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GERD and asthma

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Abstract

Asthma and gastroesophageal reflux disease (GERD) are both common diseases, and hence they often coexist. However, the coexistence of asthma and GERD is far more frequent than chance association. In fact, the relationship between asthma and GERD was firstly described in the 19th century, by Willam Osler. Afterwards, many studies were published addressing the association between asthma and GERD. However, studies have only showed that there is a relationship between GERD and asthma, the causal relationship is not yet established clearly. The difficulties in establishing the causal relationship between the two conditions will be discussed. The effects of treatment of GERD in asthmatic patients will also be reviewed.

Keywords: Asthma, Gastroesophageal reflux disease, GERD

Introduction

Gastroesophageal reflux disease (GERD) and asthma are both common diseases, and hence they often coexist. However, the prevalence of coexistence of asthma and GERD is far more frequent than by chance association alone. In fact, the relationship between GERD and asthma was firstly described in the 19th century, by Willam Osler: "attacks may be due to direct irritation of the bronchial mucosa or... indirectly, too, by reflux influences from the stomach...".[1] Afterwards, many studies have been published addressing the association between GERD and asthma. However, studies have only showed that there is a relationship between GERD and asthma, the causal relationship between the two conditions remains unclear. This article examines the relationship between GERD and asthma and discusses management of asthmatic patients with GERD.

Diagnosis of GERD in children is not easy

Gastroesophageal reflux (GER) is defined as retrograde passage of gastric contents into the esophagus with or without regurgitation and vomiting. It is a normal physiologic process occurring several times per day in the healthy infants and children. Epidemiological studies suggest that gastroesophageal reflux occurs in approximately 50% of infants younger than 2 months of age, 60 to 70% of infants 3 to 4 months of age, and 5% of infants by 12 months of age.[2]

However, GERD is present when the reflux of gastric contents causing troublesome symptoms or complications such as esophagitis.[3] In fact, symptoms of GERD vary by age. In adults, heartburn and regurgitation are the main symptoms of GERD.[4] In older children (6-17 years), the predominant symptoms are regurgitation or vomiting, water-brash, cough, epigastric pain and heartburn.[5] On the other hand, toddlers and young children (1-6 years) tend to present with food refusal, regurgitation, abdominal pain, melena, and iron deficiency anaemia.[5,6] Infants may present with regurgitation, food refusal, irritability, crying, and failure to thrive. These symptoms are non-specific. Other causes, such as food allergy, can have the similar symptoms.[7,8] Sometimes, even normal infants may have some of the symptoms. Some infants and young children may present with repetitive stretching and arching of the head and neck, referred to as Sandifer syndrome.[9] Overall, the variability of the GERD symptoms and signs in the paediatric age groups make the symptom-based diagnosis of GERD very difficult.

The issue of 'troublesome' is also complicated in paediatric population. Although the verbal child can communicate pain, but descriptions of the intensity, location and severity may be unreliable until the age of

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at least 8 years, and sometimes even later.[10,11] Thus, patients younger than 8 years old are not reliable in determination of whether a symptom is troublesome by self-report. Even worse, reporting symptoms by parent or caregiver may decrease the validity of diagnosis.

In fact, symptoms of GERD do not just restrict to esophagus. It can affect various tissue and organ systems beyond the esophagus.[12] According to the Global Consensus Definition Committee classification, the extraesophageal symptoms can de divided into definite associations (such as Sandifer syndrome and dental erosions) and possible associations.[3] Bronchopulmonary problems (such as asthma, aspiration pneumonia, pulmonary fibrosis, bronchopulmonary dysplasia, obstructive bronchitis), laryngotracheal and pharyngeal problems (such as chronic cough, chronic laryngitis, hoarseness, pharyngitis), rhinological and otological problems (such as sinusitis and serous otitis media) and infants with pathological apnoea, bradycardia and apparent life-threatening events are all included in the possible associations. The estimate prevalence of extra-esophageal symptoms in children with GERD are 4.2% (sinusitis), 2.1% (otitis), 40.2% (dental erosion), 20% (apparent life threatening events), 13.2% (asthma), 6.3% (pneumonia), 1% (bronchiectasis) and 57.7% (general respiratory symptoms).[13] Respiratory symptoms or diagnosis (such as asthma) have been the most commonly studied extra-esophageal symptoms so far.

The lack of clear practical definition of GERD and its variability in clinical manifestations in infants, children, and adolescents lead to confusion for the clinicians, both when interpreting clinical trials and when trying to understand how to employ the available diagnostic tests.

When cough, wheezing, and dyspnoea are not asthma

Asthma is a disease that is characterised by hyper-responsiveness of airways to various stimuli, which results in airway obstruction that is reversible either spontaneously or as a result of treatment.[14] Clinically, the diagnosis of asthma is suspected when there is episodic cough, wheezing, shortness of breath, and chest tightness. Family history or personal history of atopy may further contributed to the certainty of the diagnosis.[15,16] The diagnostic gold standard in older children (≥5 years) is the demonstration of reversibility of airway obstruction by standardised pulmonary function testing, before and after the administration of a bronchodilator.[17] Spirometry is the preferred measurement because of wide variability in peak flow meters and reference values. The forced expiratory volume in the first second (FEV1) is the main measure of airflow obstruction. However, reduced lung function as a characteristic feature of asthma does not become apparent until the school years in part because of the inability of the young children to perform lung function tests. This makes diagnosing asthma in young child or infant with wheeze a challenge. In addition, the same respiratory symptoms may result from other causes.[14,18-20] And GERD should also be considered as one of the possible differential diagnoses.

When chronic cough is not asthma

Several papers have been published to evaluate this question. Marchant et al performed a prospective cohort study of 108 children with chronic cough [median age 2.6 years (interquartile range 1.2 to 6.9 years)] in a tertiary hospital.[21] Chronic cough was defined as cough lasting longer than three weeks. The study protocol was based on the modified algorithmic approach that was suggested by the American College of Chest Physicians.[22,23] The major modification was the evaluation order of diagnostic tests, with bronchosopy and broncho-alveolar lavage (BAL) being performed significantly earlier than in the adult protocol. Relevant childhood investigations, such as sweat chloride test, were performed at the beginning of the investigative protocol. GERD was defined as a reflux index of greater than or equal to 4% on pHmetry or esophageal biopsy sample showing esophagitis, and treatment by standard medical therapy results in resolution of cough.[24] In this study, GERD, a common cause of cough in adults, accounted for only 3% of primary diagnosis and for 15% of secondary diagnosis (that is, present but treatment did not contribute to cough resolution) in children.

Asilsoy et al performed a prospective cohort study on 108 patients with chronic cough (age between 6 and 14 years) who were seen in a referral centre.[25] The study was conducted using the algorithm suggested by the 2006 American College of Chest Physicians guidelines for chronic cough in children.[26] Chronic cough was defined as cough lasting longer than four weeks. GERD was defined as detection of reflux via gastroesophageal scintigraphy in children with cough and responding to the treatment (lansoprazole, 15mg/day) within 2 to 4 weeks). Only 4.6% of the patients were diagnosed to have GERD in this study.

Khoshoo et al performed a prospective cohort on 40 consecutive children with chronic cough [mean age 7.8 years (range from 5 to 12 years)] seen in a referral centre.[27] Chronic cough was defined as cough lasting longer than 8 weeks. All patients underwent an extensive multispecialty workup that included pulmonary, gastrointestinal, allergy, immunology, and otorhinolaryngology testing. GERD was defined as a pH in the distal esophagus smaller than 4 for longer than 5% of the recording durationThe single most common factor associated with chronic cough in this study was GERD (27.5%).

In summary, the prevalence of GERD in children with chronic cough ranged from 3% to 27.5%. The wide range of preference may be due to the different in the definition of chronic cough, definition of GERD and the various methods used in the evaluation. Because the studies were performed in referral centers, the results may not be generalisable.

When wheezing and dyspnoea are not asthma

There is a paucity of information on this topic. Saglani et al performed a retrospective review of 47 children with a median age of 26 (range 5-28) months with severe recurrent wheeze, who had been referred to a tertiary centre, underwent a protocol of comprehensive investigations including a chest computed tomography scan, blood tests, nasal ciliary brushings, fibreoptic bronchoscopy, BAL, endobronchial biopsy and esophageal pH study.[28] Definition of GERD was an abnormal pH study (esophageal pH of smaller than 4 for longer than 4% of recording time, except in infants, when age-appropriate values were used) and BAL showed fat-laden macrophages with normal endobronchial biopsy. The prevalence of GERD in this study population was 23%. As patients in this study were highly selected, the results of this study are not generalisable.

GERD and asthma are not mutually exclusive

There is general agreement that there is an association between GERD and asthma. To examine the association between GERD and asthma in children, a systematic review of articles published from 1966 to 2008 searched by using PubMed, Embase and the Cochrane Library databases.[29] Nineteen studies examined the prevalence of GERD patients with asthma (n=3726). The authors found that the prevalence of GERD in these 3726 children with asthma ranged from 19.3% to 80.0%. The sample-sized-weighted average prevalence of GERD in patients with asthma was 22.8% (847 of 3726). Only five studies included controls with 1314 asthmatic patients and 2434 controls without asthma. The average prevalence of GERD was 22.0% in asthma and 4.8% in control. Pooled odds ratio was 5.6 (95% confidence interval: 4.3-6.9).

To examine the prevalence of asthma among GERD patients, El-Serag et al studied 1980 children with GERD (n=1980) identified by administrative database at Texas Children's Hospital.[30] There was no standardised definition of asthma or GERD. Rather, the diagnoses were made clinically by physicians. Reported prevalence of asthma in patients with GERD was 13.2%, whereas in controls, it was only 6.8% ($p<0.0001$). Odd ratio was 2.1 (95% CI: 1.8-2.5). It is hoped that future studies wound address the issue whether asthmatics experience respiratory symptoms at the time of GERD symptoms.

Explanation of wide variations in prevalence of GERD in asthmatic pPatients

The systemic review by Thakker et al showed that the prevalence of GERD among asthma patients ranged from 19.3% to 80.0%.[29] There are many reasons to explain the wide discrepancy in the prevalence of GERD in asthmatic patients in the different studies.

First, there were no clear criteria for the diagnosis of asthma. Only five studies provided criteria for asthma, that included physician's diagnosis, three or more episodes of reversible bronchospasm, Global Initiative for Asthma, American Thoracic Society criteria for asthma diagnosis.[31-35] Thus, the asthmatic population was not homogenous enough for meaningful comparison among different studies.

Second, the different target population in different studies would also influence the results. The studies that carried out in clinics or population showed the lowest prevalence of GERD from 19.3% (57/296) to 19.7% (172/872).[36] Also, some studies used questionnaire for the diagnosis of GERD in asthmatic patients. Symptom-based techniques also have significant limitations in children, because verbal descriptions of symptoms may be unreliable until the age of 8 years, and older children may not voice out during a consultation.[3] Moreover, symptoms suggestive of GERD are common in children, and it is difficult to determine which children actually have GERD.[37]

Third, the different diagnostic criteria and methodology for the diagnosis of GERD would also affect the result. The most common method for diagnosis of GERD was esophageal pH study. It is thought to be the most valid measure of reflux (upper limit of normal up to 12% in the first year of life and up to 6% thereafter).[24] Unfortunely, pH-metry is still not a perfect test as it is also limited by the inability to detect nonacid reflux. Among the nineteen studies, twelve studies used esophageal pH in children with asthma for diagnosing GERD. Definition of GERD ranged from greater than 1% to greater than 6% of reflux index in different studies. The prevalence of abnormally high acid exposure ranges from 41.8% to 80.0%. The pooled sample-size-weighted average prevalence was 62.9% (496/789). The relatively high prevalence might be due the fact that the majority of studies used a reflux-index threshold that was lower than that required by the guidelines.

There were two studies that enrolled a total of 89 children with asthma who underwent upper endoscopy.[38,39] The prevalence of endoscopic esophagitis was 15.7% while the histopathological esophagitis was 64.3%. However, the presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of GERD. Although GERD is the most likely cause of esophagitis in children, other disorders such as eosinophilc esophagitis, Crohn's disease and infections can also cause esophagitis.[40] Regarding histology, there is insufficient data for recommending histology as a tool to diagnose or to exclude GERD in children due to sampling error, lack in standardisation of biopsy location, tissue processing and interpretation of morphometric parameters.[3]

Petersen et al used barium contrast radiography in the diagnosis of GERD.[41] The prevalence was 33.3% (8/24). However, the study included small sample size. At the same time, the brief duration of the upper GI series produced false-negative results, whereas the frequent occurrence of non-pathological reflux during the examination produced false positive results. Therefore, upper GI series to diagnose GERD is not reliable.

Chopra et al used radionucleotide scan for the diagnosis of GERD.[32] The prevalence was 38.8% (31/80). Radionucleotide scan only evaluates postprandial reflux but can demonstrate reflux independent of the gastric pH. Late postprandial reflux may be missed with scintigraphy.[42] At the same time, a lack of standardised techniques and the absence of age-specific norms also limit the value of this test.

Alternative sources of variation in the data include the small sample sizes, the timing of the study in the relation to the patient's symptoms and variation in the age groups amount the studies.[13] The paucity of large well-conducted controlled studies, the varying definitions of diseases used and the wide range of investigative techniques also make it difficult to draw a strong conclusion.

Coexistence of GERD and asthma

The coincidence of GERD and asthma may have three explanations. It can due to (a) asthma causes GERD (b) GERD causes asthma or (c) common aetiological denominators for asthma and GERD.

Asthma causes GERD

Asthma is well known to promote gastroesophageal reflux by a varity of mechanisms.[43,44] First, cough, hyperinflation of the chest or airway obstruction in asthmatic patients can increase the pressure gradient across the chest and the abdomen that can alter the relationship between the crural diaphragm and the gastroesophageal junction with resultant herniation of the lower esophageal sphincter into the chest where its barrier function is impaired. This would allow reflux of acid contents into the esophagus.[45] Second, some medications used in the treatment of asthma may aggravate GERD.[46] For example, beta-agonists and methylxanthine bronchiodilators can decrease the lower esophageal sphincter pressure and promote gastroesophageal reflux. Oral corticosteroids can promote acid secretion and therefore increase the risk of GERD.

GERD causes asthma

On the other hand, several theories have been proposed to explain GERD induced asthma. The reflux theory suggests that microaspiration can directly result in airway constriction or indirectly through induction of chronic inflammatory changes, which subsequently can lead to increased airway reactivity.[47,48] Furthermore, the reflex theory states that the common embryologic origins of the respiratory and gastrointestinal systems result in shared innervation via the vagus nerve and thereby share similar autonomic reflexes.[49] It has been showed that stimulation of the esophageus by oral intake cold or acid drinks can temporarily increase bronchial reactivity and decrease peak expiratory flow rates in asthmatic patients.[50,51] It is believed that the stimulation of receptors in the distal esophagus by acidic gastric

contents can lead to vagal reflex and therefore bronchial constriction.[52]

Common aetiological denominators for asthma and GERD

Most children with asthma have some IgE mediated allergy. Airborne allergens also reach the esophagus and stomach.[53] If allergic reactions take place in the upper gastrointestinal tract, they might induce hyper-secretion of gastric acid or dysfunction of the esophagus and stomach, which in turn facilitate gastro-esophageal reflux.[54] Furthermore, autonomic nervous system disturbances are quite common among asthmatic patients.[55] It may cause disturbance of the lower esophageal splinter and increase the chance of GERD.

Relationship between treatment of GERD and asthma outcomes

Several initial studies in adults suggested that treatment of GERD improved asthma control.[1,56-61] However, the results have been variable and inconsistent in demonstrating positive effects on lung function, asthma symptoms and asthma related quality of life. The first Cochrane Systemic Review was published in 2000.[62] Nine trials met the inclusion criteria. Interventions included proton pump inhibitors (n=3), histamine antagonists (n=5), surgery (n=1) and conservative management (n=1). Treatment duration ranged from 1 week to 6 months. A temporal association between asthma and gastro-oesophageal reflux was investigated in 4 trials and found to be present in a proportion of participants in these trials. Anti-reflux treatment did not consistently improve lung function, asthma symptoms, nocturnal asthma or the use of asthma medications. In 2003, an update systemic review was performed.[63] This time, three more trials involving proton pump inhibitors met the inclusion criteria but it did not affect the conclusion. The Cochrane reviewers concluded that "in asthmatic subjects with GER, there was no overall improvement in asthma following treatment of GER". Since then several studies have been published in adult population, but they still showed inconsistent results.[64-66]

Stordal et al performed a double blinded, randomised, placebo-controlled clinical trial analysing the efficacy of a PPI (omeprazole) in paediatric patients with GERD and asthma which is poorly controlled by standard pharmacological tremtment.[67] They enrolled 38 children (mean age 10.8 years, range 7.2-16.8) with asthma diagnosed by their doctors. Questionnaires were given to the patients for identification of any symptoms of GERD, and those presenting at least 1 symptom underwent 24-hour pH monitoring. GERD was defined as reflux index equal to or greater than 5%. Patients already taking treatment for GERD were excluded from the study. Patients were randomised to omeprazole at 20 mg/d or placebo for 12 weeks. However, no significant differences were observed between the 2 groups with respect to the efficacy of omeprazole against asthma symptoms, instrumental parameters, or the use of β2-agonists. In the subgroup analysis, those children in the intervention group with a reflux index greater than 10% and more severe asthma, would have an improved score for the Paediatric Quality of Life Questionnaire, but not reached statistically significance. The authors argued that sample size might not be big enough to show statistically signifcant.

Holbrook et al performed a larger study and enrolled 306 poorly controlled asthma children without overt GERD into a randomised, double-blinded controlled trail in order to investigate effect of lansoprazole in asthma symptoms control.[68] The mean difference in change in the Asthma Control Questionnaire score was 0.2 units (95% CI, 0.0-0.3 units). There were no statistically significant differences in the mean difference in change for the secondary outcomes of forced expiratory volume in the first second (0.0 L; 95% CI, -0.1 to 0.1 L), asthma-related quality of life (-0.1; 95% CI, -0.3 to 0.1), or rate of episodes of poor asthma control (relative risk, 1.2; 95% CI, 0.9-1.5). Children treated with lansoprazole reported more respiratory infections (relative risk, 1.3; 95% CI, 1.1-1.6).

Rothenberg et al retrospective reviewed the effects of laparoscopic Nissen Fundoplication on 235 patients (age ranged from 1 month to 19 years old, mean age 7 years old) with severe GERD and steroid dependent asthma.[69] The 24 hr pH study of these patients all showed features of GERD. Bronchoscopy and BAL showed significant lipid-laden macrophages in 28% of the patients. After laparoscopic Nissen Fundoplication, 24% of the patients improved forced expiratory volume in initial post operative period. Within 2 weeks, 91% of the patients improved in asthma symptoms. Within 2 months, 80% of the patients weaned off systemic steroid. Two to seventy-two months later, 89% of the patients improved asthma symptoms. However, interpretation of the results needed to be caution as it was a retrospective study.

Translating theory to practice: management of the child with concomitant asthma and GERD

As discussed in the above section, there is no strong evidence to support empiric PPI therapy in unselected paediatric patients with wheezing or asthma. Fundoplication is only indicated for those with severe GERD. If the symptoms of asthma are very difficult to control, other causes or contributing factors should also be considered. The present consensus is that empiric treatment of asymptpmatic GERD in asthmatics is not a useful practice.[70] On the other hand, the treatment of symptomatic GERD in asthmatic patients is important to control the underlying GERD, although such treatment has limited benefits on asthma outcomes and no clear benefit on asthma control.[70]

Concluding remarks

Suffice to say, there is a significant association between GERD and asthma, although data on the direction of causality are still lacking. Manu of the initial studies had significant limitations in terms of small sample sizes, non-randomised studies with no control, inconsistent definitions used for asthma and GERD, variable outcome measures. As such, there are still a lot of questions relating to this topic that have no clear answers. It highlights the important and needs for further well-designed case-controlled trials, using standardised techniques of investigations, standardised definitions of GERD, extra-esophageal symptoms, and asthma. Future trials of anti-reflux therapies should be randomised controlled trials with appropriate control groups and make use of newer techniques such as multichannel impedance pH monitoring so that clinically useful conclusions may be drawn. Longitudinal studies assessing the temporal relationship between GERD and extra-esophageal symptoms in children are also needed.

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