Gastroesophageal reflux disease and airway hyperresponsiveness: concomitance beyond the realm of chance?*

Doença do refluxo gastroesofágico e hiperresponsividade das vias aéreas: coexistência além da chance?

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Abstract

Gastroesophageal reflux disease and asthma are both quite common the world over, and they can coexist. However, the nature of the relationship between these two diseases remains unclear. In this study, we review controversial aspects of the relationships among asthma, airway hyperresponsiveness, and gastroesophageal reflux disease in adults and in children.

Keywords: Asthma; Bronchial hyperreactivity; Gastroesophageal reflux.

Resumo

A doença do refluxo gastroesofágico e a asma são duas condições mundialmente comuns e podem coexistir. Contudo, a natureza da relação entre essas duas doenças ainda não é bem compreendida. Neste artigo, revisamos alguns aspectos controversos da relação entre asma, hiperresponsividade das vias aéreas e refluxo gastroesofágico, tanto em adultos, quanto em crianças.

Descritores: Asma; Hiper-reatividade brônquica; Refluxo gastroesofágico.

Introduction

In every country, gastroesophageal reflux disease (GERD) and asthma, both of which have significant effects on health, are quite common and can coexist. There is no consensus definition for epidemiological studies of asthma or GERD, and, depending on the age group, both conditions pose diagnostic difficulties. In addition, the worldwide prevalence of these two conditions has been increasing in recent years.[1,2]

There have been few population-based studies of the prevalence of GERD, either in adults or in children.[3] In adults, the estimated prevalence of GERD, when defined as at least one episode of heartburn per week, ranges from 10% to 20% in Western countries, whereas it is less than 5% in Asia.[4] The prevalence of GERD symptoms in children treated at pediatric clinics is less than 10%.[5] However, specific populations of children, such as those with neurological problems, esophageal atresia, or chronic respiratory diseases, those who are obese, and those who were born prematurely, are at increased risk for GERD.[1]

Asthma is a common condition that affects virtually all age groups, being the most common chronic disease in children and being particularly prevalent in developed countries. The International Study of Asthma and Allergies in Childhood (ISAAC), in an evaluation of 13,604 schoolchildren (6-7 years of age) and 20,554 adolescents (13-14 years of age), showed a high prevalence of asthma in Brazil.[6] In addition, the prevalence of wheezing 12 months prior to the medical visit in Brazil was found to be 27.2% among children and adolescents in the city of

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Financial support: None.
Submitted: 28 February 2011. Accepted, after review: 23 May 2011.

Porto Alegre, whereas, among adolescents only, the prevalence ranged from 9.6% (in the city of Itabira) to 27.1% (in the city of Salvador).[7-10]

Studies investigating the relationship between asthma and GERD continue to produce conflicting results.[11] In the present review, we discuss some controversial aspects of the relationships among asthma, airway hyperresponsiveness (AHR), and GERD—in adults and in children.

Gastroesophageal reflux and GERD: definition and mechanisms

Gastroesophageal reflux (GER), defined as the involuntary passage of gastric contents into the esophagus, is a normal physiological process that occurs several times throughout the day in healthy children and adults. Most reflux episodes are brief and asymptomatic, occurring postprandially in the distal esophagus.[1]

Various structures at the esophagogastric junction are important in maintaining an antireflux barrier: the lower esophageal sphincter (LES); the crural diaphragm (CD); and the phrenoesophageal ligament. The LES is the intrinsic sphincter, and the CD is the extrinsic sphincter. The two sphincters are anatomically superimposed and anchored to each other by the phrenoesophageal ligament. The intrinsic basal tone of the LES increases when the CD contracts; through this and other mechanisms, the LES prevents the reflux of gastric contents into the lower esophagus.[12]The pathophysiology of GERD is multifactorial and is associated with three potential abnormalities in LES motility: incompetence of the LES; inadequate gastric emptying; and delayed gastric emptying. The loss of the resting tone of the LES or the increase in its relaxation frequency favors the return of gastric contents. Likewise, if esophageal peristalsis is not sufficient to eliminate reflux, there will be greater contact between the gastric acid and the mucosa, and this factor (insufficient clearance) alone can cause esophagitis.[12] Other determinants of reflux include anatomical changes in the region, such as the mere separation of the pillars of the diaphragmatic hiatus, with or without hiatal hernia, resulting in the loss of the angle of Hiss and shortening of the esophagus.[12,13]

Whereas GER is a physiological condition, GERD refers to GER accompanied by digestive symptoms, extradigestive symptoms, or a combination of the two, together with complications that do not resolve spontaneously.[1,14] In children, gastrointestinal symptoms of GERD vary according to age, although, in general, they include retrosternal burning, epigastric pain, and regurgitation.[1,3,5] In children and adults, respiratory symptoms associated with GERD include wheezing, persistent cough, and dyspnea.[11,14] However, these symptoms are nonspecific.[1,3,14] In addition, children frequently have difficulty in characterizing the intensity of each symptom, and retrosternal burning can be reported as pain. In some cases, GERD symptoms are minimal or absent.[1,3,5]

In general, the diagnosis of GERD is made on the basis of the signs, symptoms, and complications of reflux, if any of those are significant enough to require medical attention. The diagnosis of GERD can be confirmed by esophageal biopsy via upper gastrointestinal tract endoscopy, esophageal manometry, intraluminal impedance monitoring, 24-h esophageal pH monitoring, or intraluminal impedance monitoring combined with 24-h esophageal pH monitoring.[1,14,15] None of these methods has all the characteristics needed in order to be considered the gold standard. Upper gastrointestinal tract endoscopy is the most reliable method to detect GERD-related esophagitis.[16] However, the absence of esophagitis does not exclude the diagnosis of GERD.

Manometry evaluates esophageal motility and is indicated in cases of symptoms suggestive of esophageal dysmotility; however, manometry findings are not sensitive or specific enough to confirm the diagnosis of GERD.[1] Intraluminal impedance monitoring is a noninvasive method that detects the retrograde flow of fluids and air into the esophagus.[16] However, normal values for the various pediatric age groups have yet to be defined.[1]

Despite being a valid method for measuring the frequency and duration of GER, 24-h esophageal pH monitoring is insensitive to GER that is slightly acid or alkaline.[16,17] By convention, a drop in esophageal pH to below 4.0 is considered an episode of GER. For the investigation of GER, esophageal pH monitoring has good sensitivity and specificity (87-93% and 93-97%, respectively),[14,17] although there is no

consistent evidence that the severity of exposure to GER is correlated with the symptoms and complications of GERD. According to the recently issued North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the management of GERD, esophageal pH monitoring is useful for evaluating the efficacy of antisecretory therapy, for correlating symptoms (cough and chest pain) with GERD episodes, and for identifying children in whom GER can aggravate extradigestive symptoms.[1]

More recently, intraluminal impedance monitoring combined with 24-h esophageal pH monitoring has been used for the diagnosis of GERD. Intraluminal impedance monitoring has the additional advantage of detecting episodes of GER that is slightly acid or alkaline. However, its usefulness has yet to be fully established. Other diagnostic tests, such as ultrasound of the esophagus and stomach, are not recommended for children, because they do not differentiate between pathological and physiological GER.[1]

AHR: definition and mechanisms

Asthma is a chronic disease, defined by episodic respiratory symptoms, variable airflow limitation, AHR, and airway inflammation.[18] Respiratory symptoms, variable airflow limitation, and AHR are often associated with eosinophilic airway inflammation, which is considered characteristic of asthma.[19]

Defined as excessive constriction of the airways in response to various stimuli, AHR is a seen in virtually all patients with asthma.[19,20] In general, AHR is measured by bronchial challenge with bronchoconstrictors, of which the most commonly used are methacholine, histamine, cAMP, and hypertonic saline.[20]

In asthma patients, the intensity of AHR is proportional to the severity of the asthma, AHR intensity increasing after exposure to asthma triggers (such as viral infections, allergens, and occupational agents) and decreasing after treatment with anti-inflammatory drugs.[20] In addition, it has been shown that AHR can occur in patients with airflow limitation caused by other diseases, such as COPD.[21] In such diseases, AHR is intimately associated with airway caliber. Therefore, AHR is believed to have a fixed component and a variable component. The fixed component would be predominantly the result of geometric changes in airway caliber, whereas the variable component would be associated with exposure to provoking agents or with asthma treatment.[20]

It is thought that AHR is the cause of asthma symptoms and of the variability in airflow limitation.[22] Although AHR is intimately associated with current asthma, this is an imperfect association because of the heterogeneity of airway responsiveness in the general population.[20] Recent epidemiological studies have reported the presence of asymptomatic AHR (without symptoms or a history suggestive of asthma) in 6-17% of the subjects studied.[23]

In children between 8 and 12 years of age, the reported prevalence of AHR, measured by hypertonic saline challenge testing, varies widely among countries, the lowest and highest prevalence rates identified in the ISAAC phase II being 2.1% in Albania and 47.8% in India, respectively.[24] However, the ISAAC phase II did not report the proportion of individuals with asymptomatic AHR. In a study conducted in Canada[25] and involving a random sample of non-atopic asymptomatic children without allergic rhinitis (mean age, 8 years), the prevalence of hyperresponsiveness to methacholine was found to be 50%. In children, asymptomatic AHR has been associated with atopy, allergic rhinitis, and small airway caliber, as well as with a variety of respiratory symptoms.[23] Although the significance and course of asymptomatic AHR remain unclear, it is a recognized risk factor for asthma and COPD.[20,25]

Various studies have identified a positive association between childhood AHR and the risk of developing asthma later in life.[26-28] Rasmussen et al.[27] evaluated 547 children in Australia and identified asymptomatic AHR in 7.5%. Subsequent assessments of that subgroup revealed that 44%, 27%, and 10% continued to have asymptomatic AHR after 3, 6, and 9 years, respectively. The subsequent development of asthma was more common among the children with asymptomatic AHR, especially among those who continued to have asymptomatic AHR over time, than among those without. In another study, Stern et al.[28] reported that, when present at the age of 6 years, atopy and cold air-induced AHR were independent predictors of persistent asthma at the age of 22.

There has been only one study investigating the presence of airway inflammation in children with asymptomatic AHR.[29] In that study, induced sputum samples from 13 children with asymptomatic AHR were tested and the results were compared with those obtained in children with and without asthma. The authors found that children with asymptomatic AHR do not have eosinophilic airway inflammation. The same authors suggested that, in such children, AHR is caused by inflammatory mediators or by structural changes in the airways, changes for which testing for sputum cellularity would have low sensitivity.[29]

GERD, asthma, and AHR

There has long been interest in the relationship between asthma and GERD. For many years, it was thought that GERD could certainly trigger or worsen asthma. This belief originated from the observation that subjects with asthma often have GERD and that esophageal acidification increases airway resistance, as well as from the interpretation of the results of small, and not always controlled, studies showing that antireflux medication controlled asthma.[30-32] Recent studies and systematic reviews have cast doubt on this belief and have renewed discussions of the significance of the relationship between asthma and GERD. However, there are still major difficulties that preclude a conclusive interpretation of this relationship.

The major difficulties of studies investigating the relationship between asthma and reflux include the following: the poor characterization of asthma and the absence of objective measures for the diagnosis of asthma and the classification of asthma severity; imprecise definitions of GER; the lack of a gold standard method for diagnosing GER; the inability of current methods to identify not only the different types of GER (acid, slightly acid, and alkaline) but also their magnitude; and the lack of well-established criteria for determining the value of a diagnosis of asymptomatic GER.

Despite the aforementioned difficulties, there is no doubt that GERD is common in subjects with asthma, and this has been shown in numerous prevalence studies. Two recent systematic reviews indicated that the prevalence of GERD symptoms is substantially higher in adults and children with asthma than in those without.[11,33] In a review of 28 studies of adults with asthma, the mean prevalence of GERD symptoms was 59.2% in the asthma group, compared with 38.1% in the control group. The prevalence of GER diagnosed by pH monitoring was 51%.[33] In another review, which included 20 studies of children with asthma, the mean age-adjusted prevalence of GERD was 22.8% (Figure 1).[11]

Prevalence studies employing 24-h pH monitoring have also shown that asymptomatic GER is common in adults and children with asthma. In fact, it is estimated that only 5% of all subjects with GER are symptomatic.[34] It is also estimated that 10-62% of all individuals with asthma have asymptomatic GER, the broad variability being attributed to differences in asthma severity and in the methodology used for assessing GER symptoms.[34] Similar findings have been reported in studies involving children. While compiling the literature upon which to base the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition evidence-based guidelines for the management of GERD, Vandenplas et al.[1] reviewed 16 studies, involving a total of 683 children with persistent asthma and with abnormal 24-h esophageal pH monitoring results. Approximately half of those children were asymptomatic or had few GER symptoms. These results are in line with those of a study of 69 children with asthma (1-5 years of age) in which the prevalence of asymptomatic GER was reported to be 31.8%.[35]

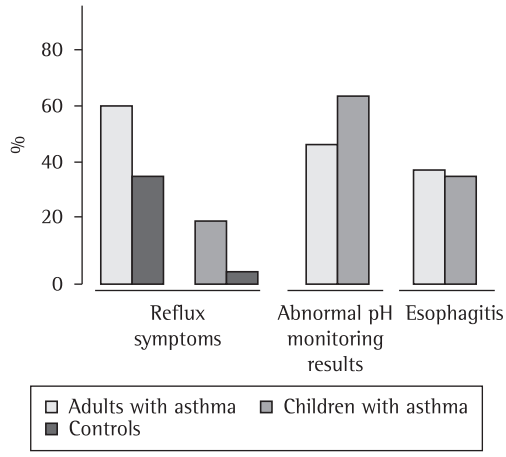

Figure 1- Prevalence of reflux symptoms, abnormal pH monitoring results, and esophagitis detected by endoscopy in children and adults with asthma.[a] [a]Data taken from Takkar et al.[11] and Havemann et al.[33]

Despite the aforementioned findings, prevalence studies have not produced sufficient evidence to determine whether the relationship between asthma and GERD is incidental or causal.[36] Even longitudinal studies have been unable to answer this question. For instance, Ruigómez et al.[37] investigated the association between asthma and GERD in two cohorts of patients treated at primary care facilities in the United Kingdom. Their results showed that, in that population, the risk of being diagnosed with GERD in the first three years of follow-up was significantly higher for the patients who were diagnosed with asthma than for those who were not so diagnosed, especially in the first year. In this aspect, the conclusion of these authors[37] was similar to that of the authors of the two aforementioned systematic reviews.[11,33] Nevertheless, patients with GERD do not seem to be at increased risk of developing asthma.[11,33,37]

The reported association between reflux and asymptomatic AHR (hyperresponsiveness without asthma symptoms) is also intriguing and raises other questions about the cause-and-effect relationship between asthma and GER. One group of authors[38] found that 36% of adult patients with GERD and without respiratory symptoms had asymptomatic AHR. The authors suggested that GER was associated with the increase in asymptomatic AHR. Those results were confirmed by another group of authors,[39] who found that the prevalence of AHR was 50% in adults with GERD, compared with 27% in the control subjects.

Finally, is difficult to demonstrate the relationship between asthma and GERD in treatment studies, because there is no standard outcome measure for the longitudinal determination of the effect that GER has on the symptoms and functional manifestations of asthma.[40] The principal reasons given to explain the lack of consistency in the results of studies of GER treatment in asthma patients include those mentioned above, plus the following: the lack of appropriate characterization of asthma patients; the lack of objective measures for the diagnosis of asthma and classification of asthma severity; the varying criteria used for diagnosing GERD; the lack of objective, or at least well-defined, criteria for quantifying improvement; and the lack of distinctions among the types of GER and the levels of GER severity. Therefore, it is not surprising that pharmacological intervention studies continue to produce conflicting results. Although some longitudinal studies of the asthma-GERD combination in children[41,42] and adults[43] have demonstrated symptomatic or functional improvement of asthma after long-term GER treatment, others have failed to show such benefits.[44-46] There is still insufficient evidence to determine whether asthma predisposes to GER or vice-versa.[36,40]

Figure 2 shows the pathophysiological mechanisms by which GER can worsen asthma and vice-versa (Figure 2), which are also still under debate. There are two mechanisms by which GER can precipitate asthma symptoms: via the vagal reflex, which is triggered by the mere presence of acid in the esophagus; and via microaspiration of gastric contents into the trachea. Conversely, it is believed that asthma itself can cause GER for two reasons: because asthma alters intrathoracic pressure during breathing, thereby triggering the vagal reflex; and because asthma patients are treated with drugs that change the LES pressure.[47-49]

Effects of GER on asthma

From a theoretical standpoint, GER affects asthma primarily through two mechanisms, which can occur in isolation or in combination: esophageal acidification; and tracheal microaspiration of refluxed material.

The theory of esophageal acidification (the reflex theory) suggests that the mere presence of gastric contents in the esophagus results in vagal stimulation, with consequent bronchospasm, given that the esophagus and the airways have the same embryonic origin and share the same autonomic innervation through the vagus.[49]

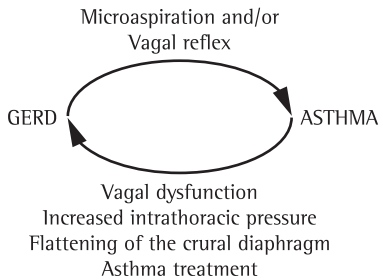

Figure 2 - Possible mechanisms to explain the high prevalence of gastroesophageal reflux and gastroesophageal reflux disease (GERD) in asthma.[a] [a]Adapted from Harding et al.[49]

Recent studies[50,51] involving the measurement of airway responsiveness after esophageal infusion of acid in asthma patients with and without GERD have not confirmed the results of previous studies,[52] which had shown increases in airway responsiveness and bronchoconstriction after such infusion. Differences in the infusion rate, in the volume of acid infused, and in how AHR was measured could explain these discrepancies. Experimental studies in animal models have also produced contradictory results, for the same reasons as those applicable to studies in humans, plus the fact that some studies used higher concentrations of hydrochloric acid than those found in non-experimental conditions.[53-56] Nevertheless, studies involving esophageal acidification in animals have shown that there is an increase in airway resistance,[54] an increase in tracheal pressure,[54] and extravasation of fluid.[55]

The theory of microaspiration holds that microaspiration of gastric contents into the trachea increases airway resistance. One group of authors[53] studied the effects of esophageal administration of hydrochloric acid in guinea pigs with and without allergic airway inflammation. Esophageal administration of hydrochloric acid, even in large volumes, did not significantly change airway resistance in either group. In contrast, intratracheal administration of small volumes of hydrochloric acid caused a substantial increase in airway resistance, even in the control group. Those authors concluded that tracheal microaspiration was the most likely mechanism to explain the effects of GER on asthma. In line with these results, a more recent study in rats[56] showed that tracheal aspiration of acids can cause the onset of acute AHR by disrupting the integrity of the airway epithelial barrier.

Effects of asthma on GER

From a pathophysiological standpoint, asthma can predispose to GER by a variety of mechanisms that can coexist: increased intrathoracic pressure; vagal dysfunction; altered CD function; and decreased LES pressure due to asthma treatment.[49] The roles that these mechanisms play in the onset of GER are still under debate. In individuals with asthma, the pressure gradient between the chest and the abdominal cavity can be increased. At the end of exhalation, the pressure gradient between the esophagus and the stomach is 4-5 mmHg.[57] Normal LES pressure (10-35 mmHg) is sufficient to endure this gradient. In asthma, in the presence of bronchoconstriction, especially in severe cases, the increased pressure gradient between the esophagus and the stomach can surpass LES pressure, resulting in GER.[58] Conversely, it is well known that subjects with asthma have increased vagal responsiveness. Therefore, asthma could also affect GER by autonomic dysregulation, which would result in a lower LES pressure gradient, favoring GER episodes.[59]Altered CD function has also been considered a mechanism by which asthma can affect GER.[12] The CD is known to contribute to the LES pressure gradient, particularly during inhalation. Hyperinflation associated with bronchoconstriction in asthma can affect the function of the CD by changing its geometry.[56]Finally, although it is believed that GER can be triggered or potentiated by the asthma treatment itself, particularly by the use of β_2-adrenergic agonists, theophylline, or high doses of oral corticosteroids, which are known to affect LES pressure, the results of studies testing the increase in GER due to these drugs are also controversial.[60]

Final considerations

In summary, because of the paucity of well-conducted studies, there is still no concrete evidence of any causal relationships among GERD, asthma, and AHR. This is partially due to methodological difficulties, which include difficulties in confirming the diagnosis and difficulties in quantifying the severity of these conditions. After these difficulties have been overcome, well-designed longitudinal studies will be able to explain the nature of the relationship between asthma and GERD, as well as the implications of therapeutic interventions for the natural history of these conditions. Therefore, this is a field of research that is open to further investigation.

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