

The Association Between Severity and Stage of Asthma Symptoms in a Distinctive Period and Gastroesophageal Reflux

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Abstract

This study was designed to investigate the association between clinical findings of GER and reflux esophagitis diagnosed by endoscopic and histopathological methods in adult patients with mild and moderate asthma. Frequency of GER symptoms was 77% in patients with mild asthma and 54% ($p>0.05$) in patients with moderate asthma. The frequencies for esophagitis diagnosed histopathologically were, in respective order, 55% and 36% ($p>0.05$). Frequency of histopathological esophagitis in cases with and without GER symptoms in the mild asthmatic patients was, respectively, 36% and 25% ($p>0.05$). These figures were 33% and 40% ($p>0.05$) for the moderately severe asthmatic patients. Also, there were no significant differences in frequency of GER symptoms or histopathological findings

between patients with or without nocturnal asthmatic attacks ($p>0.05$). Our findings show that GER disease, a condition which may affect prognosis, occurs frequently in patients with asthma. However, the study failed to show a significant association between the clinical severity of asthma and clinical-pathological findings of GER disease. Taking into account these findings it was concluded that, the presence of findings suggestive of GER should be included in the routine assessment of all asthma patients. Endoscopy and histopathological assessment should be performed in suspected cases.

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Key words: *gastroesophageal reflux, asthma, endoscopy*

Introduction

More than one possible association exists between asthma and gastroesophageal reflux (GER). Asthma and GER can be present in the same patient by chance with no interrelation. However, obstruction of the airways and drugs used in the treatment of asthma may have an aggravating effect on GER symptoms. On the other hand, in asthmatic patients, GER may initiate the asthmatic attack or may enhance the bronchomotor response to agents which may induce the attack (1). It is advanced that, due to co-innervations of the bronchi tree and of the esophagus, the acid reflux in the esophagus leads to a reflex bronchoconstriction response, thus increasing bronchi reactivity and initiating an asthmatic attack (2,3,4). The flattening of the diaphragm overlying the air trap may lead to inefficient functioning of the inferior sphincter of the esophagus during bronchoconstriction and this may also have a role.

A positive, rather than a more negative intra-abdominal pressure occurs in asthma during episodes of acute exacerbation; this increases the pressure difference and provokes GER. The applications associated with asthma treatment, through their effect on the tone of the sub-esophageal sphincter, may also provoke/aggravate GER symptoms. It was shown that theophyllines aggravate GER symptoms while beta-agonists have no

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Table 1. Clinical findings and frequency of GER symptoms in patients with asthma

	Total Patients n: 29	Mild-Int/Persistent* n: 18	Moderate Persistent n: 11
Age, yrs (mean \pm SD)	44.9 \pm 15.41	42.5 \pm 18.67	48.5 \pm 8.50
Period of illness, yrs (mean \pm SD)	11.55 \pm 9.28	11.58 \pm 8.90	11.50 \pm 10.45
FEV ₁ , L (mean \pm SD)	2.15 \pm 0.55	2.45 \pm 0.38	1.5 \pm 0.02
% Predict FEV ₁ (mean \pm SD)	79% \pm 0.15	87.55% \pm 0.12	65% \pm 0.02
Pyrosis (%)	21 (73%)	12 (66%)	9 (82%)
Gastric fluid in mouth (%)	15 (52%)	10 (55%)	6 (54%)
Chest-pain (%)	9 (31%)	8 (44%)	2 (18%)
Dysphagia (%)	6 (21%)	4 (22%)	2 (18%)
Regurgitation	4 (14%)	2 (11%)	2 (18%)

*Mild-Int/Persistent: Mild Intermittent and Mild Persistent

significant effect. Inhaled anti-asthmatics also have no effect on the sub-esophageal sphincter tonus.

Recent studies on the relationship between asthma and increased acidity in the esophagus suggest that, contrary to classical opinions, transport of GER material to the proximal part of the esophagus may be more important than the mere presence of GER (4). Thus, in addition to clinical findings suggestive of GER, histopathological evidence of reflux in the proximal esophagus may be a useful diagnostic approach.

This present study was conducted to investigate the association between the frequency of GER symptoms and esophagitis as determined by endoscopic-histopathologic methods in adult patients with mild and moderate asthma. Thus, the study is an attempt to establish the relationship of clinical and histopathological findings to the severity of the disease.

Patients and Methods

This study was conducted on 30 asthmatic adult patients who had been under observation and treatment in the past three months. The principles listed in the "Expert Panel Report 2" were observed in the diagnosis and treatment (5). Informed consent was obtained from all patients prior to the study.

In addition to history and physical examination, spirometrical measurements, early reversibility test and/or daily variability values in peak expiratory flow (PEF) determinations were conducted in all patients (5). The total IgE level was low in all patients. All patients were informed about nocturnal asthma attacks and symptom scores according to Expert Panel Report 2.

Prior to endoscopy, the patients were divided into two groups according to the severity of their asthmatic state, as determined by the clinical evaluation of the patient during the past three months. The first group consisted of patients with mild asthma (intermittent and persistent) and the second group of patients with moderate asthma. All patients were on long term inhaler steroids and used 2 short term mimetic inhaler agents when necessary.

There were no smokers among the patients nor were there any patients addicted to nonsteroid anti-inflammatory drugs. All patients were assessed for presence of classical GER symptoms such as pyrosis, gastric fluid in mouth, regurgitation, dysphagia, and chest-pain (6,7). An endoscopic and macroscopic evaluation for esophagitis was performed in all patients, regardless of GER symptoms. To increase the sensitivity of the diagnostic assessment, an esophagus biopsy was done and examined histopathologically. Histopathological diagnosis was based on the definition given by Ismail-Beigi et al. (8). The study results are given as mean and SD values. The χ^2 test was used in the statistical analysis.

Results

Thirty patients consisting of 25 females and 5 males were included in our study. Only one patient (female and with moderate persistent asthma) could not tolerate the endoscopic examination. The remaining 29 patients (mean age \pm SD:44.9 \pm 15.41) completed the study successfully. Clinical findings including frequency of GER symptoms in these patients are given in Table 1. There were no statistical differences with regard to age or duration of disease between patients who were classified as having mild asthma and those who were classified as having moderate asthma. Although there were some apparent differences in the clinical findings between the two groups of patients, these were not of statistical significance.

Frequency of cases with GER symptoms appeared to be higher in the mild-intermittent group of asthma patients. Frequency of esophagitis, detected by endoscopy and by histopathology also appeared to be higher in this group. However, none of these differences were statistically significant (Table 2).

The frequency of endoscopic and histopathological esophagitis in mild and moderate asthma patients regardless GER symptoms is depicted in Table 3. Although some differences, such as a higher frequency of GER symptoms in the mild asthma group and a consistently higher ratio of endoscopic and histopathologic esophagitis in patients who

Table 2. Frequency of GER symptoms and endoscopic-histopathologic esophagitis by asthma symptoms and clinical stage

Clinical Stage	Mean duration of disease (years)	Patients with GER symptoms	Endoscopic esophagitis	Histopathologic esophagitis
Mild-Intermittent/Persistent (n: 18)	11.58±8.90	14 (77%)	5 (27%)	10 (55%)
Moderate Persistent (n: 11)	11.50±10.45	6 (54%)	2 (18%)	4 (36%)
χ^2 test		p>0.05	p>0.05	p>0.05

Table 3. Frequency of endoscopic and histopathologic esophagitis by GER symptoms and clinical stage of asthma

Clinical Stage	Clinical GER Symptoms	n (%)	Endoscopic esophagitis	Histopathologic esophagitis
Mild -Intermittent / Persistent (n:18)	Symptom (+)	14 (77%)	4 (28%)	5 (36%)
	Symptom (-)	4 (22%)	1 (25%)	1 (25%)
χ^2 test			p>0.05	p>0.05
Moderate Persistent (n:11)	Symptom (+)	6 (54%)	2 (33%)	2 (33%)
	Symptom (-)	5 (45%)	-	2 (40%)
χ^2 test			p>0.05	p>0.05
Total group (n:29)	Symptom (+)	20 (69%)	6 (30%)	7 (35%)
	Symptom (-)	9 (31%)	1 (11%)	2 (22%)
χ^2 test			p>0.05	p>0.05

Table 4. Frequency of GER symptoms and endoscopic-histopathologic esophagitis in patients with or without nocturnal asthma attacks

	n (%)	Endoscopic Esophagitis	Histopathologic Esophagitis	Clinical GER Symptoms
Nocturnal attacks (+)	17 (59%)	4 (24%)	8 (47%)	9 (53%)
Nocturnal attacks (-)	12 (41%)	2 (17%)	4 (33%)	5 (42%)
χ^2 test		p>0.05	p>0.05	p>0.05

GER: Gastroesophageal reflux

presented classical GER symptoms, the differences between the groups were not significant.

A comparison of patients having nocturnal asthma attacks revealed higher frequency of GER symptoms as well as higher frequency of esophagitis diagnosed endoscopically and histopathologically (Table 4). These findings were not statistically significant ($p>0.05$).

Discussion

Asthma and GER can occur concomitantly in asthmatic patients. GER may also initiate an asthmatic crisis or may enhance the bronchomotor response to other factors/agents which may induce an asthmatic crisis. Conversely, obstruction of airways or drugs used in treatment of asthma may aggravate GER in asthmatic patients (1). For these reasons, all patients with asthma or asthma like symptoms should be routinely investigated for presence of GER symptoms (9,10).

The frequency of GER in the asthma patients is reported as 34-89% (11) This frequency is high compared to the general population. Many of these patients show the classical GER symptoms, but about one third are asymptomatic and have silent reflux (1). Sontag and his colleagues

reported endoscopic evidence of esophagitis in 42.5% of adult asthma patients (12). In another study, GER frequency in asthma was reported as 57% (13). In yet another study, frequency of asymptomatic reflux in patients with intrinsic asthma was reported to be similar to the nonasthmatics. However, the reflux episodes were provoked by increase in abdominal pressure in the asthmatics, a finding which also points to the importance of obesity as a facilitating factor for development of GER (14).

Clinical GER symptoms and reflux which reached the upper esophagus has also been reported in patients who had chronic nonspecific lung-airway disease other than asthma (15).

Endoscopically, esophagitis and GER were found to be very common in asthma with respective ratios as high as 60-72% and 50-75% (16-18). High ratios were also reported for pediatric asthma patients.

Erosions and ulcerations, which are typically endoscopic signs of esophagitis are reported to be present in less than 1/3 of GER cases in the general population. When erosion and ulceration are not seen by endoscopy, it is difficult to reach a diagnosis of esophagitis. For this reason, although

the specificity of endoscopy in the diagnosis of GER-disease is high (93-96%), its sensitivity is low (68%). The sensitivity of the diagnostic assessment may be increased to 85% with endoscopic biopsy (85%) (11).

In our group of mild (intermittent+persistent) asthma patients, the frequency of esophagitis was 27% by endoscopy, and 55% by histopathological examination. These ratios were 18% and 36%, in the same sequence, in the moderate asthma group.

Endoscopy, when applied in conjunction with biopsy and histopathological evaluation, is the gold standard for the diagnosis of reflux esophagitis (6). However, in routine practice, long term intraesophageal pH observation may be preferred initially. In fact, investigation of GER disease depends on the available laboratory facilities. The sensitivity and sensitivity of long term pH observation in the diagnosis of GER-disease has been reported as 85% and 95% (11). However, facilities to use this method may not be available in all centers. Also, many researchers believe that this method has limited usage and endoscopy is usually resorted to in patients in whom the diagnosis remains equivocal(1,11). Endoscopy should be the first alternative in clinical practice because it allows the direct observation of the esophageal mucosa and also because biopsy can be taken from the esophagus during the procedure (1-4, 6,11).

Spechler and Vigneri reported that GER symptoms were related to the presence of erosion, but that histopathological evidence of erosion was not a consistent finding. These authors reported pyrosis as the most frequent among the typical GER symptoms (19,20). The consistent relationship between the existence of pyrosis and GER-disease was confirmed by endoscopic, histological investigations and by long-term pH observing. However, an association between the severity of symptoms and the grade of the esophagitis could not be established. In the follow-up of patients with GER-disease, a strong relationship was observed between the recurrence of pyrosis and the exacerbation of esophagitis (21).

In our study, pH monitorisation was not applied because we thought this method would not yield precise evidence for existence of histopathological esophagitis. The frequency of histopathological esophagitis was found to be higher in our mild asthma patients who had clinical GER symptoms, but this finding did not carry statistical significance. In the group having moderate persistent asthma, a nonsignificant high value was found for cases without symptoms. A relationship between the severity of GER symptoms and degree of esophagitis could not be established. In both groups, pyrosis was the most frequent among the GER symptoms. When both groups of asthmatic patients were analyzed together, again, significant differences were not found between patients with or without nocturnal asthma symptoms, thus an association could not be established between the severity of the asthma and histopathological esophagitis nor the presence of clinical GER symptoms.

In patients who have both asthma and GER-disease, the lower esophagus pressure is usually decreased. However, the esophageal manometer has a very little clinical value in the evaluation of GER (1).

In conclusion, our findings on the frequencies of GER and reflux esophagitis in asthma patients were generally consistent with previous reports, but higher than some reports. We could not find any significant association between GER frequency and severity or stage of asthma. These results point out that the presence of GER disease should be investigated in all asthma patients regardless of the severity of the asthma.

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