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Is gastroesophageal reflux contribute to the development chronic cough by triggering pulmonary fibrosis

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Original Article

ABSTRACT

Background/Aims: Previous studies have shown that the prevalence of abnormal acid reflux in fibrotic lung disease patients is high, and in particular, patients with secondary pulmonary fibrosis show higher esophageal acid exposure than normal controls. There are also some findings that, in patients with pathological reflux, pulmonary fibrosis may develop. The aim of this study is to investigate if pulmonary fibrosis is involved in the pathogenesis of chronic cough due to Gastroesophageal Reflux.

Materials and Methods: A prospective study was performed in twenty-one patients with chronic cough due to gastroesophageal reflux who was diagnosed as reflux esophagitis by upper gastrointestinal endoscopy, histology, and in ten healthy controls without GER or any lung disease. All participitants underwent laryngoscopic examination and gastroesophageal scintigraphy with late lung imaging. Bronchoalveolar lavage fluid total and differential cell counts, T and B cell subsets, and the concentrations of IL- 1β and TNF-α were measured.

Results: Reflux extending into the proximal esophagus was noted in 52.5%, and posterior laryngitis was present in 90.5% of the patients. No evidence of pulmonary aspiration was noted in the patients with reflux on scintigraphic examination. No significant difference was found between the GER and control groups in terms of cellular content, IL-1β and TNF-α levels or mean T cell subsets and B cell counts in bronchoalveolar lavage fluid. Forced expiratory volume in one second, forced vital capacity FEV_1/FVC, total lung capacity, and carbon monoxide diffusion capacity values were within normal limits in the gastroesophageal reflux group.

Conclusion: Our findings do not support the hypothesis that gastroesophageal reflux leads to chronic cough by triggering alveolar epithelial injury and subsequent pulmonary fibrosis.

Keywords: Gastroesophageal reflux, chronic cough, pulmonary fibrozis, bronchoalveolar lavage, TNF-α, IL-1β

INTRODUCTION

Chronic cough has more than 20 causes, and in up to 62% of cases more than one cause can be involved. The three most common causes of chronic cough are upper airway cough syndrome (formerly referred to as postnasal drip syndrome), GER, and cough-variant asthma (1). In general, studies show that gastroesophageal reflux (GER) is a cause of chronic cough (GERC) in approximately 25% of adults (2-8). Although, the precise pathogenetic mechanisms of GERC is unknown, in these studies, two major pathophysiologic mechanisms have been proposed including an esophagotracheobronchial cough reflex and micro or macroaspiration, GER can stimulate the afferent limb of the cough reflex by irritating the upper respiratory tract without aspiration (*eg*, the larynx). There is evidence from a randomized and controlled study by Ing and colleagues that strongly suggests that GER may irritate the lower airway respiratory tract by macroaspiration or microaspiration (9).

It is increasingly recognized that gaseous or particulate proximal acid or nonacid reflux is associated with a

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variety of respiratory conditions including asthma, COPD, and bronchiectasis (10,11), fibrotic lung disease (12) and chronic cough (13,14). Detection of pepsin and bile salts in BAL fluid provides unequivocal evidence of aspiration of refluxate into the lower respiratory tract, which is referred to as microaspiration in the absence of a classical major clinical aspiration event (15). The prevalence of abnormal acid reflux in fibrotic lung disease patients is high and, in particular, patients with secondary pulmonary fibrosis show higher esophageal acid exposure (12,16). Sacco et al. showed that a significant proportion of pH-positive patients with respiratory symptoms have BAL abnormalities that suggest airway inflammation and gastric content aspiration (17). The hypothesis that repeated microaspiration of particles secondary to gastroesophageal reflux leads to alveolar epithelial injury and subsequent fibrosis (18). It is therefore possible that distortion of peripheral airway architecture could sensitive rapidly adapting receptors (RARs) in small airways thereby lowering the cough threshold. Alternatively, c-fibres in the pulmonary interstitium, which have been reported to inhibit the cough reflex in certain species, could be destroyed by the progressive fibrotic process (19). However, our current knowledge is not sufficient to suggest whether the reflux episodes trigger subclinical alveolitis or fibrosis in the pulmonary parenchyma of patients with GER in the long term.

In order to investigate the possibility that pulmonary fibrosis involved in the pathogenesis of GERC, bronchoalveolar fluid (BAL) was obtained from volunteers and from patients with GERC in whom reflux extending to the proximal esophagus and/ or pulmonary. Differential cell counts and T cell surface markers in the BAL fluid were analyzed. We also measured BAL fluid levels of interleukin (IL)-1β as a fibroblast growth factor and tumour necrosis factor-α (TNF-α) as an index of inflammation to investigate whether GER contributes to development of chronic cough by triggering alveolar epithelial injury and subsequent fibrosis.

MATERIALS AND METHODS

Patient group

Patients aged between 18 and 70 years old who were admitted to the Internal Medicine, Chest Disease and Otolaryngology outpatient clinics of our institute with chronic cough accompanied by reflux symptoms were included in the present study. Criteria for the chronic cough to be considered associated with GERD were: 1) presence of retrosternal burning and/or regurgitation symptoms, 2) endoscopic and histologic findings of reflux esophagitis, 3) normal chest radiograph, 4) no previous history of smoking or use of angiotensin-converting enzyme (ACE) inhibitors, 5) normal daily peak expiratory flow (PEF) variability, 6) cough not responding to the treatments of postnasal drip syndrome, asthma and non-asthmatic eosinophilic bronchitis.

Twenty-one patients (14 females, 7 males; mean age 44.6±11.7 years) with chronic cough associated with GER, who were shown to have distal and/or proximal reflux or pulmonary aspiration on scintigraphic examination, were included in the study. Patients with a history of asthma, interstitial lung disease, chronic obstructive pulmonary disease (COPD), tuberculosis and chronic hepatitis C, those being treated for these disorders, those who were unable to cooperate with PFTs, smokers, and those who did not consent to the BAL procedure were excluded.

Ten subjects with chronic cough (6 males, 4 females; mean age 41.3±9.7 years) but without GER or any findings of lung disease served as the control group. Laryngeal endoscopy, PFTs, diffusion capacity measurement, GER scintigraphy, and BAL were performed in the control group. None of these subjects had otolaryngeal, pulmonary or gastroesophageal disease and smoking.

Informed consent was obtained from all study participants, and the study was approved by our Institutional Ethics Committee.

After identifying consecutive patients with cough due to GERD, symptom scores for reflux were recorded; laryngoscopy, gastroesophageal reflux scintigraphy including late thoracic images, spirometry, and BAL were performed.

Symptom questionnaire

Reflux symptoms were scored on a frequency scale ranging from zero to 4 (0=never, 1=once a month, 2=once a week, 3=once a day, and 4=several times a day). We prepared symptom-related questions to assess symptoms including heartburn, regurgitation, dysphagia, epigastric fullness, epigastric pain and dysphonia.

Upper gastrointestinal endoscopy

Upper gastrointestinal (GI) endoscopy was performed by an experienced gastroenterologist, who was blinded to the aim of the study, using a video gastroscope (Fujinon GE 400, Tokyo, Japan). The diagnosis of esophagitis was established according to the Los Angeles Classification (20). Four biopsy specimens were obtained from visible mucosal breaks in the distal esophagus. The diagnosis of histological esophagitis was established if at least two of the following three features were present: basal cell hyperplasia, increased papillary height, and epithelial inflammation with ≥5 eosinophils per high-power field, neutrophils or lymphocytes (21).

Laryngoscopy

Laryngoscopy was performed by a single operator, who was blinded to the results of other examinations, using a fiberoptic laryngoscope. When the operator observed symmetric thickening of the mucosal surface of the posterior third of the true vocal cords, the term "posterior laryngitis" was applied, particularly in the arytenoid area and posterior commissure (22).

Measurement of pulmonary functions

Spirometric testing was performed by trained and certified pulmonary technicians using a whole-body plethysmograph

(Med Graphics Elite DL, USA) with a computer interface. In order to assist the operator in daily calibration, spirometric testing, and analysis, calibration and analytic programs were installed on a computer. Heights and weights were measured before measurement of pulmonary functions. Measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and DLCO were performed according to the guidelines of the American Thoracic Society (23). All values were expressed as percentages of predicted values (pred %) for age, sex and height.

Gastroesophageal reflux scintigraphy

After an overnight fasting, all subjects underwent gastroesophageal reflux scintigraphy through the administration of 50 mL orange juice labeled with 1000μCi (37Mbq) of ^{99m}Tc sulfur colloid, immediately followed by the administration of 250 mL orange juice to wash down the activity in the mouth. This suspension had a ^{99m}Tc labeling efficiency of 90%, and the efficiency remained stable for the following 18 hours. Synchronous dynamic imaging in the anterior and posterior projections was performed with the patient in the supine position, covering both the stomach and thorax in the field-of-view, using a dual-head gamma camera (E-cam, Siemens, USA) equipped with low energy high-resolution collimators at 10 seconds/frame for 60 minutes in a 64x64 matrix. After the acquisition of dynamic images, anteroposterior static thoracic images were obtained at the 1st, 6th and 18th hours for the detection of signs of pulmonary aspiration of gastric contents (24). During the examination, number of reflux episodes, duration of the most severe episode, overall duration, and percentage of reflux material into the esophagus were recorded.

Image and data analysis

All studies were analyzed visually for evidence of reflux; reflux was quantified using regions of interest over the esophagus and stomach by the following formula: $R= E (t) - E (b) \times 100/G_0$; where R is the percentage of reflux material into the esophagus, E (t) is the esophageal counts at the time of reflux detection, E (b) is the paraesophageal background counts, and G_0 is the gastric counts at the beginning of the study (24).

Reflux was considered abnormal, if it was ≥4% (pathologic reflux). GER episodes were defined as distal, in which reflux radioactivity was limited to the distal third of the esophagus and as proximal, in which reflux radioactivity detected throughout the esophageal body.

Bronchoalveolar lavage analysis

Before each procedure, the patients were administered atropine (0.5 mg) subcutaneously. Lidocaine (10%) was used to anesthetize the upper airway. A flexible bronchoscope (Pentax EB-1970K 2011) was introduced into the airways; the airways were then examined systematically. BAL was performed with the infusion of 20 mL warmed sterile saline solution into a segmental middle lobe or lingula bronchus, followed by its aspiration and collection; the process was repeated for 5 times. The combined fluid was collected in a sterile container, and immediately transferred to the laboratory for processing. BAL fluid recovery was measured, and the collected fluid was filtered using sterile gauze to remove mucus. The fluid was then centrifuged at 500 xg for 10 min to obtain a cellular pellet. The cellular pellet was resuspended in a volume of 20 mL, and total cell count was performed. Cell viability was determined using a Neubauer hemocytometer and trypan blue exclusion staining. The results were expressed as the total number of cells. May-Grünwald Giemsa stained cells smeared on a glass slide were used for differential cell count. Totally 400 cells per sample were counted to calculate the percentage of each type of cell in the BAL fluid.

Flow cytometry

Flow cytometry was used to analyze lymphocyte subpopulations in the BAL fluid. Specifically, the BAL fluid was centrifuged at 500 xg for 5 min, and the supernatant and pellet were separated. The residual cell pellet was used to analyze lymphocyte subpopulations by flow cytometry using specific CD3-CD19, CD4, CD8, CD16-56, and DC45 monoclonal antibodies with a Becton Dickinson FACSCalibur device and corresponding kits.

Levels of TNF-α and IL-1 β in BAL fluid supernatants were measured using human specific kits (Human TNF-alpha, Human IL-1β; Biosource International, Camarillo, CA).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 15.0. Reflux questionnaire results of patients and controls were compared using Mann-Whitney U test or student t-test according to their distribution characteristics. The results were expressed as mean±standard deviation. A p value <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the gender and age distribution between the study patients and the controls (p>0.05). Laryngoscopy, upper gastrointestinal endoscopy, PFTs, diffusion capacity measurement, GER scintigraphy, and BAL showed normal findings in the control group.

Regarding the reflux symptoms, pyrosis and regurgitation were severe in 52.4%, dysphagia was severe in 23.8%, and epigastric pain was present in 91% of the patients. Upper GI endoscopy revealed grade A esophagitis in 13, grade B esophagitis in 5, and grade C esophagitis in 3 patients.

On scintigraphic examination, patients were grouped according to the extent of pathological GER (GER-p) as GER-proximal (GER-pp) and GER-distal (GER-pd) groups. Scintigraphic reflux characteristics of patients with GER-pp and GER-pd are presented in Table 1. Of 21 patients, 11 (52.3%) had GER-pp and 10 (47.6%) had GERpd. Comparison of scintigraphic reflux charac-

teristics of GER-pp and GER-pd groups revealed no significant difference in terms of number of reflux episodes and overall duration of reflux episodes. However, duration of the most severe reflux episode and amount of gastric content (in percentages) were significantly higher in the GER-pp group than in the GER-pd group (p=0.024 and p=0.002, respectively). The evidence of pulmonary aspiration could be demonstrated in none of the patients in the sixth hour late lung images. No significant difference was observed between the two groups in terms of severity of esophagitis.

There was no significant difference between the patients with GER-p and the healthy controls in terms of PFT results including FEV_1, FVC, FEV_1/FVC, forced expiratory flow (FEF_{25-75}), total lung capacity (TLC), DLCO (p>0.05). PFT results of the patients with GER-p and the controls are presented in Table 2. Similarly, there was no statistically significant difference between GER-pp and GER-pd groups in terms of the results of PFT parameters.

Flow cytometric analysis revealed no statistically significant difference between patients with GER-p and healthy controls in terms of total cell count, differential cell count and lymphocyte subsets in BAL fluid (Tables 3 and 4).

There was no significant difference between patients with GER-p and healthy controls in terms of IL-1β (4.5±2.1 vs. 4.2±1.8 pg/mL; p=0.983) and TNF-α (3.8±5.7 vs. 0.5±1.5 pg/mL, p=0.327) levels in BAL fluid. When the results were reanalyzed according to the extent of reflux, no statistically significant difference was noted between GER-pp and GER-pd groups in terms of TNF-α and IL-1β levels, as well as total and differential cell counts, and lymphocyte subsets in BAL fluid (p=0.605, p=0.1, and p=0.426, respectively).

Table 1. Reflux characteristics of patients with pathological proximal and pathological distal gastroesophageal reflux

Reflux characteristics	GER-pp Group (n=11) Min-Max	GER-pd Group (n=10) Min-Max	p
Number of reflux episodes	2-21	2-14	0.468
Duration of the most severe reflux episode (sec)	20-80	10-40	0.024
Overall duration of the reflux episodes (sec)	40-650	2-370	0.131
Amount of gastric content (%)	4.3-13.4	4.9-6.3	0.002

[a]Mann-Whitney U test.
GER-pp: pathological proximal gastroesophageal reflux; GER-pd: pathological distal gastroesophageal reflux; Min-Max: minimum-maximum

Table 2. Results of pulmonary function tests of patients with GERC and in controls

Parameters	Patients with GER-p (n=21)	Control Group (n=10)
FEV_1 (pred %)	89.3±15.8	95.91±7.83
FVC (pred %)	90.8±15.8	97±10.63
FEV_1/FVC (%)	78.6±9.2	86.46±8.04
Bronchial reversibility	6.15±2.49	5.03±3.93
FEF_{25-75} (pred %)	91.7±28.4	90±16.5
TLC (pred %)	92.5±14.7	92.21±11
DLCO (pred %)	111.0±22.2	116.0±12.1
DLCO/VA (pred %)	123.5±17.3	119.5±12.8

GERC: chronic cough due to gastroesophageal reflux; GER-p: pathological gastroesophageal reflux; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; FEF: forced expiratory flow; TLC: total lung capacity; DLCO: carbon monoxide diffusion capacity; VA: alveolar volume

DISCUSSION

In this study we have analyzed the BAL fluid in patients with chronic cough due to GER in whom reflux extending to the proximal esophagus and/ or pulmonary, to investigate the possibility that pathological reflux episodes might contribute to the development of GERC by triggering pulmonary fibrosis. No statistically significant difference was found between the patients with pathological reflux and the control group in terms of PFT results, total and differential cell counts, total lymphocyte and lymphocyte subsets in BAL fluid. The levels of IL-1 β and TNF-α were all less. This is in contrast with studies in progressive IPF and adult/acute respiratory distress syndrome

Table 3. Total and differential cell counts in BAL fluids of patients with GERC and controls

	Patients with GER-p (n=21) Mean±SD	Control Group (n=10) Mean±SD	p
Neutrophil (x10^3/mL)	46.1±36.5	53.6±66.8	0.918
Lymphocyte (x10^3/mL)	24.1±27.7	12.9±8.5	0.223
Eosinophil (x10^3/mL)	16.5±19.2	12.4±14.0	0.705
Macrophage (x10^3/mL)	985.4±866.9	397.2±370.9	0.605
Total cell (x10^3/mL)	1073.9±897.8	475.1±417.5	0.426

GERC: chronic cough due to gastroesophageal reflux; GER-p: pathological gastroesophageal reflux; SD: standard deviation

Table 4. Lymphocyte subsets in BAL fluids of patients with GERC and controls

Lymphocyte subsets	Patients with GER-p (n=21) Mean±SD	Control Group (n=10) Mean±SD	p
CD19 (%)	5.7±5.3	2.2±1.8	0.586
CD3 (%)	82.8±16.0	88.2±9.0	0.531
CD4 (%)	47.6±19.0	45.9±17.2	0.202
CD8 (%)	25.9±13.1	37.2±16.4	0.865
CD4/CD8	3.8±5.7	1.5±0.9	0.918
Total	93.7±12.7	68.7±31.0	0.773

GERC: chronic cough due to gastroesophageal reflux; GER-p; pathological gastroesophageal reflux; SD: standard deviation

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(ARDS) in which increased levels of IL-1 β and TNF-α were reported in the BAL fluid (25). These findings do not support the hypothesis that pathologic reflux episodes in GER patients might contribute to the development of GERC by triggering pulmonary fibrosis.

Demonstration of aspiration of the gastric content to distal and proximal esophagus, larynx and/or lower respiratory tract by late thoracic images during pathological reflux episodes using scintigraphic examination is helpful for clarifying the mechanism of potential pulmonary involvement. Bestetti et al. (26) and Gali et al. (27) showed proximally extending pathological reflux episodes in 51.7% and 61% of their patients, respectively by using scintigraphic examination. Bestetti et al. also (26) demonstrated pulmonary aspiration in late thoracic images acquired during scintigraphy in 30% of the patients. However, in our previous study gastroesophageal scintigraphy revealed proximal reflux in 37.2% of our patients, but pulmonary aspiration in only 6% (28).

In the present study, 52,3% of the patients had GER-pp, but none of them had pulmonary aspiration. The fact that none of our patients with GER-p had pulmonary aspiration may suggest that the upper esophageal sphincter or laryngeal protective reflexes prevented pulmonary aspiration. The patients in the study by Bestetti et al. (26) were composed of those with several unexplained respiratory symptoms, whereas our study sample consisted of a homogenous patient group with chronic cough alone.

No statistically significant difference was found in terms of FEF_{25-75}, FEV_1, FVC, FEV_1/FVC, vital capacity (VC), TLC and DLCO between patients with GERC and controls in our study. Similar to our findings, an additional prospective study involving 45 patients also failed to find a statistically significant difference in terms of FEV_1, FVC, FEV_1/FVC, TLC, FEF_{25-75} values among groups with different extents of reflux (29).

Detection of inflammatory total cell count and types in BAL fluid is extremely important in the diagnosis of IPF. A great increase especially in macrophage populations, in addition to neutrophils and eosinophils, is typical in BAL fluid of patients with IPF. An increase in lymphocytes is observed in 20% of the patients (30,31). Salaffi et al. (32) found lymphocyte and neutrophil ratios and CD8 level in BAL fluid to be significantly higher, and CD4/CD8 ratio to be significantly lower in IPF patients with alveolitis as compared to controls. Similar to the findings of study by Salaffi et al. (32), it has also been reported that lymphocytes are deposited especially in peribronchiolar region and alveolar wall, and CD4/CD8 ratio is decreased in patients with IPF (30,31). The levels of pro-inflammatory mediators, which play a role in the development of pulmonary fibrosis, such as platelet-derived growth factor, transforming growth factor, TNF-α, connective tissue growth factor and IL-1β are increased in BAL fluid of patients with IPF (33,34). Kline et al. also (35) found that IL-1β levels in BAL fluid of patients with IPF and sarcoidosis was higher than that of controls. In this study, there were no statistically significant differences in total and differential cell counts, total lymphocyte (CD3, CD19, CD16+56,CD19); CD4/CD8 ratios, and IL-1β and TNF-α in BAL fluid of the patients and controls.

The notion of recurrent micro-aspiration as a potential cause of pulmonary fibrosis is an old one, with reported case series dating back over half a century (36) but clinical studies came latter showed significantly higher prevalence of esophageal acid reflux in the pulmonary fibrosis and in connective tissue disease in particular scleroderma (12,16,37,38). However, GERD is common in the general population (10%-20% in the Western World) and up to 50 reflux events per 24 hours is considered normal, so it is not possible to draw a firm conclusion regarding a cause-and-effect relationship. Conceivably, reflux could be a secondary event in patients with IPF because of mechanical effects. Advanced fibrosis is associated with decreased lung compliance and increased negative pleural pressure, thus potentially promoting reflux of gastric contents into the esophagus (39).

Our study showed that all of our chronic cough patients with GER-p had not pulmonary aspiration may suggest that the upper esophageal sphincter or laryngeal protective reflexes prevented pulmonary aspiration (40-42). It also possible that the reflux may make it only as far as the larynx and that the cough in patients with GER can be protective mechanism preventing pulmonary aspiration.

In conclusion, our observations do not support the hypothesis that GER might contribute to the development of chronic cough by triggering pulmonary fibrosis.

Conflict of Interest: No conflict of interest was declared by the authors.

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