Original Article
The prevalence of gastro-esophageal reflux in asthmatic children

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Received December 7, 2015; Accepted March 19, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Gastro-esophageal reflux disease (GERD) is the most common esophageal disorder in children. It causes various pulmonary manifestations and bronchial asthma is one of them. The study aims to assess the prevalence of GERD in a group of moderate persistent or severe persistent asthma and to evaluate the clinical response of asthma to anti-reflux treatment. The study included 38 cases and found a significant difference in both symptoms related to asthma and those related to GERD throughout the study. Also, there was a significant increase in forced expiratory volume in one minute (FEV1) and a significant decrease in the frequency of use of rescue medication. Furthermore, GERD has a role in worsening asthma symptoms and there will be potential benefit of anti-reflux therapy on asthma. Patients with persistent asthma, should be screened for reflux, if no diagnostic method can be performed for whatever reason, trial therapy with Proton pump Inhibitors (PPIS) is indicated. In conclusion, patients with persistent asthma should be screened for reflux and receive treatment for better control of their asthma.

Keywords: Bronchial asthma, gastro esophageal reflux disease

Introduction

Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals, this inflammation causes recurrent wheezing, breathlessness, chest lightness and cough, particularly at night and/or in the early morning. These symptoms associated with widespread but variable airflow it is at least particularly reversible either or with treatment. The inflammation causes an increase in airway responsiveness to a variety of stimuli [1].

It is important to include GERD in the differential diagnosis with unexplained or refractory otolaryngologic and respiratory complaints. Many children with extra-esophageal don’t have typical GERD symptoms making the diagnosis difficult [2].

GERD can cause various pulmonary manifestations as chronic cough, bronchial asthma bronchitis, pneumonia and interstitial fibrosis. Out of these, bronchial asthma is one of the most common manifestations of GERD [3].

The association of asthma with gastroesophageal reflux disease has attracted particular attention because about half of the patients with asthma have GERD [4].

Proper management of GERD is important for asthma control [5].

GERD is a common condition in the pediatric population. It was clear that reflux plays a role in worsening of asthma symptoms and the potential effect of anti-reflux therapy on asthma needs further investigations [6].

Patients and methods

All studied children cases proved to have GERD and they received both prokinetic drug Domperidone (0.6 mg/1 g) and proton pump inhibitor, Omeprazole in a dose 0.7-3 mg/1 cg 1 day for one and half month. This study was approved by the Ethical Committee of the Institute of Postgraduate Childhood Studies, Ain Shams University. All participants were guaranteed
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confidentiality, and only the principal investigator has full access to the data.

The studied patients were 16 males (42.1%) and females (57.9%). Twenty eight (28) patients (73.7%) had moderate persistent bronchial asthma, while 10 patients (26.3%) had severe persistent bronchial asthma.

All children were subjected to:

- Full history including the following:
  - A) History of asthma:
    - Asthma symptoms
    - History of use of anti-asthma therapy
  - B) GERD symptoms
  - C) History of other extra-esophageal symptoms or signs of GERD such as recurrent ear infection hoarseness or dental caries.
  - D) History of drug intake other than anti-asthma therapy.
  - E) Family History of asthma or other atopic diseases; in-addition to family history of peptic ulcer and GERD.
  - F) History of smoking either active or passive.
  - The patients were classified according to the GINA (asthma) guidance of asthma management into moderate or severe persistent bronchial asthma.

- Full clinical examination and calculation of body mass index (BMI).

**Investigations**

**Laboratory investigations**

Serum gastrin (G-17) level was determined by radioimmunoassay using a commercial kit (Diagnosis Products Corporation, Los Angeles), with total coefficients of variation (CV) for two controls ranged from 4 to 10% according to the previous literature [7].

A - Pulmonary function test by means of spirometry

B - Chest X-ray.

C - Barium swallow was done using barium sulphate.

D - Upper gastro-intestinal endoscopy using a flexible fiberoptic endoscope (Olympus XPE type GIF).

All studied children proved to have GERD received in addition to their anti-asthma therapy; both prokinetic drug Dompevidone (0.6 mg kg dose), and proton pump inhibitor (1*1*1) Omeprazole in a dose of 0.7-3. co mg/kg/day for one and half month.

**Follow up scheme:** Follow up was done weekly in order to assess the progress of illness, patients and compliance with medication, and the final assessment was done after 6 weeks of treatment with anti-reflux medication. Pulmonary function forced expiratory volume in one minute (FEV1) by spirometry was performed at 4 and 6 weeks.

![Figure 1. Sex distribution of patients according to asthma severity.](image-url)
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The data were analyzed using SPSS version 17.0. The median age of onset of asthma in the included patients was 3.5 years (0-12 years; the mean duration of asthma was 9.1 ± 3.4 years (range =3-14 years) and their BMI 23.6 ± 4.2 years.

Results

The median age of onset of asthma in the included patients was 3 years (0-12 years), their mean age was 12.9 ± 2.6 years, the mean duration of illness was 9.1 ± 3.4 years (range =3-14 years) and their BMI was 23.6±4.3 (Figure 1A and 1B).

At the beginning of the study 36 patients (94.7%) were complaining of cough and night time symptoms. 37 patients (97.4%) were complaining of chest tightness. Wheezes were the main clinical finding found in all patients. Regarding the gastric symptoms: 25 patients (65%) had abdominal pain or retrosternal pain, heart burn was the complaint in 19 patients (50%) and 11 patients (28.9%) had vomiting. 23 patients (60.5%) had a personal history of atopy (Figure 2A and 2B).

Seven patients (15.4%) had frequent ear infections, five patients (13.2%) had a history of hoarseness and three patients (7.9%) had dentalcaries.

Statistical analysis

At the beginning of the study 36 patients (94.7%) were complaining of cough and night time symptoms. 37 patients (97.4%) were complaining of chest tightness. Wheezes were the main clinical finding found in all patients. Regarding the gastric symptoms: 25 patients (65%) had abdominal pain or retrosternal pain, heart burn was the complaint in 19 patients (50%) and 11 patients (28.9%) had vomiting. 23 patients (60.5%) had a personal history of atopy (Figure 2A and 2B).

Seven patients (15.4%) had frequent ear infections, five patients (13.2%) had a history of hoarseness and three patients (7.9%) had dentalcaries.
Family history was recorded positive in 11 patients (33.4%) for gastritis, 5 patients (14.7%) for peptic ulcer, 22 patients for smoking, 16 patients (47.1%) for atopy, asthma in 12 cases (35.3%) and 22 patients had positive history of smoking (Figure 2).

At base line; the chest score was 4 (3-4), after 1 week of follow up the chest score was 4 (4-4), after 2 weeks the chest score was 4 (2-4) while after 3 weeks the chest score was 3 (1-4). By the end of one month the chest score was 1 (0-4) and after the 5th week of follow up the chest score was 1 (0-2). Finally, after the 6th follow up week the chest score was also 1 (0-1) (Figure 3A).

By Friedman's test, there was a significant difference in chest score at the start of the study and during the follow up period (Fr=183.88, P<0.001).

There was also a significant difference in the abdominal score from the start of the study and during follow up (Fr=143.74, P<0.001).

At base line; the abdominal score was 1 (0-3), after the 1st week it was 1 (0-3) and after 2 weeks it was also 1 (0-4). After 3 weeks of follow up the abdominal score was 0 (0-4) and by the end of the 5th week and 6th week it was 0 (0-0) (Figure 3B).

A significant difference was found between all-time points: 1st between baseline and after one month of follow up and treatment (Z(T)=4.92, P<0.001), between baseline and after 6 weeks (Z(T)=5.14, P<0.001) and between the frequency after one month and 6 weeks (Z(T)=4.33, P<0.001) (Table 2).

Figure 5A and 5B shows the distribution of the two groups of patients with moderate persistent bronchial asthma and severe persistent bronchial asthma; and the prevalence of GER in the studied patients and family history of GERD. There was no significant association between prevalence of GER and family history of GERD with FEP=1.00.

Figure 5C shows the distribution of the two studied groups of patients, the prevalence of GER in the studied patients and family history of peptic ulcer. However, there was no significant association between prevalence of GER and family history of peptic ulcer (FEP=1.00).

The mean ± SD duration of illness in GER +ve group was 8.9 ± 3.59 years while in GER -ve group, it was 9 ± 3.08 years; but this difference was also statistically non-significant (t=0.03, P=0.978).

Comparing the chest score throughout the study: There was significant difference between the chest score at base line and after 3 weeks (Z=-4.030, P<0.001), after 4 weeks (Z=-4.80, P<0.001), after 5 weeks (Z=-4.91, P<0.001) and after 6 weeks (Z=-5.261, P<0.001). Also there was a significant difference between the chest score after one week and after 3 weeks (Z=-5.261, P<0.001), after 4 weeks (Z=-5.030, P<0.001), after 5 weeks (Z=-5.351, P<0.001) and after 6 weeks (Z=-5.252, P<0.001).

**Table 1.** Comparison between FEV1 throughout the study

<table>
<thead>
<tr>
<th></th>
<th>FEV1 2-FEV1 1</th>
<th>FEV1 3-FEV1 1</th>
<th>FEV1 3-FEV1 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-3.52</td>
<td>-4.80</td>
<td>-4.91</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.000*</td>
</tr>
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</table>

*Significance P<0.05.
Also, there was a significant difference between the chest score after two weeks and after 3 weeks (Z=3.923, P<0.001), after 4 weeks (Z=5.016, P<0.001), after 5 weeks (Z=5.222, P<0.001) and after 6 weeks (Z=5.207, P<0.001).

Also, there was a significant difference between the chest score after three weeks and after 4 weeks (Z=-4.628, P<0.001), after 5 weeks (Z=-5.005, P<0.001) and after 6 weeks (Z=-5.004, P<0.001).

Also, there was a significant difference between the chest score after four weeks and after 5 weeks (Z=-3.571, P<0.001), and after 6 weeks. Also, there was no significant difference between the abdominal score after four weeks and after 5 weeks; and after 6 weeks. Also, there was no significant difference between the abdominal score after five weeks and after 6 weeks (Table 3).

Table 4 shows that fasting level of serum gastrin was significantly higher in severe persistent asthma (87.36 ± 12.34) than moderate persistent asthma (67.56 ± 11.23) with a P value <0.001 and post prandial levels of gastrin in moderate persistent asthma (77.86 ± 9.73) was significantly higher than fasting level of gastrin (67.56 ± 11.23) with a P value <0.001, postprandial level of gastrin in severe persistent asthma (97.53 ± 11.32) is significantly higher than post prandial level in moderate persistent asthma with a P value <0.001.

Discussion

Asthma is a worldwide problem [8]. Approximately 300 million people worldwide suffer...
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In individuals with severe asthma, co-morbidities are common, and the most prevalent is GERD [11].

According to a global definition, GERD can cause esophageal and extra-esophageal symptoms, which can co-exist or not in the same individual. Respiratory manifestations of GERD represent one of the most prevalent and challenging of these extra-esophageal symptoms [12].

According to our results, GERD was present in 78.9% of the patients with moderate-severe persistent bronchial asthma. These rates are comparable with the upper limits reported in the literature [13].

Differences in reporting the incidence of GERD result from differences in diagnostic tools including PH monitoring endoscopy and radiological manipulations [14].

Other studies reported that GERD was diagnosed in 75% of children with chronic asthma who were refractory to medical treatment [15].

Retrosternal pain was reported in 65.8% of the patients in our study, heart burn in 50%, 28.9%, had vomiting and none of them had dysphagia. These results are near to the results reported in other studies and the older age of our cases helped them to describe their symptoms.

Epigastric discomfort, regurgitation and dysphagia were reported in 77%, 55% and 24% of adult patients with asthma, respectively, and these symptoms were significantly more frequent compared to healthy controls. Although some children do not have GERD related symptoms and this condition is likely to result from that adults describe their symptoms better than children. So GERD symptoms may be less prevalent in the childhood than in the adult-

Figure 5. Patients with moderate persistent bronchial asthma and severe persistent bronchial asthma; and the prevalence of GER (A, B). The prevalence of GER in the studied patients and family history of peptic ulcer (C).
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In a systematic review of 28 epidemiological studies the prevalence of GERD symptoms was found in 59.2% of asthmatic patients, compared to 38.1% in controls [17]. In the current study barium swallow was done for diagnosis of GERD and it showed that 68.4% of the studied adolescents have GERD. Barium swallow is a non-invasive easy and the most accepted in both patients and their care-givers. In addition, we used EGD for those who were negative for reflux in barium studies. 33.3% of GERD-ve children in barium swallow were proved to have GERD in endoscopic examination while 66.7% were GERD-ve in endoscopy.

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The risk of esophagitis in individuals with GERD increases with age, although most of the cases have neither histological nor macroscopic sings of esophagitis [18]. Endoscopy negative esophagitis with absence of macroscopic sings of damage may be also associated with asthma [4].

So in the current study, we used both Omeprazole (PP1) and domperidone as a prokinetic drug for controlling reflux. Current guidelines recommend consideration of evaluation for GERD in patients who have poorly controlled asthma. Especially with nighttime symptoms, even in the absence of GERD symptoms or if GERD is present, realment recommendations include using of a PPI [19].

Our results showed that after treatment with Omeprazole and Domperidone there was a significant improvement of asthma regarding symptoms with a significant decrease in the occurrence of symptoms throughout the study, (for the whole studied patients; P<0.001 while for the GERD +ve patients; P=0.001). A significant decrease m the need for SABA (for the whole studied patients; F=69, P≤0.001 while for the GERD +ve patients; F=54.8, P≤0.001).

A significant improvement In FEVI across time (for the whole studied patients; F=72.4, P≤0.001 while for the GERD +ve patients; F 3370 P=0.001). In addition, there was an improvement in asthma symptoms in the form of reduced use of medications and improvement in pulmonary functions in 100% of the studied patients. By the end of 4 weeks of the study, 95% of patients (36/38 patients) achieved moderate improvement of their chest symptoms while 5% of patients (2/38 patients) achieved complete improvement of their asthma symptoms.

The study contributed that result to the small sample sizes [20].

In our study all of the studied patients (38 patients) were suffering from nocturnal asthma and the chest score-Including night-time symptoms-throughout the study showed significant improvement (for the whole studied patients; F=204.6, P≤0.001 while for the GERD +ve patients; F X 161, P≤0.001). Our results were agreed with the study carried out by Devaulf which revealed that PPI treatment improves nocturnal asthma symptoms [21].

Obesity is known to be a risk factor for increased reflux [22]. In our study, there was no significant difference in BMI patients with moderate persistent asthma and those with severe persistent asthma (t=1.7, P=0.1), although it was higher in tile latter, hi addition, there was also no significant difference in BMI in patients diag-

Table 3. Comparing abdominal score throughout the study

<table>
<thead>
<tr>
<th>Compared scores</th>
<th>Z test</th>
<th>Asymp. Sig. * (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal score 1-abdominal score 2</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Abdominal score 1-abdominal score 3</td>
<td>1.589</td>
<td>0.112</td>
</tr>
<tr>
<td>Abdominal score 1-abdominal score 4</td>
<td>4.115</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 1-abdominal score 5</td>
<td>4.736</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 1-abdominal score 6</td>
<td>4.724</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 1-abdominal score 7</td>
<td>4.724</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 2-abdominal score 3</td>
<td>1.930</td>
<td>0.054</td>
</tr>
<tr>
<td>Abdominal score 2-abdominal score 4</td>
<td>4.337</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 2-abdominal score 5</td>
<td>4.736</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 2-abdominal score 6</td>
<td>4.724</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 2-abdominal score 7</td>
<td>4.724</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 3-abdominal score 4</td>
<td>4.300</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 3-abdominal score 5</td>
<td>4.532</td>
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</tr>
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<td>4.500</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 3-abdominal score 7</td>
<td>4.500</td>
<td>0.000</td>
</tr>
<tr>
<td>Abdominal score 4-abdominal score 5</td>
<td>3.207</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal score 4-abdominal score 6</td>
<td>3.274</td>
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<td>Abdominal score 4-abdominal score 7</td>
<td>3.274</td>
<td>0.001</td>
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<td>Abdominal score 5-abdominal score 6</td>
<td>1.414</td>
<td>0.157</td>
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<tr>
<td>Abdominal score 5-abdominal score 7</td>
<td>1.414</td>
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<tr>
<td>Abdominal score 6-abdominal score 7</td>
<td>0.000</td>
<td>1.000</td>
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*Significance P<0.002.
nosed with GERD and those without GERD (t=1.2, P=0.3).

Obesity may be a risk factor for GERD [23]. Some studies have reported a higher prevalence of asthma among obese individuals [24]. Thus, obesity may be a strong predisposing factor for both GERD and asthma and a risk factor for both conditions [25].

The lack of association between BMI and GERD diagnosis in our study may be due to different age of our studied patients compared to other studies.

By the end of the 6th week more improvement was achieved with a decline in the percentage of the first group to decrease from 95% to 53% (20/38 patients) and subsequent increase in the second group to reach 47% (15/38 patients).

Our results are in agreement with Yuksel et al. [26]. There was a significant difference in the mean symptoms score, use of bronchodilators and the number of asthma attacks per patient after treatment were all significantly decreased [27].

More than 12 studies reported that anti reflux treatment markedly improved asthma symptoms [28].

Treatment with omeprazole markedly improved both asthma symptoms and pulmonary function [29]. On the contrary, a randomized placebo-controlled study with PPI included 207 asthmatics with reflux symptoms. There was no improvement in daily asthma symptoms or pulmonary function and it was concluded that improvement in asthma outcome may be obtained in the tile subgroup with more severe asthma [31]. We have similar results in our patients who were suffering from moderate persistent and severe persistent asthma.

Regarding atopy; in our studied patients, the associations between reflux symptoms and asthma diagnosis were not significantly different between those who were atopic (13 patients/30 GERD +ve) and those who were not atopic (19 patients. 30 GERD +ve), also there was no significant difference regarding personal atopy (21/38 patients; or family history of atopy (21/38 patients) and the diagnosis of GERD (X^2=0. 215. P=0.6), and this agrees with the results obtained by Hancox et al. [27].

Our results also are near to the results of the study reported by Sopo et al. in which there was no difference in outcome in atopic and non atopic asthma. The study contributed that result to the small sample sizes [22].

In our study, serum gastrin was elevated postprandial in both moderate and severe persistent asthma and the fasting levels of gastrin were higher in severe persistent asthma than moderate persistent asthma.

This may be attributed to the biological properties of gastrin which influences the release of HCL from the parietal cells of the stomach which influences the basal tone of Lower Esophageal Sphincter (LES) and plays a role in stomach emptying [32].

**Conclusions and recommendation**

Gastro esophageal reflux has a role in worsening asthma symptoms; so patients with persistent asthma should be screened for GERD and patients with persistent asthma show some improvement after anti reflux therapy concerning severity of symptoms and the number of attacks.

In patients with moderate-persistent or severe-persistent asthma in which no diagnostic meth-
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od can be performed for whatever reason; trial therapy with PPIs is indicated, as the most effective treatment with good tolerance.

Disclosure of conflict of interest

None.

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