

Gastroesophageal reflux disease and asthma: an intriguing dilemma

Background: Gastroesophageal reflux disease (GORD) is characterized by typical reflux symptoms and multiple atypical extraesophageal symptoms. Gastric asthma is a prominent extraesophageal manifestation of GORD. There is persistent debate about the pathophysiologic mechanisms triggering asthma by GOR.

Methods: We conducted a review of the literature.

Results: The pathogenic mechanism could be either a vagally transmitted reflex or an intratracheal aspiration of refluxed material. In both hypotheses, the role of inflammatory mediators has been proposed.

Conclusions: Neurogenic inflammation is a good theoretic basis for a pathogenic interpretation of the disorder. In atopic patients, food allergy has been recently proposed as a possible cause of GOR and associated respiratory symptoms, and it should be considered in the diagnostic work-up of all patients with GORD.

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A relationship between the typical gastroesophageal reflux (GOR) symptoms of heartburn, regurgitation or dysphagia, and asthma was suggested by Osler more than a century ago (1). It was more than a century later that Kennedy first suggested that silent GOR could be a "little known" cause of pulmonary symptoms, including bronchospastic conditions arising especially during the night (2). Gastroesophageal reflux disease (GORD) has other extraesophageal manifestations as well, particularly pulmonary and ear, nose, and throat conditions (3) (Table 1). However, difficulty has always arisen in deciding either whether GOR itself will initiate or exacerbate asthma, or whether asthma itself or its treatment may cause GOR to occur in a particular patient (4). In the general population, 7–43% are estimated to suffer from GORD to some extent (3, 5, 6). The prevalence of GORD among asthmatics is high, ranging from 34% to 89% in different studies (7–11), although there have been reports of a normal prevalence of increased GOR (12) in asthmatics; moreover, an increased prevalence of GORD in asthmatics does not

imply a truly causal relation in associating the two diseases.

Pathophysiology of triggering asthma by GOR

Three main mechanisms may be involved in producing GOR-induced or -aggravated asthma:

- 1) microaspiration of gastric acid into the respiratory airways after reflux (13)
- 2) a vagally mediated reflex inducing bronchoconstriction (14)
- 3) a sensitized vagal system inducing or enhancing airways hyperresponsiveness (15, 16).

Microaspiration into airways has been directly investigated in animals (17), as well as in man, by scintigraphic studies (18), with simultaneous pH-metry in the esophagus and trachea (19, 20) and with associated proximal and distal pH-metry in the esophagus (11, 16, 21). In cats, intratracheal acid infusion caused an immediate but short-lasting increase

Table 1. Clinical extraesophageal spectrum of gastroesophageal reflux disease

Diseases
Pneumonia
Asthma
Chronic bronchitis
COPD
Pulmonary fibrosis
Bronchiectasis
Pharyngitis
Laryngitis
Sinusitis
Symptoms
Sore throat
Lump throat
Chronic cough
Hoarseness

of total lung resistance that was prevented by bilateral-cervical vagotomy (17). Twenty percent of patients with GORD and respiratory disorder had microaspiration detected scintigraphically, while there were no such events in the control group (18). Simultaneous pH-metry can detect the coincidence of GOR with the occurrence of tracheal pH decrease and surgically induced improvement of both pH-metry and asthmatic complaints (19). Moreover, the strongest bronchospastic responses are associated only with GOR episodes resulting in tracheal pH lowering (20). Finally, while the prevalence of abnormal distal GOR is constantly related to respiratory symptoms (21) or to airway hyperresponsiveness (16), an abnormal proximal GOR has been variably regarded as a marker (11) or not a marker (16) of microaspiration.

In patients without respiratory diseases, the increase of intraesophageal acid instillation is directly related to the lowering of airway flow, arterial blood oxygen saturation, and heart rate (22). An esophagus-bronchial reflex that, like the esophagus-cardiac reflex, was vagally mediated since it could be abolished by atropine in the absence of respiratory symptoms (22) led to these findings. Similar findings are observed in patients with cough-variant asthma, because the reflex is abolished or reduced by inhaled ipatropium bromide, which acts on efferent tracheobronchial pathways, or by lignocaine, which, when it is locally instilled into the lower esophagus before acid challenge, blocks the afferent pathway (23).

The third mechanism by which GOR may aggravate asthma is based on changes in airway hyperresponsiveness (24). GOR or esophageal acid infusion caused a decrease in the peak expiratory flow rate (PEF) in GOR-positive asthmatics as well as in subjects with asthma only or isolated GOR. PEF deterioration did not fully recover after esophageal acid clearance in GOR-positive asthmatics, whereas an improvement was observed in subjects with either asthma or GOR only.

In GOR-positive asthmatics, there was also an increase in specific airway resistance (*SRaw*) that continued to

increase until long after acid clearance (15, 16). This effect was possibly induced by a prolonged vagal tone (24), perhaps as a part of a more complex neuromuscular (afferent or efferent) disorder with altered visceral sensitivity and shared transmitter dysfunction (6), or it may represent a late-phase reaction reflecting inflammatory release (16), and resulting in protracted bronchoconstriction in asthmatics.

New insights into the pathophysiology of GORD-associated respiratory symptoms

Recent demonstration that irritable bowel syndrome (IBS), symptoms of GOR, and symptomatic bronchial hyperresponsiveness (BHR) occur more frequently together than expected in the general population, and that the conditions are independently associated with each other (6), provides intriguing new insights into the pathophysiology of associated gastrointestinal and respiratory disorders. Moreover, White et al. have shown an excessive prevalence of BHR in IBS patients (25), and a common cause has been proposed for GOR and IBS because of their frequent coexistence (26). These associations are difficult to explain because two physiologic systems are involved (6). However, these findings taken together raise the possibility of an underlying disorder, which, although yet indefinable on the basis of epidemiologic studies, produces both respiratory and gastrointestinal complaints. Candidate mechanisms that have been proposed for this are as follows:

- 1) a generalized disorder of bronchial, gastrointestinal, and other smooth muscles (27)
- 2) a more complex neuromuscular disorder (6)
- 3) a common cause of the respiratory and gastrointestinal symptoms with the involvement of inflammatory mediators (28).

The third and particularly intriguing mechanism, however, has not been proven up to now. The so-called neurogenic inflammation (29) may support a pathogenic interpretation because one might hypothesize that stimulation of sensory receptors of the parasympathetic as well as the nonadrenergic, noncholinergic nervous system may lead to increased cholinergic bronchoconstriction, to an altered function of other smooth muscles, or to nonallergic urticaria responding to GOR therapy (30), via release of inflammatory mediators of neurogenic origin. The question, however, remains: what are the common causative agents in subjects suffering from associated GOR, IBS, and symptomatic BHR?

Food allergy as a candidate mechanism for producing symptoms in gastrointestinal and respiratory systems

Some recent studies have suggested a relationship between GOR and food allergy (FA), and provided

evidence that both disorders are frequently associated with severe reactive airway disease (RAD) in children (31). Data support the hypothesis that, in certain atopic patients with microaspiration of gastric contents into the airways, food allergens sensitize T cells in the peribronchial lymphoid tissue and induce the production of food-specific IgE antibodies that sensitize airway mast cells. Subsequent exposure to these food allergens might then induce IgE-dependent mediator release from mast cells as well as T-cell and eosinophil activation, thus contributing to airway inflammation and subsequent symptomatic BHR. To validate this hypothesis, an intense reflux is necessary. In fact, recent data from unselected asthmatics attending an allergy department do not support an etiologic relationship between GOR and asthma, but do suggest a significant association between the number of reflux episodes and BHR (32).

Moreover, delayed gastric emptying, which is one of the most important functional causes of GOR, has been recently proven to be significantly modified by intake of food allergens. In a group of children selected for FA, as demonstrated by positive skin prick tests and positive double-blind, placebo-controlled food challenge, GOR was proven by a 24-h pH probe, and the median time of gastric emptying (MTGE) was investigated by a ⁹⁹Tc technique. The basal MTGE of 70 min dropped to 27 min during food exclusion and rose to 61 min after food challenge (33).

We have conducted a study evaluating *in vivo* cutaneous mast-cell releasability, as measured by area of codeine-induced cutaneous wheal (ACCW) by skin prick testing, in a group of atopic patients with proven IgE sensitization to food allergens and with associated mild IBS and/or GOR, as assessed by clinical criteria. Preliminary results demonstrated that during food-allergen exclusion the median basal ACCW value

significantly decreased in patients with associated improvement of GOR and/or IBS, but did not decrease in those with stable symptoms and in atopic healthy controls with food allergen sensitization only. These data suggest that in a subgroup of food-sensitized patients IBS and/or GOR are dependent on FA to some extent, and that in these cases symptoms and release of mast-cell-derived inflammatory mediators are directly related (C. Astarita et al., in preparation).

Conclusions

There is a group of patients with both GOR and asthma. Some of these patients have asthma triggered or aggravated by GOR. However, the finding of both disorders in the same patient is a clinical situation commonly found within the outpatient clinic. Both a vagally mediated reflex and intratracheal microaspiration seem to play a role in the pathophysiology of GOR-associated respiratory symptoms. In both disorders, the role of inflammatory mediators has been proposed and is actually under investigation. The occurrence in the general population of IBS, GOR, and symptomatic BHR together more frequently than expected suggests the possibility of an underlying and still indefinite disorder producing both respiratory and gastrointestinal symptoms. Neurogenic inflammation seems to be a good basis for a pathogenic interpretation of the phenomenon. Food allergy has been recently proposed as a possible functional cause of GOR or of GOR and associated asthma in atopic patients. The preliminary data of our group indicate that FA may explain some cases of associated GOR and IBS, and suggest that FA should be considered in the diagnostic work-up of all patients with GORD.

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