

The potential role of gastroesophageal reflux in the pathogenesis of food-induced wheezing

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Severe reactive airways disease (RAD) in children is frequently associated with gastroesophageal reflux or food allergy. However a relationship between these two confounding factors has yet to be investigated. We postulate that, in certain patients with micro-aspiration 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 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 RAD. In the current report, we describe the case of a patient with severe asthma who had food allergy and gastroesophageal reflux whose clinical findings support this hypothesis. We also provide additional evidence for a high rate of food sensitization in patients with bronchopulmonary dysplasia (BPD), RAD and GER. We conclude that additional studies are warranted to examine the possibility that patients who have RAD and GER require an evaluation for food allergy.

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Gastroesophageal reflux (GER) has been implicated as a contributing factor to the development of respiratory disease in infants. The incidence of GER in children with chronic pulmonary disease ranges from 16%–75% (1,2–5). GER has also been implicated as a contributing factor in reactive airways disease (RAD). Shapiro & Christie report an incidence of GER in 47% of chronic steroid-dependent asthmatic children (6). Although the actual pathophysiologic sequence of events is unclear, they are thought to be either due to vagovagal reflex stimulation of the airways or to direct tracheobronchial aspiration of gastric contents leading to bronchospasm.

The term food hypersensitivity is used to indicate the circumstance in which food has been proven objectively to produce symptoms, and an immunologic mechanism can be incriminated. The incidence of true food hypersensitivity is not likely to exceed 1%–2% of young children, and the prevalence of true food allergic reactions decreases as children get older (7). *Symptoms of RAD* are consistently reproducible when children with food hypersensitivity are challenged with food allergens. In one double-blind, placebo-controlled study of children with chronic severe asthma and positive skin testing to foods, symptoms were evoked in 11/38 children,

and were characteristic of immediate type hypersensitivity with gastrointestinal and respiratory symptoms (8).

While both GER and food allergy have independently been associated with RAD, the relationship between them has yet to be investigated (6,8–10). It is possible that with micro-aspiration 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 bind to airway mast cells. Subsequent oral challenge 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 RAD. In the current paper, we report the case of a patient whose clinical findings support this hypothesis, and provide additional evidence for a high rate of food sensitization in patients with bronchopulmonary dysplasia (BPD) and GER.

Material and methods

Case report

SS is a 17-year-old Caucasian woman who was admitted to The National Jewish Center for Immunol-

ogy and Respiratory Medicine in Denver for evaluation of severe, poorly controlled asthma. She had been diagnosed with asthma at age 4 years. Increased respiratory secretions and worsening of respiratory status were associated with ingestion of milk. During a previous hospitalization at age 14, a prick skin test to milk was noted to be strongly positive (11 mm wheal with pseudopod formation), along with generalized hives and angioedema on a double-blind placebo-controlled food challenge (DBPCFC) to milk at 4 g. Although she did not develop respiratory symptoms during the DBPCFC, she developed episodes of wheezing, along with a prolonged expiratory phase following ingestion of whole milk. She underwent pH probe testing for evaluation of GER, which showed a markedly elevated Johnson and DeMeester score of 72.6 (normal < 14). A gastric emptying study revealed multiple episodes of GER up to the cervical esophagus. Delayed gastric emptying was indicated by 40% activity remaining in the stomach 3 h following administration of one mCi 99 MTC SC. She subsequently underwent reparative surgery with a Nissen fundoplication. This resulted in significant improvement in her baseline pulmonary function tests from an FEV₁ of 1.37L (55% predicted) pre-surgery, to an FEV₁ of 2.76L (110% predicted) following the fundoplication. One year following the surgery, an IgE RAST and prick skin test to milk were negative. An open food challenge showed only mild wheezing with ingestion of >8 g of milk and a mild decline in FEV₁ from 110% to 83% of predicted values.

Food sensitization in patients with BPD: study populations

We looked for evidence of IgE sensitization to foods in archived sera from 16 subjects with BPD, who also exhibited both RAD and GER. GER was defined by positive barium swallow radiographic studies and/or pH probe studies. The age range of the study group was 0–5 years. The control group comprised 15 age-matched children with BPD and associated RAD, but with no evidence of GER.

Determination of food sensitivity

Patients' sera were tested for specific IgE levels to milk, egg, soy, wheat, peanut and cod fish allergens using the Pharmacia CAP System RAST FEIA (radioallergosorbent test) system (Kabi Pharmacia Diagnostic AB, Uppsala, Sweden). This is an *in vitro* test system for the determination of circulating specific IgE antibodies. The system uses solid phase bound allergens (ImmunoCAP) that react with antibodies in the serum. Units are expressed as kUA/liter where A represents allergen-specific antibody. Values < 0.35 kUA/liter represent absent or unde-

tectable levels of allergen-specific antibody. Cross-reactivity with IgA, IgD, IgM or IgG has not been observed in this system.

Statistical analysis

Data are expressed in actual numbers for each patient population. Statistical comparisons were made using Fisher's Exact test to test the association between food sensitization by specific IgE measurements and GER/RAD in the BPD population. Differences between groups were considered significant at *p* values < 0.05.

Results

We postulated that due to her GER with episodes of microaspiration, patient SS sensitized T cells in her airways and/or peribronchial lymphoid cells. This led to RAD with subsequent consumption of milk. Although much respiratory improvement occurred following the surgical repair, the hypersensitivity to milk persisted on an oral challenge. We speculate that this is consistent with local, but not systemic, IgE production in the airways, and the homing of milk-specific memory T cells back to the lungs where the insult initially occurred. Thus, it was recommended that she continue to avoid the consumption of large quantities of milk.

Based on this index case, we wished to further examine whether there was an increased prevalence of food sensitization and RAD in infants with bronchopulmonary dysplasia (BPD), who frequently have GER. Although there are no data documenting the precise incidence of GER in this group, our clinical experience suggests that up to 50% of BPD patients have evidence of GER (Groothuis, unpublished observations).

Of the 16 BPD patients with wheezing and GER studied, eight had positive IgE antibody to at least one of the six most common food allergens, i.e. milk, egg, soy, wheat, peanut and cod (11,12). These findings are in contrast to only one of fifteen control BPD patients with no history of GER being positive for IgE to foods. A significant association between food sensitization and GER was noted, with a *p* value of 0.015. Due to our inability to retrieve this group of premature infants, we were unable to carry out double-blind, placebo-controlled food challenges in this population.

Discussion

The current report describes the case of a patient with severe asthma who had food allergy and GER. We believe that this association is not coincidental and may be explained by the novel hypothesis that,

Table 1. IgE sensitization to foods

Subject group	Number	Specific IgE to foods	Specific IgE to foods % Negative
BPD + RAD/wheezing with GER	16	8	8 (50%)
BPD + RAD/wheezing with NO GER	15	1	14 (93.33%)

p value = 0.0155 by Fisher's Exact Test

in certain patients with GER followed by micro-aspiration of food into their airways, food allergens sensitize T cells in the peribronchial lymphoid tissue and induce the local production of food-specific IgE antibodies. 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 RAD.

A weakness of our case report is the failure to demonstrate milk-induced wheezing during the course of a DBPCFC leaving open the possibility that she simply had a false positive reaction on open challenge. However, it should be noted that this patient did develop urticaria and angioedema during the course of the DBPCFC and was therefore clinically allergic to milk. Thus, we believe that it is more likely the positive reaction on open challenge simply reflected the need for ingestion of larger amounts of milk to induce wheezing, i.e. a dose-response relationship.

In this study, we have also provided evidence for a high rate of food sensitization in patients with bronchopulmonary dysplasia (BPD), RAD and GER. The prevalence of food allergies appears to be higher than expected in patients with BPD and GER, as demonstrated by the eight-fold increase in sensitization to foods in the study group as compared to the control group. We postulate that repeated exposure to food allergens may be contributing to exacerbations of RAD in this group of children. If this is true, removal of the offending food from their diet should reduce pulmonary morbidity by reducing the number and severity of RAD exacerbations. These data allow us to conclude that patients with RAD and GER have a high rate of food sensitization. Future prospective DBPCFC studies, however, are needed to determine if the foods to which they are sensitized represent clinically important food allergy.

The important role of T cells in the pathogenesis of chronic asthma has been well demonstrated by finding large numbers of Th2-like T cells expressing IL-4 and IL-5 in bronchial biopsies and bronchoalveolar lavage (BAL) fluid of asthmatics (13). Recent articles have highlighted the mechanisms by

which memory T cells home to the tissues where they are initially sensitized (14,15). The infiltration of T cells into a particular organ is determined by a recognition/adhesive interaction between T cells and venular endothelial cells within the tissue. The T cells express homing receptors (HR) which are tissue specific. These ligand and counter-ligand interactions have been well described for several tissues, including Cutaneous Lymphocyte Antigen (CLA) for the skin and L-selectin for peripheral lymph nodes (PLN).

Recent work by Abernathy-Carver and coworkers (16) has shown that memory T cells from allergic patients with milk induced eczema selectively expand their CLA+ T cell subpopulation following exposure to casein. The non-atopic normal population or patients with milk-induced colitis did not show a selective expansion of CLA expressing T cells in response to casein, although all groups showed casein-induced lymphocyte proliferation. In contrast, atopic children with milk induced eczema exhibit a selective expansion of CLA+ memory T cells in response to casein. The specificity of this observation was further shown by demonstrating that PBMC from children who had milk induced eczema did not show selective expansion of T cells expressing the PLN HR, L-selectin, compared to the control groups.

These data suggest that heterogeneity in the regulation of HR expression on antigen specific T cells may play a role in tissue directed allergic responses. Indeed, since memory T cells express HR that preferentially return them to extralymphoid tissues associated with the secondary lymphoid tissues in which they were first activated, the site of antigen exposure is likely to play a role in determining HR expression and hence, the tissue pattern of atopic symptoms. Renz & coworkers (17, 18) examined the effects of airway sensitization by nebulization of ovalbumin in a murine model. With local sensitization, BALB/c mice responded with an early rise in IgE, as well as increased bronchial reactivity to ovalbumin, and an expansion of ovalbumin specific T cells in the peribronchial, but not splenic, lymph nodes.

We therefore postulate that aspiration of food results in sensitization of airways, stimulating memory/effector Th2-like cells (expressing mRNA for IL4 and IL5 but not IFN- γ) that have the capacity of homing back to the airways on subsequent ingestion of the offending foods. This could thereby contribute to food-induced airway inflammation and RAD. Further studies are obviously needed to confirm this hypothesis. These would require DBPCFC of BPD patients with positive food skin tests, or asthmatics with a history of GER and aspiration. Furthermore, it will be of interest to determine whether T cells

from patients with food-induced asthma express homing receptors that differ from those found in patients with food-induced eczema.

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Abbreviations used in this paper

AD:	Atopic Dermatitis
BAL:	Bronchoalveolar lavage
BPD:	Bronchopulmonary dysplasia
CLA:	Cutaneous Lymphocyte-associated Antigen
DBPCFC:	Double-blind placebo-controlled food challenge
GER:	Gastroesophageal Reflux
HR:	Homing Receptor
IgE:	Immunoglobulin E
PBMC:	Peripheral blood mononuclear cells
PFTs:	Pulmonary Function Tests
PLN:	Peripheral lymph nodes
RAD:	Reactive Airways Disease
RAST:	Radioallergosorbent Testing
TH2:	T Helper type 2 cell

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