

# Gastroesophageal Reflux in Children with Refractory Asthma

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## Abstract:

**Objectives:** To investigate the association between clinical and macroscopic findings of GER and severity of refractory asthma (statistical study).

**Methods:** A prospective study in a university-based practice of 75 children who were diagnosed with refractory asthma because they exhibited no satisfactory response for at least three months of treatment. Medical history, physical examination, spirometrical measurements and prick skin test were conducted on all patients. Endoscopic and macroscopic evaluations for esophagitis were performed on all patients regardless of the presence of GER symptoms.

**Results:** Endoscopy was done for 75 children with refractory asthma. GER was symptomatic in 65% of all patients with no statistical significance ( $p>0.05$ ) and the most frequent symptom was abdominal pain (67%). The frequency of these symptoms was 50% in mild asthma, 58% in moderate asthma and 72% in severe asthma with no statistical significance ( $p>0.05$ ). The frequency of macroscopic esophagitis was 71%, distributed in three asthmatic groups as in order of 75% in mild asthma, 58.3% in moderate

asthma and 76.6% in severe asthma ( $p>0.05$ ). Regarding the relationship between GER and nocturnal attacks or spasmodic cough, the frequency of the latest was 66.7%. The differences have no statistical significance regarding GER symptoms ( $p>0.05$ ), but they are statistically significant regarding the reflux esophagitis ( $p<0.05$ ). Also endoscopic reflux was as frequent as 76.3% in non allergic patients, and this result is statistically significant ( $p<0.05$ ).

**Conclusion:** In spite of the fact that there was no relationship between the severity of asthma and the symptoms of GER, or its endoscopic findings, the frequency of GER in asthmatic children was higher than its frequency in other children.

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## Introduction

Refractory asthma is considered a challenging case in the sense that it is rather difficult to control asthma attacks. Although often neglected in this type of asthma, the role of gastroesophageal reflux (GER) has been recently referred to in many reports in which the prevalence of GER in children with asthma, as measured by extended esophageal monitoring is approximately 50-60%.<sup>1</sup> In other articles, it is 34-89%.<sup>2</sup> The frequency of reflux esophagitis is 60-72%.<sup>1</sup> The interrelationship between GER and asthma is unexpectedly complex. This study attempts to investigate the association between clinical and macroscopic findings of GER and the severity of asthma.

GER may induce bronchoconstriction via many mechanisms: (1) Direct mechanism (reflux theory) by which pulmonary tree becoming in direct contact with GER material;<sup>3,4,6</sup> (2) Indirect mechanism (reflex theory) by which the gastric acid may stimulate the vagal nerve endings in the lower esophageal wall. This may cause bronchospasm due to the co-innervation of pulmonary tree and the lower esophageal wall.<sup>1,3,4,6</sup> (3) Neuropeptides mechanism by which the gastric acid may provoke the release of chemical mediators called rapid kinins like P substance and other neuropeptides.<sup>1</sup>

While the above mentioned mechanisms may explain the role of GER in enhancing asthmatic attacks, several other mechanisms may explain the role of asthma in increasing GER. Firstly, chronic cough in asthma patients may cause a rather positive abdominal pressure which provokes GER.<sup>7</sup> Secondly, the flattening of the diaphragm traps the overlying air which leads to the inefficient functioning of the lower esophageal sphincter.<sup>8</sup> And finally, some asthma drugs like theophyllin may aggravate GER by relaxing the lower esophageal sphincter.<sup>8</sup> Recent studies have shown that the transport of GER material to the proximal esophagus is more important than the mere presence of reflux.<sup>8</sup> Thus, the macroscopic evidence of GER may be a useful diagnostic approach.<sup>8</sup>

## Methods

This study was conducted on 75 asthmatic children who fulfilled the inclusion criteria.

These were patients who had been under intensive treatment according to the National Heart Lung Blood Institute (NHLBI) guidelines (Grade 2 or more). All of them were diagnosed with refractory asthma because they exhibited no satisfactory response (objectively and subjectively) for at least three months of what is presently considered intensive treatment. This period was chosen

not to be confounded by characterizing variability of asthma. The age of the patients should be at least 2 years in order to confirm the diagnosis of asthma. Non-allergic patients (negative prick skin test), or allergic patients who are not responding to anti-allergic treatment besides asthmatic medication were also included in this study. Patients with diseases which give symptoms similar to asthma (cardiac dysfunction, cystic fibrosis, COPD) were excluded from this study.

In addition to medical history, physical examination, and spirometrical measurements, daily variability values in peak expiratory flow (PEF) were conducted on all patients. Prick skin test was also performed on all patients. Prior to endoscopy, parents of the patients were given an informed consent explaining the risks and benefits of participating in this study. Patients were divided into three groups according to the severity of their asthmatic state, which was determined by the clinical evaluation of the patients during the past three months. The first group consisted of patients with mild asthma, the second of patients with moderate asthma, and the third of patients with severe asthma. All patients were on long term inhaler steroid and used short term mimetic inhaler when necessary. No patient was addicted to nonsteroid

anti-inflammatory. All patients were assessed for the presence of classical GER symptoms such as vomiting, abdominal pain, gastric fluid in the mouth, regurgitation, dysphagia, and chest pain.<sup>7</sup> Endoscopic and macroscopic evaluations for esophagitis were performed on all patients regardless of the presence of GER symptoms. Endoscopy was performed by an enterologist blinded to the case of patients.

## Results

The results from this study are given in mean and SD values. Winks software was used for statistical analysis, and the appropriate test was used each time. 75 patients consisting of 55 boys and 20 girls were included in the study. The mean age of patients was  $6.89 \pm 3.19$ . 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 the patients who were classified as having mild asthma and those who were classified as having moderate or severe asthma. Although there were some apparent differences in the clinical findings between the three groups of patients, these were not of statistical significance.

**Table 1:** Clinical Findings and Frequency of GER Symptoms in Patients with Asthma

Clinical Findings	Total patients n:75	Mild persistent n:8	Moderate persistent n:24	Severe persistent n:43	p value
Age	-	8.25±3.57	6.62±3.44	6.81±2.97	0.4415
Period of asthma (year)	-	7.32±3.92	4.99±3.05	5.2±2.49	0.1213
Abdominal pain	28	2 (25%)	9 (37.5%)	17 (39.5%)	0.737
Vomiting	16	1 (12.5%)	5 (20.8%)	10 (23.3%)	0.79
Abdominal pain + vomiting	5	1 (2.5%)	-	4 (9.3%)	0.78

The frequency of cases with GER symptoms appeared to be higher in the group of patients with severe asthma. While the frequency of esophagitis detected by endoscopy also appeared to be higher in this group. However, none of these differences were statistically significant, (Table 3). The frequency of endoscopic esophagitis in asthmatic patients regardless of GER symptoms is depicted in Table 3.

**Table 2:** Symptoms of GER with endoscopic GER in patients with Asthma

Symptoms of GER	Number of patients	Endoscopic GER	Percentage
Present	49	38	77.5%
Absent	26	15	57.5%
Total number of patients	75	53	-
p value	-	-	0.11

**Table 3:** Frequency of Endoscopic Esophagitis by GER Symptoms and Clinical Stage of Asthma

Clinical stage of asthma	Clinical GER symptom	Number of patients with Clinical GER symptom	Number of patients with Endoscopic GER	Total number of patients with Endoscopic GER
Mild persistent (n:8)	Symptoms(+)	4 (50%)	2 (33%)	6 (75%)
	Symptoms(-)	4 (50%)	4 (67%)	
Moderate persistent (n:24)	Symptoms(+)	14 (58%)	10 (71%)	14 (58.3%)
	Symptoms(-)	10 (42%)	4 (29%)	
Severe persistent (n:43)	Symptoms(+)	31 (72%)	22 (67%)	33 (76.7%)
	Symptoms(-)	12 (28%)	11 (33%)	
<i>p</i> value		0.331	0.237	

There was a higher frequency of GER symptoms was observed in the severe asthma group and a consistently higher ratio of endoscopic esophagitis in patients who exhibited classical GER symptoms, but the differences were not significant. A comparison with patients having nocturnal asthma attacks or nocturnal spasmodic cough revealed higher frequency of GER symptoms, which was not statistically significant, as well as higher frequency of esophagitis diagnosed endoscopically, which was statistically significant, (Table 4). While a higher frequency of endoscopic GER was noted in non allergic patients (negative prick skin test) with statistical significance. (Table 5)

**Table 4:** Frequency of GER Symptoms and Endoscopic GER in Patients with or without Nocturnal Asthma Attacks or Nocturnal Spasmodic Cough

Symptoms	Number of patients (%)	Endoscopic GER	Clinical GER symptoms
Presence of nocturnal attacks or spasmodic cough	50 (66.7%)	41 (82%)	34 (68%)
Absence of nocturnal attacks or spasmodic cough	25 (33.3%)	12 (48%)	15 (60%)
<i>p</i> value	-	0.002	0.492

**Table 5:** Frequency of endoscopic GER with Prick skin test-

Patient	Number	Endoscopic GER	Percentage( %)
Prick skin test(+)	21	11	52%
Prick skin test(-)	54	42	76.3%
Number of patients	75	53	-
<i>p</i> value	-	-	0.046

**(Table 6:** Medication of patients according to( NHLBI

Severity of Asthma	Grade2(consistent mild)	Grade3(consistent moderate)	Grade4(consistent severe)
Number of patients ( %)	Low dose of ICS(long term) or leukotrien antagonist+short term B2 agonist when necessary	Moderate dose of ICS(long term)+short term B2 agonists when necessary	High dose of ICS(long term)+oral steroid+ short term B2 agonist when necessary

ICS: *inhaler cortico steroid*

## Discussion

GER and asthma may be present by chance in the same patient.<sup>8,9</sup> GER may also initiate an asthmatic attack or aggravate one

induced by another factor.<sup>10</sup> On the other hand, asthma may increase the ratio of GER.<sup>11</sup> For these reasons, it is important to investigate GER in asthmatic patients who are refractory to classical asthmatic treatment. It has even been recommended to investigate the presence of GER in all asthmatic patients.<sup>12</sup>

Many reports classified long term pH-metry as the gold standard in diagnosing GER because its sensitivity is as high as 85% and its specificity is 95%.<sup>2,11,13,14</sup> However, many researchers believe that endoscopy remains the better approach in which diagnosis is equivocal, even though the sensitivity of endoscopy is 68%, which is less than pH-metry, and its specificity is 93-96%.<sup>2-7,9,11</sup>

In this study, endoscopy was used for many reasons: (1) The availability of laboratory facilities; (2) The technique of pH-metry is difficult for the patient and the clinician; (3) The changes in mucosa caused by GER are more important than the mere presence of GER,<sup>3</sup> and these changes can only be detected by endoscopy; (4) 30-88% of GER in children is non acidic, and it cannot be revealed by pH-metry.<sup>15-16</sup>

GER was symptomatic in 65% of all the asthmatic patients. This ratio is consistent with Simpson's study in which the frequency of GER symptoms was 66% of all asthmatic patients.<sup>11</sup>

Spechler and Vigneri have reported that GER symptoms are related to the presence of macroscopic esophagitis, but the histopathologic microscopic changes are inconsistent findings.<sup>13,14</sup> The most frequent symptom in their study was abdominal pain.<sup>13,14</sup> In a Turkish study, it was also abdominal pain, as was the case in this current study where 67% of all patients were symptomatic for GER.

GER symptoms increase as the severity of asthma increases. However, this does not have any statistical significance, which means that there is no significant difference between the three groups regarding the frequency of GER. Thus, there was no relationship between GER symptoms and severity of asthma and this result is consistent with the Turkish study.<sup>8,11</sup> The frequency of reflux esophagitis in this study was 71%. This ratio is higher than the Turkish study which was 57%.<sup>11</sup> Hence the finding is consistent with another at 60-72 %.<sup>17</sup> However, this ratio is higher than general population.

This study revealed that the endoscopy shows a higher percentage of GERD lesions with increased severity of asthma. This result is consistent with two endoscopic studies from Japan which examined the association between the severity of asthma and endoscopic findings. Overall, they indicated that the severity of asthma is associated with an increased risk of GORD.<sup>18,19</sup>

## Conclusion

In conclusion, GER is so frequent in refractory asthma that it should be investigated in all asthmatic patients regardless of the severity of asthma, especially when the patient has any symptoms referring to GER or nocturnal symptoms, or has negative prick skin test.

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