPR

Key words: laryngopharyngeal reflux disease; RSI; RFS; NBI; LPR grading

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presence/absence, and indicates a pathological situation when RFS ≥ 7, but it is not able to estimate the grade of LPR disease.

Two groups were identified: patients evaluated with white light laryngoscope with RFS ≥7 were enrolled in Group A, while patients with RFS <7 were enrolled in Group B. RSI score was performed to estimate the grade of symptomatology of the patients, but it was not considered so relevant for LPR diagnosis and grading, in consideration of the high subjectivity of the answers. Therefore, it was not

Table I. *Reflux Symptoms Index and Reflux Finding Score*

REFLUX SYMPTOMS INDEX	
Hoarseness or a problem with voice	0 1 2 3 4 5
Clearing your throat	0 1 2 3 4 5
Excess throat mucus or postnasal drip	0 1 2 3 4 5
Difficulty swallowing food, liquids, or pills	0 1 2 3 4 5
Coughing after eating or after lying down	0 1 2 3 4 5
Breathing difficulties or choking episodes	0 1 2 3 4 5
Troublesome or annoying cough	0 1 2 3 4 5
Sensations of something sticking in your throat or lump in your throat	0 1 2 3 4 5
Heartburn, chest pain, indigestion, or stomach acid coming up	0 1 2 3 4 5
REFLUX FINDING SCORE	
Subglottic edema	2=present 0= absent
Ventricular obliteration	2= partial 4= complete
Erythema/ hyperemia	2= arytenoids only 4=diffuse
Vocal fold edema	1= mild 2= moderate 3= severe 4= polypoid
Diffuse laryngeal edema	1= mild 2= moderate 3= severe 4= obstruction
Posterior commissure hypertrophy	1= mild 2= moderate 3= severe 4= obstruction
Granuloma/ granulation	2=present 0= absent
Thick endolaryngeal mucus	2=present 0= absent

taken into consideration for the division of the groups. The RFS score is also subjective, but this error was reduced by training the authors in RFS evaluation criteria. According to this, endoscopic evaluation of LPR with RFS was conducted by the same author using a white light flexible endoscope connected to a camera and a high-definition monitor (Full HD). Moreover, the exam was recorded and independently evaluated some days later, by other two authors in order to confirm the results.

Considering that with white light laryngoscopy the presence of LPR could be under-rated, the patients of both groups underwent RFS evaluation conducted with narrow band imaging (NBI) system endoscope (Olympus, Japan) which is an optical technology able to identify the micro vessel on the mucosa surface (6). Also in this case, endoscopic evaluation of LPR with RFS was conducted by the same author and the exam was recorded and independently evaluated by two other authors.

Comparison of both RFS scores, calculated with white light and NBI, was performed and patients affected by LPR visible only with NBI system were identified (Figs. 1-3).

As previously stated, the RFS score defines only the presence or the absence of LPR but is not able to grade it. Therefore, the NBI score was performed to improve the evaluation of LPR signs, including a grading score that could help to classify different types of LPR damage. Beginning from RFS score, the most important LPR signs were considered and the NBI score was calculated (Table II).

NBI maximum total score was 13. NBI grading score of LPR included:

- Grade 1 (0-2 points) = Absent or Mild LPR
- Grade 2 (3-7 points) = Moderate LPR
- Grade 3 (8-13 points) = Severe LPR

Statistical analysis was performed using Stat view statistical software version 8.0. The Student's t-test was employed to compare the data of the study. A value of $p<0.05$ was considered statistically significant.

RESULTS

As mentioned in the methods section, fifty-two patients were enrolled in the study. Thirty-four patients with RFS≥7, evaluated with white light laryngoscope, were classified as Group A (30 males, 4 females; average 57.53 years of age). Eighteen patients,

Table II. *NBI Score*

Erytema/ Hyperemia	0= absent 1= arytenoids only 2= diffuse erythema
Vocal Fold Edema	0= absent 1= mild 2= moderate 3= severe 4= contact ulcerus 5= polypoid
Posterior Commissure Hypertrophy	0= absence of green spots 1= presence of green spots that involves <25% of posterior commissure 2= presence of green spots that involves between 25 and 50% of posterior commissure 3= presence of green spots that involves between 50 and 75% of posterior commissure 4= presence of green spots that involves >75% of posterior commissure
Granuloma	0= absent 1= Initial 2= Present

evaluated with white light laryngoscope and with RFS <7 belonged to Group B (17 males, 1 female; average 56 years of age). No statistically significant difference emerged between two groups regarding age (p=0.34).

In Group A, analysis of the data showed an average value of RSI of 18.35 (range 13-27) while in Group B the average value of RSI was 13.78 (range 6-26). No statistically significant difference emerged between the two groups (p=0,03). These data confirmed that the RSI was too subjective and barely useful in LPR

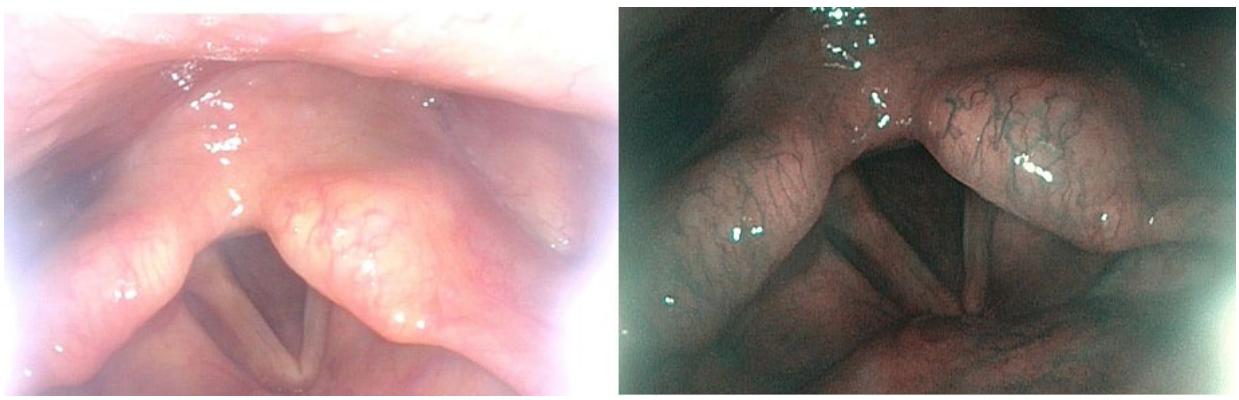

Fig. 1. *Comparison between laryngoscope performed with white light and NBI. Patient is not affected by LPR.*

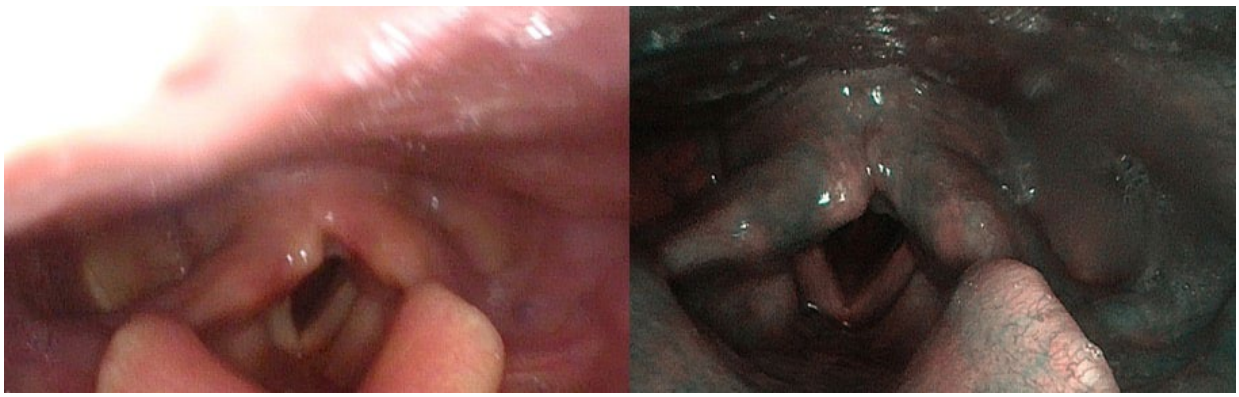

Fig. 2. *Comparison between laryngoscope performed with white light and NBI. The presence of green spots is evident in the posterior commissure that involves about 50% of the region with NBI technique.*

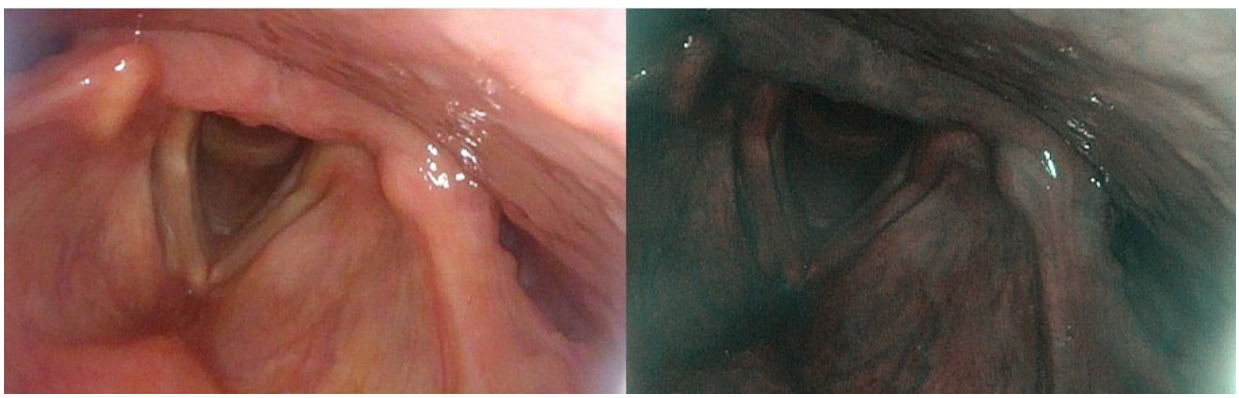

Fig. 3. *Comparison between laryngoscope performed with white light and NBI. A diffuse increasing of vascularization is presented with NBI technique.*

screening, so it was decided not to consider it for the creation of the groups. In Group A, the average RFS values, evaluated with white light, was 11.94 (range 8-15) while in Group B the average of RFS was 4.89 (range 3-6). A statistically significant difference was observed between the two groups ($p<0.00003$). In Group A, the average value of RFS, evaluated with NBI laryngoscopy, was 12.65 (range 9-21), while in group B, it was 7.89 (range 3-13). A statistically significant difference was observed between the two groups ($p<0.001$). In Group A, a comparison of RFS values calculated with white light and RFS values calculated with NBI resulted statistically different ($p< 0.005$).

In Group B, a comparison between RFS values calculated with white light and RFS values calculated with NBI resulted statistically different ($p<0.005$). Moreover, analysing the data of RFS estimated with white light, it was possible to diagnose LPR in 65% of patients enrolled in the study (34/52 patients). In contrast, the data regarding RFS evaluated with NBI showed that 88% of patients presented signs of LPR (46/52 patients).

A statistically significant difference emerged between the number of patients suffering from LPR diagnosed with white light compared to the NBI technique ($p<0.001$). According to the methods described, it is evident that the RFS is a score able to estimate the presence or the absence of LPR disease, but not able to grade LPR lesions. Therefore, use of the NBI score was proposed. The average NBI score in Group A was 7.6 (range 3-11). In group B, the average NBI score value was 4.4 (range 1-6). The NBI score in the two groups statistically differed ($p=0,00106$). In group A, 22 patients (64%) presented a Grade 3 NBI score, 12 patients (35%) Grade 2 and none of the patients Grade 1. In group B, 6 patients (33%) presented a Grade 1 NBI score, 10 patients (55%) Grade 2 and 2 patients (11%) Grade 3.

According to these results it is possible to point out that NBI increased the possibility of recognizing LPR disease in comparison to white light laryngoscopy. In fact, in group B, 12 patients (67%) affected by LPR, were considered healthy according to white light laryngoscope evaluation, despite a moderate/severe pathological grade employing NBI. These data confirmed that NBI increased the chance of a precise evaluation of the severity of LPR in respect to white light laryngoscopy.

DISCUSSION

Clinical diagnostic assessment of LPR is still not well-defined. The gold standard is Multichannel Intraluminal Impedence pH monitoring (MII pH). The latter presents some limitations as it could be associated with false positives since the number and type of reflux episodes may vary during the day; it is invasive and expensive with a poor reproducibility due to the position of the proximal sensor (in the case of suspected LPRD), and without a clear pH cut-off level (7-8).

Moreover, the proximal sensor could be inaccurate, resulting in pseudo-reflux because, during the exam, the superior and inferior esophageal sfincters are opened (9). Other diagnostic methods for LPR, used in clinical practice, include RSI and RFS that are easy to administer. However, RSI presents some limitations as it is a subjective score that evaluates LPR complaints with a visual analogue scale, and is related to socio-cultural factors without taking into consideration all LPR symptoms. Moreover, RSI does not consider the duration and frequency of symptoms during LPR disease. According to all these limitations, it was decided not to take RSI into consideration.

On the other hand, RFS is a more objective score. Thus, three authors, trained for the evaluation of LPR signs, independently analysed the signs to minimize potential errors of interpretation. In the event of disagreement between the three observers, the patient was excluded from the study group.

RFS performed with white light was used to identify two groups of patients, one affected by LPR (Group A) and the other non-LPR (Group B). The groups resulted statistically different, confirming that the score is able to distinguish LPR patients from healthy ones.

In recent years, the international literature has indicated that NBI laryngoscopy is useful for diagnosing not only laryngeal neoplastic disease but also inflammatory diseases (10-11). Galli et al. studied NBI for rhino-pharyngo-laryngeal reflux in paediatric patients and observed that NBI furnished evidence of LPR signs not observed by white light (12).

The aim of the present study was to evaluate the possible use of NBI in adult patients as an integrated endoscopic examination in LPR diagnosis, owing to its ability to highlight superficial microvessels and the vascularity of the mucosa. Our outcomes showed that RSF assessed by white light examination recognized LPR signs in 65% of the patients, while the same score calculated with NBI laryngoscopy recognized 88% of patients affected by LPR disease. This information testified to the greater sensitivity of NBI laryngoscopy in LPR diagnosis in comparison to the white light one.

As previously described, RFS is a score able to indicate the presence/absence of LPR disease but is unable to estimate its grade. This prompted us to devise an NBI classification system. The score was based on the ability of NBI to assess the micro-vessels of the larynx and to better visualize some initial lesions, such as granuloma. Therefore, the four points of the RFS were considered and adapted to define specific LPR grades based on characteristic signs.

Erythema/hyperaemia is better evidenced with green light, showing an increased presence and localization of micro-vessels. White light examination is less able to analyse contact ulcera in the vocal fold and initial granuloma than the NBI technique, so they were included in the score. Furthermore, the most important point in the NBI score regards the presence of green spots in the posterior commissure. Considering the percentage of surface taken up by green spots in this area, it is possible to quantify the damage caused by chronic insults.

This study showed that NBI laryngoscopy recognized 23% of patients with LPR signs more than the white light method, which indicates that white light is able to recognize LPR disease when there are severe signs of LPR, but is unable to recognize the less severe signs that only NBI showed. This is confirmed by the data regarding the severity of LPR observed with our system of classification. The patients of Group A showed mainly LPR grade 3 (65%), while in group B LPR Grade 2 was predominant (55%).

In conclusion, the results of this preliminary study suggest that NBI could improve the identification of LPR signs, thanks to its ability to identify green spots and vascularity. This study could be a starting point for further ones, based on larger populations, able to assess the also grade of the LPR disease.

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