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ONLINE FIRST

Esophagus

ISSN 1612-9059

Esophagus
DOI 10.1007/s10388-020-00726-9

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https://doi.org/10.1007/s10388-020-00726-9

ORIGINAL ARTICLE

Predictors of reflux aspiration and laryngo-pharyngeal reflux

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Received: 29 November 2019 / Accepted: 12 February 2020
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Abstract

Background Gastro-esophageal reflux disease (GERD) can present with typical or atypical or laryngo-pharyngeal reflux (LPR) symptoms. Pulmonary aspiration of gastric refluxate is one of the most serious variants of reflux disease as its complications are difficult to diagnose and treat. The aim of this study was to establish predictors of pulmonary aspiration and LPR symptoms.

Methods Records of 361 consecutive patient from a prospectively populated database were analyzed. Patients were categorized by symptom profile as predominantly LPR or GERD (98 GER and 263 LPR). Presenting symptom profile, pH studies, esophageal manometry and scintigraphy and the relationships were analyzed.

Results Severe esophageal dysmotility was significantly more common in the LPR group ($p = 0.037$). Severe esophageal dysmotility was strongly associated with isotope aspiration in all patients ($p = 0.001$). Pulmonary aspiration on scintigraphy was present in 24% of patients. Significant correlation was established between total proximal acid on 24-h pH monitoring and isotope aspiration in both groups ($p < 0.01$). Rising pharyngeal curves on scintigraphy were the strongest predictors of isotope aspiration ($p < 0.01$).

Conclusions Severe esophageal dysmotility correlates with LPR symptoms and reflux aspiration in LPR and GERD. Abnormal proximal acid score on 24-h pH monitoring associated with pulmonary aspiration in reflux patients. Pharyngeal contamination on scintigraphy was the strongest predictor of pulmonary aspiration.

Keywords LPR · GERD · Reflux aspiration · Esophageal motility · Scintigraphy

Background and purpose

Gastro-esophageal reflux disease (GERD) can present in a number of ways and atypical symptoms are frequently difficult to diagnose as reflux and treat. Common symptoms of GERD include heartburn and regurgitation, whilst cough, sore throat, recurrent pneumonia, globus, and hoarseness are generally regarded as "atypical" symptoms. Based on the symptom profile, GERD is sub-classified as esophageal or extraesophageal [1]. Laryngo-pharyngeal reflux (LPR) is believed to be caused by the contamination of the larynx and pharynx with gastric contents. Symptoms of chronic cough, throat clearing, and globus sensation are non-specific and can be attributed to other conditions [2, 3]. Currently, there is no reference standard for the diagnosis of LPR. Proximal pH monitoring is deficient technically as many of the proximal reflux episodes are non-acidic and cannot be reliably measured in the pharynx. Findings of impedance reflux measurements in the upper esophagus, even though not dependent on acid measurement, are often difficult to interpret [4]. Furthermore, none of the above methods have been validated in the diagnosis of cough. Untreated LPR with recurrent upper airway contamination can have serious consequences which range from paradoxical vocal cord motion to laryngeal stenosis, asthma, recurrent pneumonia, pulmonary fibrosis, and laryngeal malignancy [5, 6]. The current algorithms for work-up for GERD and LPR include history and physical examination, trans-nasal laryngoscopy and gastro-intestinal endoscopy, 24-h pH monitoring, esophageal impedance, esophageal manometry, barium swallow, and scintigraphy; none of which is definitive [7–9].

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Published online: 21 February 2020

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Ineffective esophageal motility (IOM) has been thought to be a major factor in GERD and LPR [10, 11]. However, the exact role of the IOM has not been established [12–14]. We present the findings of esophageal manometry, dual-channel 24-h pH monitoring, and scintigraphy in two clinically distinct groups of patients classified as LPR or GERD.

We hypothesized that severe esophageal dysmotility is an important determinant of LPR and lung aspiration of refluxate. This hypothesis was tested in 361 consecutive patients with resistant to medical management reflux referred for surgical opinion.

Patients and methods

Patient population

Data were extracted from prospectively populated research database containing records of patients with GERD that was approved by the University of Notre Dame Australia Human Research Ethics Committee (019091S) on 23rd of July 2019. This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patient provided informed written consent to participate in research.

A senior surgical consultant assessed all patients and prospectively clinically categorized their symptoms as predominantly GERD or LPR based on the dominant symptom. Consecutive patients with symptoms typical of GERD (predominant heartburn, and chest pain) or LPR (predominant cough, throat clearing, voice change, laryngospasm, recurrent pneumonia, mucus sensation and globus) who underwent esophageal manometry, pH studies, and scintigraphy were included. All patients had been referred for surgical consideration to a tertiary referral center due to severity of symptoms and/or resistance to maximal medical therapy. The cohort is, therefore, highly selected with a high pre-test probability of severe GERD/LPR.

pH Monitoring

Antimony crystal dual-channel catheters and Digi trapper Mark III recorder (Medtronics, Synectics Medical, Minneapolis, Minnesota, USA) were used for pH monitoring and data collection as a part of assessment process. The distal esophageal probe was placed 5 cm above the manometrically identified upper border of lower esophageal sphincter, and the proximal probe placed 15 cm above the distal probe. pH data were analyzed using the Synectics PW esophagram reflux analysis module (Medtronics, Synectics Medical, Minneapolis, Minnesota, USA). Monitoring was conducted in ambulatory settings.

Manometry

Esophageal manometry was performed using a standard technique with a water-perfused dent sleeve eight-channel catheter (Dent Sleeve International, Mississauga, Ontario, Canada). Data were recorded with a multichannel recording system (PC polygraph HR Medtronics, Synectics Medical, Minneapolis, Minnesota, USA). Analysis of esophageal motility was done by the PolyGram software program (Medtronics, Synectics Medical, Minneapolis, Minnesota, USA). Esophageal motility was classified as normal (less than two ineffective swallows), mild ineffective esophageal motility (IOM) (2–3 swallows with ineffective peristalsis), moderate IOM (4–5 swallows with ineffective peristalsis), or severe IOM (six or more swallows with ineffective peristalsis) using criteria modified from Kahrilas et al. [10, 11].

Scintigraphy

Scintigraphy was conducted using computer-generated isotope counting minimizing potential inter-observer bias. This particular method of scintigraphy in diagnosis of GERD and LPR has been previously described in detail and validated by this group, and control values have been published [8, 9, 15]. Patients were fasted overnight and then placed before Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with stomach, chest, and upper airway in the field of view. Patients were administered 40–60 MBq of 99mTc DTPA diluted in 150 ml of water, followed by a 50-ml water to promote clearance of isotope from pharynx and esophagus. Images were obtained for 2 min at 15 s per frame into a 64×64 matrix, followed by a 30-min dynamic image while supine for 30 s per frames. Aspiration was proven on delayed images at 2 h by the presence of isotope in the lungs (Fig. 1). Isotope time-activity curves (Fig. 2) were recorded for the pharynx and upper esophagus supine and erect, and classified as falling, flat, or rising curves (Fig. 3). It was considered that a falling curve reflected clearance of refluxate and rising curve accumulation of refluxate.

Statistical analysis

Data analysis was undertaken using nonparametric statistical methods as much of the analysis was of ordinal data with multiple studies for each patient. Analysis of variance (ANOVA), Mann–Whitney U test, Student's t test, Fisher's exact test, and Pearson/Spearman correlation coefficient (two-tailed) with significance levels of 0.05 were utilized. Receiver-operating characteristics (ROC) were assessed to evaluate the best predictors for pulmonary aspiration. Cluster analysis of the principal

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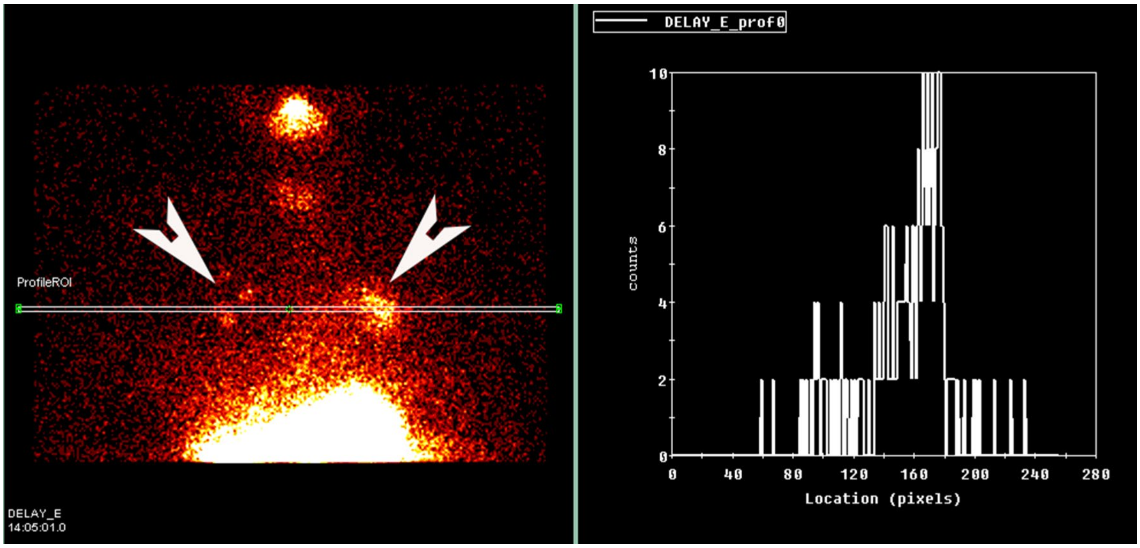

Fig. 1 Left of the screen is a delayed scintigraphy study showing aspiration of tracer into both lungs (white arrowheads) and the double white-line marking for computer-generated isotope count. Right of the screen is a computerized report as profile showing the count through the regions white lines. A high isotope count is apparent for the left lung activity (location 160–190 pixels)

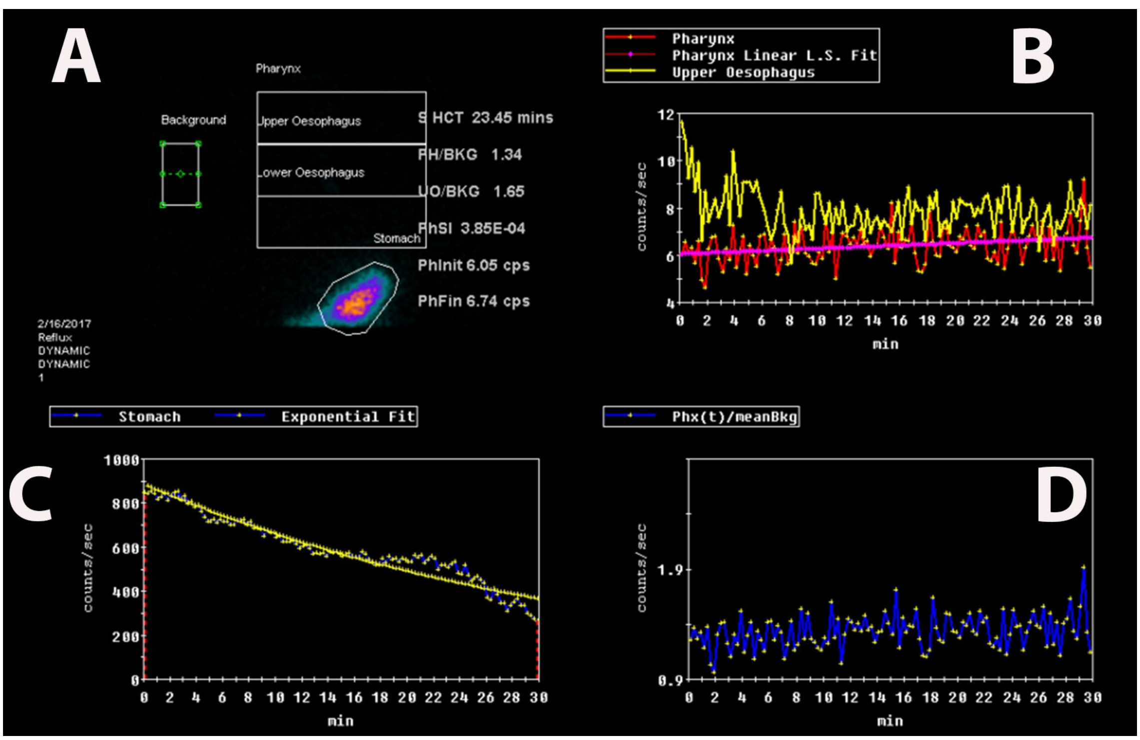

Fig. 2 Typical graphical analysis of the scintigraphic study showing the markings of the regions of interest for the pharynx, esophagus, stomach, and background in the top left panel (**a**). **b** Analysis of the time-activity curves for the pharynx (pink/red) and upper esophagus (yellow). A rising curve is apparent for the pharynx (purple line ascending). **c** Fitted curve for estimation of liquid gastric emptying which has a time to half clearance of 22.5 min (shown in panel A). **d** Graphical representation of the ratio of pharyngeal-to-background time-activity curves (mildly raising time-activity curves indicate low-volume reflux contamination)

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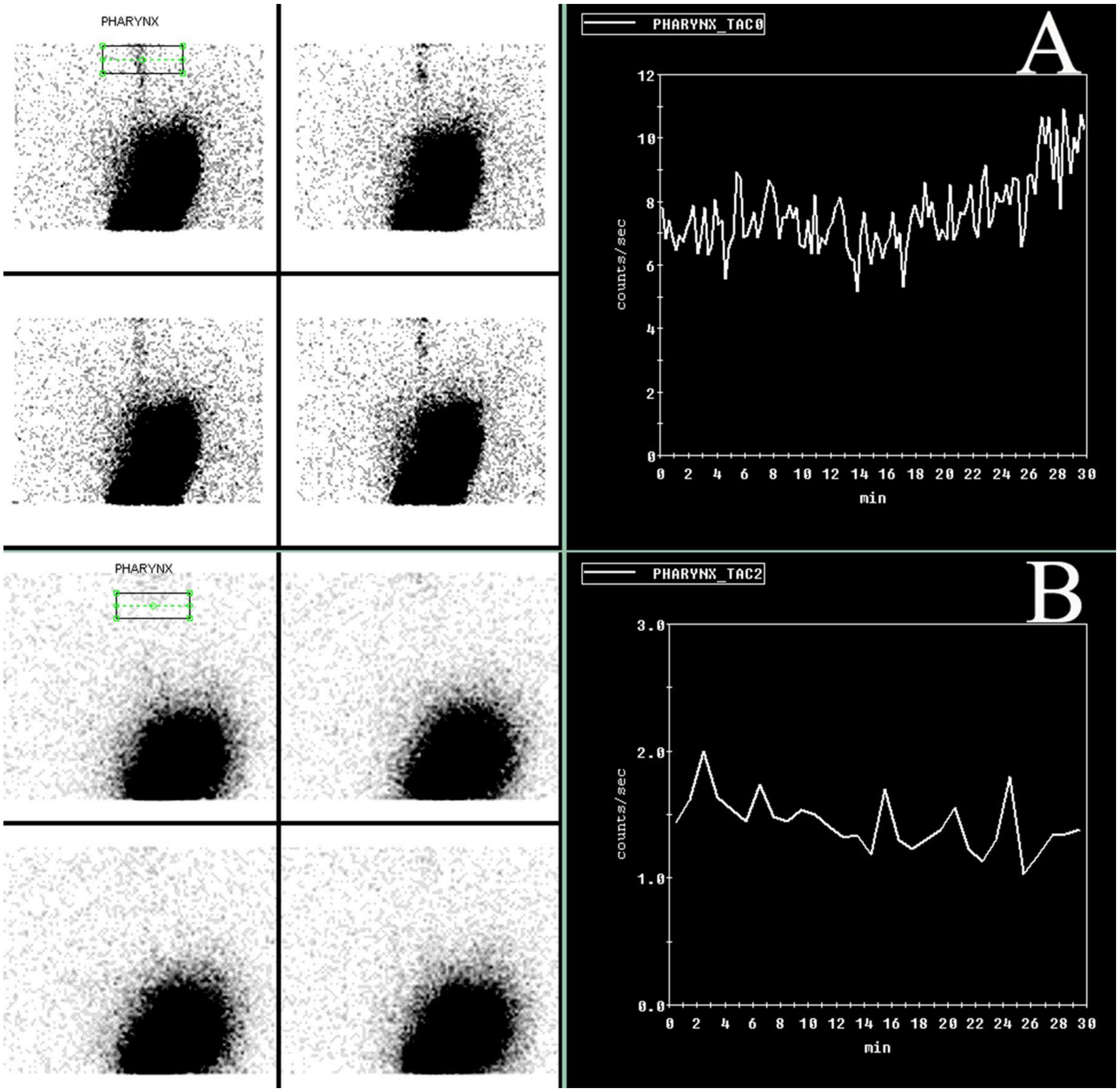

Fig. 3 Typical graphic analysis showing computer-generated count for isotope contamination in the pharynx. To the left of the screen, there are scintigraphic images marked for counting and to the right of the screen graphs showing results for the areas marked. Y-axis reflects isotope count and X-axis reflects time of study. Panel A showing clearly rising isotope count (contamination due to reflux), whilst panel B showing flat count (no evidence of reflux reaching pharynx)

variables was undertaken to evaluate linkages between ten key variables and for the groups (LPR vs. GERD). Cluster analysis is a multivariate procedure for detecting natural groupings in data [16]. Euclidean distance (root-mean-squared) was utilized and displayed as a vertical icicle plot. Univariate and multivariate analyses were used to evaluate possible etiologies of dominant symptom profiles (LPR vs. GERD). The Statistica V8 software (Statsoft, Oklahoma, United States) package was used for data analysis.

Results

Population and clinical data

Inclusion criteria were met by 361 patients (223 female and 138 male). The mean age was 60.8 years (SD 14.6; range 16–90 years). There were 98 patients in the GERD subgroup (47 female and 51 male) with average age of 56 years (SD 13.61, range 23–84). The LPR subgroup

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Table 1 Demographic characteristics and summary of the main findings of this study according to the symptom profile group

	GERD	LPR	All patients
Number of patients			
Male	51	176	227
Female	47	87	134
Total	98	263	361
Age			
Average	56	63	60.8
SD	13.61	14.95	14.6
Range	23–84	16–90	16–90
LOS pressure mean (mmHg)[a]	7.4	6.9	7.0 (95% CI 6.1–7.8)
Severe IOM[b]			
n	29	105	134
%	28%	40%	37%
Pulmonary aspiration[c]			
n	19	75	94
%	19%	29%	26%
24-h pH proximal acid exposure[d]			
n abnormal	32	71	103
Mean time %/24 h (SD)	0.9% (SD 4.3)	1.9% (SD 6.4)	1.8% (SD 6.2)

[a]Reduced LOS was associated with pulmonary aspiration ($p=0.001$) and proximal esophageal acid exposure ($p=0.019$)

[b]Significant difference between the groups ($p=0.037$)

[c]Result did not reach statistical significance ($p=0.08$)

[d]Proximal esophageal acid exposure on 24-h pH monitor was associated with pulmonary aspiration ($p=0.003$)

included 263 patients (176 female and 87 male) and mean age of 63 years (SD 14.95, range 16–90).

Patient demographic data and key results are summarized in Table 1.

Manometry

The outstanding feature of manometric findings was that 40% of the LPR group patients had severe IOM compared with 28% in the GERD group. This was a significant difference ($p=0.037$). Normal esophageal motility was found in 48% with LPR symptoms and in 60% with GERD symptoms, and was not statistically significant.

The mean lower esophageal sphincter pressure was reduced at 7.0 mm Hg (Median 3.4, SD 8.1 (95% CI 6.1–7.8) mm Hg). No significant difference was found between the LPR and GERD groups for mean LOS pressure.

Manometry: correlations between IOM, aspiration, and symptom profile

Severe IOM was strongly associated with isotope aspiration in both groups ($p=0.001$).

There was a strong correlation (Spearman) between IOM and isotope curves in the pharynx and upper esophagus both when supine and upright ($p<0.01$).

Significantly more rising isotope activity curves (grade 3) were demonstrated in patients with LPR than with GERD symptoms ($p=0.0017$). There was, however, no statistically significant difference in isotope aspiration between the groups ($p=0.08$).

Reduced lower esophageal sphincter pressure was associated with an increased proximal acid exposure ($p=0.019$) and risk of isotope aspiration ($p=0.001$).

pH Studies

pH Studies were abnormal in 70% of patients. Total proximal acid exposure was a mean of 4.2%/24 h (SD 6.2). Total distal acid exposure was a mean of 9.3%/24 h (SD 12.7).

pH Studies: correlation of aspiration and pH study

There was a correlation between total proximal acid on 24-h pH monitoring and pulmonary isotope aspiration ($p=0.003$) in both groups. There was no correlation between total distal acid on 24-h monitoring and aspiration ($p=0.87$).

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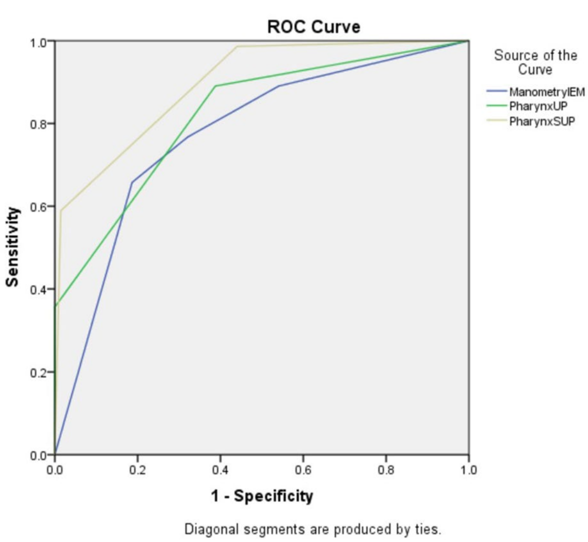
Scintigraphic studies

Aspiration of refluxate into the lungs was found in 94 patients (26%). When examined by symptom profile, there were 19 patients in the GERD group (19%) and 75 (29%) in the LPR group with pulmonary aspiration.

Scintigraphic parameters and pulmonary aspiration

Rising activity curves in the pharynx were strong predictors of isotope aspiration ($p<0.01$), both when upright and supine. While a higher proportion of patients with aspiration were from the group with LPR symptoms (29% vs. 19%), this apparent difference was not significant with the two-tailed Fisher's exact test ($p=0.08$).

For all patients, the negative predictive value of a declining time-activity curve for aspiration for the pharynx in the upright and supine positions was 98%. A rising time-activity curve for the pharynx in the upright and supine position had a positive predictive value of 88% for aspiration. A similar pattern for the esophageal curves gave a negative predictive value of 97% and a positive predictive value of 85%.



Area Under the Curve

Test Result Variable(s)	Area
ManometryIEM	.773
PharynxUP	.820
PharynxSUP	.896

Fig. 4 Receiver-operating characteristic (ROC) analysis. Pharyngeal supine activity is the best predictor of lung aspiration of refluxate, followed by pharyngeal upright activity and manometry

Receiver-operating characteristic (ROC) analysis of pulmonary aspiration

The three best variables for predicting aspiration were the presence of severe IOM and the rising time-activity curves for pharyngeal tracer activity in the upright and supine positions. This is clearly shown in Fig. 4. The largest area under the curve was for pharyngeal tracer activity when supine (0.896) followed by the pharyngeal curve when upright (0.820) and severe IOM (0.773).

Cluster analysis

The purpose of luster analysis is to simply demonstrate central role of IEM in patients with pulmonary aspiration.

Strong linkages were found between pulmonary aspiration demonstrated by scintigraphy, all scintigraphic time-activity curves for the upper esophagus and pharynx, IOM, and clinical symptom profile (Fig. 5).

Discussion

The diagnosis of laryngo-pharyngeal reflux (LPR) is a clinical challenge. Clinical scoring systems to establish the probability of LPR in patients with upper aero-digestive symptoms have been proposed in the past [17]. Between 18.5% and 30% of general population will test as having high probability of LPR using the current Reflux Symptom Index, which is also reported to be an overestimation of the true incidence of LPR [18, 19]. Hull Airway Reflux Questionnaire is a useful and validated tool in diagnosing LPR

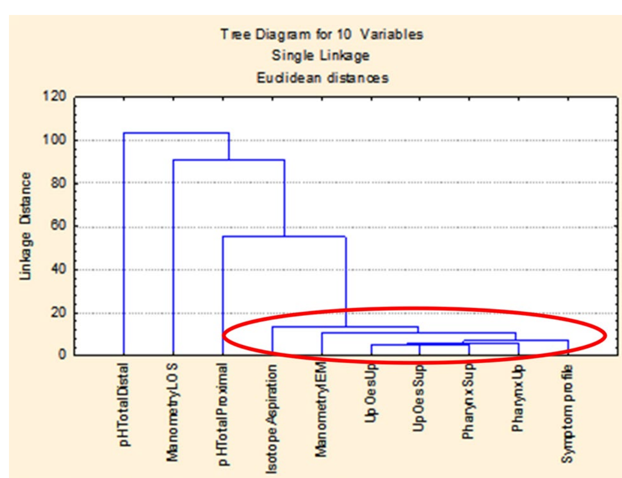


Fig. 5 Cluster analysis. The analysis shows tight linkages between manometry, upright and supine pharyngeal and upper esophageal scintigraphic activity, and the patient symptom profile

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symptoms due to reflux. However, it is a screening tool and does not positively diagnose airway reflux [20].

Scintigraphic study using the described technique may demonstrate, where no other test can, a significant proportion (~20%) of patients with severe GERD who also have clinically silent pulmonary aspiration.

A less foreseen but suspected result of this study was the association between esophageal dysmotility and lung aspiration of refluxate, as shown in the ROC analysis. Manometric measures of the lower esophageal sphincter pressures did not discriminate for this complication, as low pressures had a high prevalence in this treatment-resistant group of patients, reflecting disease severity. The prevalence of severe IOM was not significantly different between the LPR and GERD groups. This may be due to a selection bias as GERD patients in this cohort represent the more severe end of the spectrum of disease resistant to maximal medical therapy.

The importance of identifying patients with pulmonary aspiration is of patent clinical importance due to the potential for irreversible changes in the laryngopharynx and lungs. Preliminary data from an ongoing study of 120 patients with scintigraphic evidence of pulmonary aspiration show that while medical therapy may improve the symptoms of LPR or GERD, it does not reverse pulmonary aspiration [15].

Pulmonary aspiration can be treated with laparoscopic fundoplication with improvement demonstrated by scintigraphy as well as clinical resolution of symptoms [8, 21]. Previous work by this group found that over 90% of patients with clinical and scintigraphic evidence of LPR pre-operatively reported significant resolution of symptoms and scan improvement after surgery [8, 21].

Early research on esophageal dysmotility has suggested reduced esophageal clearance in individuals with IOM [22, 23]. In this study, patients showed a high degree of impaired esophageal motility, which was associated with pulmonary aspiration. The presence of refluxate in the upper esophagus can stimulate cough via "reflex" afferent pathways and the presence of gastric contents in the pharynx can cause direct irritation to the upper airways, also resulting in cough [24]. The impairment of esophageal clearance secondary to diminished esophageal motility may offer a plausible explanation for the development of symptoms through combined "reflux" and "reflex" pathways, allowing continued esophageal exposure or proximal exposure to gastric contents [25].

In our cohort, the average age in the LPR group was 7 years greater than the GERD group. Reasons for this variance are unclear. Many alternative causes of atypical reflux symptoms may require serial elimination extending the period to diagnosis. The lack of a simple positive predictive test for diagnosis of LPR may also contribute. Upper aero-digestive contamination was frequent in the GERD group. Delayed development of respiratory symptoms from the pulmonary disease could be due to changes in the mucociliary escalator defense mechanisms as a result of chronic exposure to gastric contents, further delaying time to diagnosis [5, 26]. Perhaps, trivializing the symptoms by the patient and the medical profession may contribute to delayed presentation and referral.

Limitations of this study were the collection of data over 8 years during which time the technique of scintigraphy was refined. There is substantial selection bias as all patients in this study were referred for consideration of surgery due to severity of symptoms and often multiple failed therapeutic strategies.

Conclusion

Severe esophageal dysmotility, raised proximal acid on 24-h pH monitoring, and pharyngeal contamination on scintigraphy are associated with pulmonary aspiration and LPR symptoms. Upper aero-digestive tract contamination with reflux is common in patients with LPR and severe treatment-resistant GERD. The results of this study indicate that reflux scintigraphy by this particular technique is invaluable in assessing patients with severe GERD, LRP, and unexplained pulmonary symptoms.

Funding No funding was received towards this research. Research database is approved by the University of Notre Dame Australia Human Research Ethics Committee (019091S) on 23rd of July 2019.

Compliance with ethical standards

Ethical statement This research conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All patient provided informed written consent to participate in research.

References

1. Vakil N, Van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20.
2. Barry DW, Vaezi MF. Laryngopharyngeal reflux: more questions than answers. Clevel Clin J Med. 2010;77:327–34.
3. Martinucci I, de Bortoli N, Savarino E, et al. Optimal treatment of laryngopharyngeal reflux disease. Ther Adv Chronic Dis. 2013;4:287–301.
4. Ravi K, Katzka DA. Esophageal impedance monitoring: clinical pearls and pitfalls. Am J Gastroenterol. 2016;111:1245–56.
5. Lee JS, Collard HR, Raghu G, et al. Does chronic microaspiration cause idiopathic pulmonary fibrosis? Am J Med. 2010;123:304–11.

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6. Postma GN, Halum SL. Laryngeal and pharyngeal complications of gastroesophageal reflux disease. GI Motil. 2006. https://doi.org/10.1038/gimo46.
7. Abou-Ismail A, Vaezi MF. Evaluation of patients with suspected laryngopharyngeal reflux: a practical approach. Curr Gastroenterol Rep. 2011;13:213–8.
8. Falk GL, Beattie J, Ing A, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21:3619–27.
9. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun. 2015;36:625–30.
10. Kahrilas PJ, Dodds WJ, Hogan WJ, et al. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology. 1986;91:897–904.
11. Kahrilas PJ, Dent J, Dodds WJ, et al. A method for continuous monitoring of upper esophageal sphincter pressure. Dig Dis Sci. 1987;32:121–8.
12. Simrén M, Silny J, Holloway R, et al. Relevance of ineffective oesophageal motility during oesophageal acid clearance. Gut. 2003;52:784–90.
13. Fornari F, Blondeau K, Durand L, et al. Relevance of mild ineffective oesophageal motility (IOM) and potential pharmacological reversibility of severe IOM in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;26:1345–54.
14. Abdel Jalil AA, Castell DO. Ineffective esophageal motility (IEM): the old-new frontier in esophagology. Curr Gastroenterol Rep. 2016;18:1.
15. Burton L, Falk GL, Parsons S, et al. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. Mol Imaging Radionucl Ther. 2018;27:113–20.
16. Scott AJ, Knott M. A cluster analysis method for grouping means in the analysis of variance. Biometrics. 1974;30:507–12.
17. Koufman JA, Aviv JE, Casiano RR, et al. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg. 2002;127:32–5.
18. Kamani T, Penney S, Mitra I, et al. The prevalence of laryngopharyngeal reflux in the English population. Eur Arch Otorhinolaryngol. 2012;269:2219–25.
19. Spantideas N, Drosou E, Bougea A, et al. Laryngopharyngeal reflux disease in the Greek general population, prevalence and risk factors. BMC Ear Nose Throat Disord. 2015;15:7.
20. Morice A, Spriggs J, Bell A. Utility of the Hull airways reflux questionnaire in the assessment of patients in the acute admissions unit. Eur Respir J. 2011;38:3513.
21. Khoma O, Falk SE, Burton L, et al. Gastro-oesophageal reflux and aspiration: does laparoscopic fundoplication significantly decrease pulmonary aspiration. Lung. 2018;196:491–6.
22. Chen CL, Szczesniak MM, Cook IJ. Identification of impaired oesophageal bolus transit and clearance by secondary peristalsis in patients with non-obstructive dysphagia. Neurogastroenterol Motil. 2008;20:980–8.
23. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology. 1988;94:73–80.
24. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. Chest. 2006;129:80s–94s.
25. Phua SY, McGarvey LP, Ngu MC, et al. Patients with gastro-oesophageal reflux disease and cough have impaired laryngopharyngeal mechanosensitivity. Thorax. 2005;60:488–91.
26. Pearson JP, Parikh S, Orlando RC, et al. Reflux and its consequences the laryngeal, pulmonary and oesophageal manifestations. Conference held in conjunction with the 9th International Symposium on Human Pepsin (ISHP) Kingston-upon-Hull, UK, 21–23 April 2010. Aliment Pharmacol Ther. 2013;33(Suppl 1):1–71.

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