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Original Research Article

Does laryngopharyngeal reflux disease impair nasal mucociliary transport? A case control prospective study

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ABSTRACT

Background: Laryngopharyngeal reflux disease (LPRD) is the retrograde reflux of gastro duodenal contents above the level of upper oesophageal sphincter into larynx and pharynx. LPRD can lead to upper respiratory pathology by direct contact of nasal and nasopharyngeal mucosa with the regurgitated gastric acid. Refluxate can damage the cilia, thereby prolonging the mucociliary clearance time (MCT) and consequently affecting the innate defence mechanism of upper airway. Our objective was to analyse the relationship between MCT and LPRD in patients without any nasal pathology.
Methods: This study was a prospective case control study, with 45 patients each in the study and reference group. Study group included patients with symptoms of LPRD who fulfilled the reflux symptom index (RSI) score of more than 13 points. The reference group included subjects without LPRD, with RSI less than 13. In both groups, conditions causing impaired MCT like allergic rhinitis, sinusitis, rhinitis and history of smoking were excluded. Chronic sinusitis cases were excluded in both groups using sino-nasal outcome test -22 scoring system. Nasal MCT was measured in all these participants using the Saccharin test. Duration more than 20 minutes was taken as prolonged mucociliary clearance time.
Results: MCT was prolonged in 62% of subjects (28 out of 45) in the study group whereas, in the reference population MCT was normal.
Conclusions: LPRD is a contributing factor for impaired nasal mucociliary transport.

Keywords: Laryngopharyngeal reflux, Mucociliary clearance, Mucociliary transport, Nasal mucosa, Rhinosinusitis

INTRODUCTION

Laryngo pharyngeal reflux disease (LPRD), also known as "silent reflux", is the retrograde reflux of gastro duodenal contents above the level of upper oesophageal sphincter into larynx and pharynx.[1] Patients with LPRD commonly have non-specific signs and symptoms and are hence prone to prolonged suffering.[2]

Nasal mucociliary clearance (NMC) is a primary innate defence mechanism of the nose and paranasal sinuses. Mucus secreted into the upper airway tract traps inhaled particulate matter, allergens and pathogens and is then transported in to the pharynx by the cilia, where it is swallowed.[3] Cilia beats at a frequency of 7 to 16 Hz in a metachronous fashion at body temperature.[4] Impaired NMC can predispose to chronic infection of the nose, paranasal sinuses and respiratory tract. Factors affecting NMC are physiochemical qualities and quantities of the mucous along with the property of cilia propelling it.[5] Impairment of NMC predisposes to chronic infections of the nose, paranasal sinuses, and respiratory tract.

LPRD can lead to upper respiratory pathology by direct contact of nasal and nasopharyngeal mucosa with the regurgitated gastric acid.[6] Gastric acid negatively affects the ciliary motility and morphology of respiratory mucosa.[7] Studies have shown that LPRD affects the ciliary motility, thereby prolonging the mucociliary clearance time (MCT).

The objective of this study is to measure the MCT in patients with LPRD and to analyse the association between them.

METHODS

A prospective case control study was conducted in the Department of Otorhinolaryngology, in a tertiary care teaching hospital in Coastal Karnataka, South India from January 2018 to July 2019. This study was conducted after approval from the Institutional Ethics Committee under the tenets of The Declaration of Helsinki and in accordance with National Ethical Guidelines for Biomedical Research involving human participants of Indian Council of Medical Research (ICMR), 2017.

Purposive sampling was done. Based on 5% level of significance and 80% power with effect size 0.6, a sample size of 90 participants was estimated of which 45 constituted the study group and 45 the reference group. Participants in the age range 18 to 50 years were considered for enrolment in the study. Study group included subjects diagnosed with LPRD based on reflux symptom index score (RSI) and 70 degree rigid video laryngoscopy findings. A nine-item questionnaire was administered to calculate RSI score for the assessment of symptoms in patients with LPRD. The scale for each individual item ranges from 0 (no problem) to 5 (severe problem), with a maximum score of 45 (Table 1). Diagnosis of LPRD was made if the score was more than 13.[8] Patients with symptoms of LPRD with RSI greater than 13 and laryngoscopic findings of erythema and oedema of arytenoid, diffuse laryngeal oedema, posterior commissure hypertrophy or thick endolaryngeal mucous were included in the study group. Reference group comprising of 45 individuals age and gender matched with the study group having no features of LPRD were enrolled into the study. Patients with history suggestive of allergic rhinitis or non-allergic rhinitis and chronic smokers were excluded. Patients with chronic rhinosinusitis (CRS) were excluded by sinonasal outcome test-22 scoring system.[9] A detailed patient information brochure was given to every individual included in the study and informed written consent was obtained.

Table 1: RSI score.[8]

How did the problems listed below affect you since last six months (please circle the appropriate answer)						
1. Hoarseness or voice problems	0	1	2	3	4	5
2. Throat clearing	0	1	2	3	4	5
3. Excess mucus or postnasal drip (descends behind the nose to the throat)	0	1	2	3	4	5
4. Difficulty in swallowing solids, fluids or tablets	0	1	2	3	4	5
5. Coughing after eating or lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Annoying cough	0	1	2	3	4	5
8. Sensation of a lump or foreign body in the throat	0	1	2	3	4	5
9. Burning, heartburn, chest pain, indigestion, or stomach acid coming up (reflux)	0	1	2	3	4	5

0= No Problem, 5= Severe problem.

Table 2: Sino nasal outcome test.[9]

	No problem	Very mild problem	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be
1.Need to blow nose	0	1	2	3	4	5
2.Sneezing	0	1	2	3	4	5
3.Runny nose	0	1	2	3	4	5
4.Cough	0	1	2	3	4	5
5.Post nasal discharge (dripping at back of your nose)	0	1	2	3	4	5
6.Thick nasal discharge	0	1	2	3	4	5
7.Ear fullness	0	1	2	3	4	5
8.Dizziness	0	1	2	3	4	5
9.Ear pain or pressure	0	1	2	3	4	5
10.Facial pain or pressure	0	1	2	3	4	5
11.Difficulty falling asleep	0	1	2	3	4	5

Continued.

	No problem	Very mild problem	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be
12.Waking up at night	0	1	2	3	4	5
13.Lack of good night's sleep	0	1	2	3	4	5
14.Waking up tired	0	1	2	3	4	5
15.Fatigue during day	0	1	2	3	4	5
16.Reduced productivity	0	1	2	3	4	5
17.Reduced concentration	0	1	2	3	4	5
18.Frustrated or restless or irritable	0	1	2	3	4	5
19.Sad	0	1	2	3	4	5
20.Embarrassed	0	1	2	3	4	5
21.Sense of taste or smell	0	1	2	3	4	5
22.Blockage or congestion of nose	0	1	2	3	4	5

While RSI and rigid videolaryngoscopy was done by one examiner for both study and reference groups, the saccharin test for measurement of MCT was done by another for the purpose of blinding to eliminate bias.

Subjects were made to sit in an air conditioned procedure room which was devoid of dust particles. Saccharin particle measuring approximately 1mm in diameter was placed on the medial surface of the inferior nasal turbinate, at least 1mm behind the anterior end with the help of 0 degree rigid nasal endoscope. The subjects were instructed not to sniff, sneeze, cough, smoke, eat or drink during the test. Subjects were asked to report the taste as soon as it was noted. The time from the placement of the saccharin particle to the initial perception of the sweet taste was recorded in minutes and was accepted as the saccharin transit time, which was interpreted as the MCT. Maximum waiting time was 60 minutes. If taste was not appreciated in 60 minutes, taste sensation of the patient was tested by placing saccharin particles directly over the tongue. Test was interpreted based on the time taken to perceive the taste. MCT was graded as follows. Normal was 0-20 minutes, prolonged was 20 to 30 minutes, severely prolonged was 30 to 60 minutes, grossly prolonged was more than 60 minutes.[10]

Statistical analysis

Data obtained were recorded in MS Excel work sheets and analysed using computer software programme (IBM SPSS version 22.0; SPSS Inc, Chicago, Illinois, USA) running on Windows operating system. Chi-square was used to compare MCT values between the groups. A p value <0.05 was considered to be statistically significant.

RESULTS

This study included a total of 90 participants within the age group of 18 to 50 years residing in the coastal belt of South India. Study group had 45 subjects with LPRD diagnosed using RSI criteria and rigid video laryngoscopy. Reference group included 45 healthy volunteers. Both the groups were matched in terms of age and gender. All 90 participants appreciated the saccharin taste in mouth. In the study group, maximum time taken to appreciate the taste was 29 minutes and minimum time was 8 minutes. MCT was not severely or grossly prolonged in any of the individuals. In the reference group, maximum mucociliary clearance time was 15 minutes and minimum were 8 minutes.

Mean value of MCT in the study and reference group were 18.57±6.5 minutes and 12.09±1.53 minutes respectively.

Table 3: Age group and MCT.

Age group in years	MCT in minutes		Total
	<20 mins	**>20 mins**	
18-28	9	6	15
29-39	18	9	27
40-50	35	13	48
Total	62	28	90

P value=0.147 (Significant).

The relationship between age and MCT was not statistically significant in this study (Table 3) (p=0.147). Chi-square with differentiation value was $\chi^2_{(2)}$=6.789.

Table 4: MCT in study and control group.

Reflux index score	MCT <20 mins (normal)	MCT >20 mins (prolonged)	Total
>13 (study group)	17	28	45
<13 (reference group)	45	0	45
Total	62	28	90

P value= 0.000 (Significant).

MCT was observed to be prolonged in 62% (n=28) of the study group participants. In the control group, all 45 patients had MCT less than 20. This was statistically significant (p=0.000) with Chi-Square with differentiation value $\chi 2_{(2)}$=42.787 (Table 4).

DISCUSSION

LPRD is a disease of unhealthy lifestyle. Obesity unhealthy food habits, tobacco and alcohol consumption and sedentary life style are the etiological factors for LPRD. Reflux contents, which regurgitate into the pharynx can further advance to the larynx, oral cavity, nasopharynx, nasal cavity and paranasal sinuses leading to various manifestations like laryngitis, sinusitis and otitis media.[11,12]

Studies have proven than LPRD is associated with upper airway diseases like secretory otitis media in children and chronic refractory sinusitis.[13,14]

Medically refractory CRS in adults has been found to be associated with gastroesophageal disease (GERD) and LPRD.[15,16] The theories promulgated for impaired MCT are direct mucosal injury by hydrochloric acid and pepsin present in the refluxate impairing ciliary function, vagus mediated auto immune response causing nasal mucosal oedema impairing ciliary motility and *Helicobacter pylori* present in the gastric refluxate induced direct mucosal injury.[6,7,17,18]

There are studies showing the association between upper airway disease and reflux disease in paediatric population. Contencin et al demonstrated a study depicting the presence of acid in nasopharynx using nasopharyngeal pH probe.[19] Bothwell et al conducted a study in a group of 28 children with CRS and GERD and reported that the need for sinus surgery was dramatically reduced after starting anti reflux treatment.[20] A study including 30 children observed GERD as a risk factor for CRS unresponsive to standard medical management.[21] Acid reflux was diagnosed by using dual probe pH monitor placed in oesophagus and nasopharynx.

Among adult population, Ulualp et al reported a higher prevalence of pharyngeal acid reflux in patients with CRS and posterior laryngitis as compared to control group which included healthy volunteers and patients with CRS without posterior laryngitis.[15] DelGaudio et al demonstrated direct nasopharyngeal reflux of acid using pH probe with sensors placed in nasopharynx in patients with refractory rhinosinusitis.[22] Chambers et al observed that presence of gastroesophageal reflux disease was a predictor of poor outcome after functional endoscopic sinus surgery.[23]

Delehaye et al studied the correlation between GERD and nasal MCT using saccharin test in a group of 50 patients and concluded that GERD can lead to impaired mucociliary clearance even without laryngopharyngeal symptoms.[24]

Ozmen et al in the study demonstrated a higher incidence of nasopharyngeal acid reflux and presence of pepsin in nasal lavage in patients with CRS.[25]

Durmus et al, measured MCT using saccharin test in 50 cases diagnosed with GERD and LPRD and 30 healthy controls.[26] There was no statistically significant difference between the saccharin transit test results of the study and control group. Wong et al reported that only 0.2% of 809 reflux episodes had reached the nasopharynx using 24h ambulatory pH monitoring in 40 CRS subjects. These two studies showed a negative correlation between reflux disease and CRS.[27]

The present study shows statistically significant increase in mucociliary clearance time in patients with LPRD when compared to healthy individuals. In both groups, factors known to impair MCT were excluded. The theories for impaired MCT have been mentioned above.

Past studies have investigated the association of acid reflux disease in patients with upper respiratory diseases like CRS and Otitis media. In the present study an attempt was made to analyse the effect of LPRD on nasal MCT in patients without any nasal pathology affecting NMC. A statistically significant association was observed between LPRD and MCT. Hence, we conclude that LPRD can impair nasal mucociliary transport. Since impaired MCT is a factor contributing to Chronic rhinosinusitis, we suggest that all patients with CRS should be evaluated for LPRD and anti-reflux treatment should be started if required.

The gold standard investigation for diagnosis of LPRD is 24 hours ambulatory dual probe pH monitoring which was not used in our study. It is expensive, invasive and time consuming.

CONCLUSION

LPRD is a factor contributing to impaired NMC. Hence it is imperative to consider this as an important etiological factor for chronic rhinosinusitis and address it to ensure better treatment outcomes.

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