

Original Article

The effect of a cow's milk-free diet on asthma control in children: a quasi-experimental study

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Abstract: Background: Food allergy which usually develops in the first year of life is a risk factor for persistent asthma in young children. Cow's milk has been demonstrated to be the most commonly identified food allergen in children. Considering the central role of non-IgE-mediated food allergies in the development of hidden gastro-esophageal reflux and consequently asthma, we evaluated the effect of eliminating food allergens to better control asthma. Method: A total of eighty infants and children up to the age of 12 referred to the Asthma Clinic of Mofid Children Hospital for a period of one year were enrolled in this study. In those patients whose asthma remained uncontrolled (Childhood Asthma Control Test ≤ 19) despite a 2-week period of treatment, we advocated a 2-week diet based on eliminating cow's milk in conjunction with asthma conventional therapy. For breast-fed infants, mothers were requested to eliminate these products from their daily intake regimens and for formula-fed infants, the elemental based formula was started. Results: Three of the patients were lost in follow-up and six of them were excluded from the study because of non-compliance. The Asthma Control Test score which was less than or equal to 19 in the entire study population, increased to 20 or more after we began a diet based on the elimination of cow's milk in all but 13 participants. Conclusion: To conclude, the results were promising, demonstrating that a cow's milk protein elimination diet is a prudent approach in the management of patients with recalcitrant asthma, and can be considered as the missing link in asthma treatment.

Keywords: Asthma, childhood, food allergens, atopy, children, cow's milk, diet

Introduction

Food allergy has become an increasingly severe health problem in recent decades. Considering the emergence of the "second wave" of allergy, and the increase in the prevalence of food allergies, the role of food allergy in the development of asthma becomes more important [1]. Food allergy and allergen sensitization (such as cow's milk and egg) which usually develops in the first year of life is a risk factor for bronchial hyper-responsiveness and persistent asthma later in young children [2, 3]. Several studies have demonstrated cow's milk as the most commonly identified food allergen in children [4]. Asthma is the most common chronic dis-

ease of childhood and may be life-threatening, despite the development of inhaled corticosteroids which are expected to achieve better control of the disease and improve the quality of life in these patients. Atopic march denotes the typical progression of allergic disease to another with common genetic and environmental predisposing factors [5].

Food allergies fall into two main categories: IgE-mediated and non-IgE mediated reactions, with the latter being less understood. The majority of previous studies have evaluated the interrelationship of asthma and food allergies with IgE-mediated mechanisms. The availability of current laboratory tests to investigate these types

of reactions and the immediate onset of clinical manifestations following the ingestion of the culprit food makes the topic more tangible for researchers. However, some experts hold firmly on to the belief that this interplay is predominantly due to the common atopic background in both conditions (IgE mediated food allergy and asthma). A potential causal relationship is rarely considered responsible for this liaison in this setting [3], with a strong tendency to exclude chronic or isolated respiratory symptoms as common presentations of food allergy [1].

Generally, neither non-IgE-mediated food allergies nor their extra-gastrointestinal complications have been studied in comprehensive trials due to the lack of specific clinical manifestations and lab tests, as well as the commonly delayed onset of signs and symptoms. Two of the most common presenting features of non-IgE-mediated food allergies include gastroesophageal reflux and Eosinophilic Esophagitis [6] which may manifest as silent reflux and make the diagnosis rather difficult, and this can become a comorbidity of hyperreactive airway disease and asthma [7]. Given these facts, we emphasized a causal relationship in the development of asthma following gastroesophageal reflux disorder because of the close anatomic proximity of the respiratory and gastrointestinal organs and also the presence of a common pathophysiologic allergic mechanism in both disorders (e.g. the presence of eosinophils and related cytokines in non-IgE-mediated food allergies such as eosinophilic gastroenteritis and asthma). Referring to the work of Roberts et al., determination of food allergens and their removal from children's diets may subsequently improve the patients' level of asthma control, particularly in children with severe refractory asthma [8].

Given the central role of non-IgE-mediated food allergies in the development of hidden gastroesophageal reflux, which in turn may trigger or exacerbate asthma, we proposed that asthma control may improve by eliminating food allergens.

Considering a causal relationship between the development of childhood asthma with allergy as the underlying pathophysiologic mechanism, and cow's milk as the most common food allergen in children's diets, we decided to eliminate it from the diet of those patients unresponsive

to conventional asthma therapy to improve any hidden gastroesophageal reflux [9] with subsequent probable effect on the development of asthma. This study aims to provide supporting evidence to demonstrate an interrelationship between asthma and food allergy as two prevalent allergic disorders and also to suggest a potential treatment plan in asthmatic patients unresponsive to conventional asthma therapies. Therefore, the management of asthma which is a common and chronic threat to health may become more understood and easier to treat.

Methods

Patients

Infants and children up to 12 years old referred to the Asthma and Allergy Clinic of Mofid Children Hospital for a period of one year were enrolled in this quasi-experimental study.

The inclusion criteria consisted of infants and children up to 12 years old with uncontrolled asthma after 2 weeks of treatment according to Global Initiative for Asthma Management and Prevention (GINA) [10], provided that other differential diagnoses including chronic rhinosinusitis, cystic fibrosis, bronchopulmonary dysplasia, tuberculosis, foreign body aspiration, congenital malformation, primary ciliary dyskinesia, primary immunodeficiency, congenital heart disease and IgE-mediated types of food allergy were ruled out and the patients were sufficiently trained to use the inhaler correctly. Exclusion criteria were defined as patients being unwilling to continue their participation in the study. The sampling method for the determination of the subjects to be investigated was based on complete census enumeration to prevent selection bias. After confirming the diagnosis of asthma by an allergist expert in this field according to the Global Initiative of Asthma guideline [10], those asthmatic patients without a favorable response to the standard conventional controller therapy according to the GINA step 2 (consisting of the low dose inhaled corticosteroid) for a period of two weeks were enrolled to the study.

Initial assessment

A Childhood Asthma Control Test (C-ACT) [11] questionnaire was completed for every patient to gather information regarding their age, sex,

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Table 1. Demographic information of the patients participating in the study

Parameters	Number of Patients
Age	
Less than 2 years	3 (4%)
2-4 years	24 (30%)
5-10 years	51 (63%)
More than 10 years	2 (3%)
Sex	
male	34 (42%)
female	46 (58%)
Adherence to elimination diet	
Yes	71 (89%)
No	9 (11%)
Serum IgE concentration	
Above threshold	30 (83%)
Below threshold	50 (62%)

and asthma control, with patients whose combined score was 19 or less deemed as having uncontrolled asthma [12].

Most of the patients with uncontrolled asthma were also evaluated with a skin prick test and Immunoblotting (Mediwiss Analytic, Moers, Germany) for common food allergens.

Intervention

In those patients whose asthma remained uncontrolled despite a 2-week period of treatment (C-ACT score <19), extra-gastrointestinal (respiratory) presentations of a probable silent gastroesophageal reflux disease (GERD) was considered as the cause, with cow's milk protein as the most common inciting food allergen, inducing allergic GERD. Therefore, we advocated a 2-week diet based on eliminating cow's milk and related dairy products, in conjunction with standard asthma therapy. For breast-fed infants, mothers were requested to eliminate these products from their daily intake regimens and for formula-fed infants, the elemental based formula was started.

Of note, considering the non-IgE-mediated immunological mechanism involved in the gastroesophageal reflux (GERD) related food allergy, the diet was determined irrespective of the food-specific IgE results.

Post-intervention assessment

The patients' responses to the cow's milk eliminated diet were re-evaluated by the Childhood Asthma Control Test (C-ACT) [11, 13].

ACT scores rising to 20 or more after 2 weeks of a diet in which cow's milk was eliminated, was considered as a favorable outcome in these patients.

Statistical analysis

Statistical analysis was performed using SPSS 16 software (version 16). Descriptive statistics were used to summarize data based on age groups, sex, adherence to the elimination diet, serum IgE concentration, and food allergens. Chi-square test was used to compare skin prick test results before and after an elimination diet. The qualitative variables were presented as a frequency and percentage. *P* values of less than 0.05 were considered a significant threshold in the analysis.

Ethics

This study was carried out in accordance with the recommendations of the Ethics Committee of Shahid Beheshti University of Medical Sciences with written informed consent taken from all subjects' caregivers. The protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with the reference number of IR.SBMU.MSP.REC.1397.668.

Results

Demographic data

A total of eighty patients with uncontrolled asthma and an Asthma Control Test score of 19 or less were enrolled in the study. **Table 1** summarizes the demographic characteristics of the participants. Most of the patients were females aged 5 to 10 years old. Three of the patients were lost in follow-up and six of them were excluded from the study because of non-compliance (**Figure 1**), mainly due to the difficulties imposed on the family. The period of elimination lasted for only two weeks, which seems to be safe. Total serum IgE concentration in nearly two-thirds of the patients was below the threshold. Given the fact that measuring total serum IgE is not an important tool in the diagnosis of allergic diseases, it seems that its level is even less important in non-IgE mediated allergies.

Of note, since the clinical history of the patients enrolled in the study did not indicate an IgE reaction to food, specific IgE to common foods (including skin prick test or Immunoblot test)

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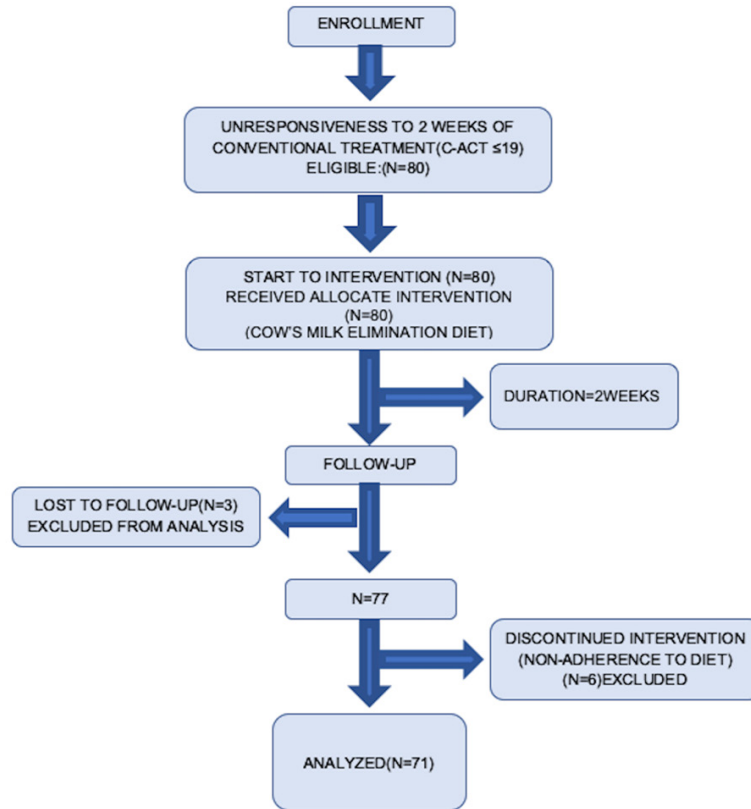


Figure 1. Recruitment and participant flow through the study based on the consort diagram. Eighty patients with uncontrolled asthma were identified. Three of them were lost in follow-up and six discontinued the study.

Table 2. Specific IgE results

Food Allergen	Total number of patients with specific IgE
Milk	9
Egg white	5
Egg yolk	2
Hazelnut	4
Almond	4
Walnut	2
Peanut	2
Potato	3
Soya	2
Tomato	3
Wheat	4
Tuna Fish	2
Celery	5
Sesame	2
Apple	3

was not determined for all the 41 patients (51%) [These tests were not performed on thir-

ty-nine patients (49%)] Milk and egg allergens were among the most common food allergens. Therefore, avoidance of cow's milk protein was implicated for all patients irrespective of specific IgE results.

Table 2 demonstrates specific IgE results in common foods.

Investigations before and after intervention

Table 3 is a comparison of Asthma Control Test scores in patients with positive and negative results in either the skin prick test or the in-vitro test who eliminated cow's milk from their diet. ACT scores of more than 19 patients with a positive prick test were increased dramatically (nearly to 7 folds) after the intervention. These results were also seen in patients with negative skin prick test.

After intervention results

The Asthma Control Test score of nineteen or less in all the study population increased to over nineteen after the elimination of cow's milk from their diet in all but thirteen participants. Nine of these thirteen patients showed no improvement. Four of them reported some initial improvements but later did not show significant resolution of symptoms during the progression of the study (**Table 4**). Although this group of patients was strongly suspected of not adhering to the diet completely, they were considered to demonstrate treatment failure.

Discussion

Considering the well-known close link between asthma and food allergy in atopic patients in terms of the "atopic march" [13, 14], in this study the beneficial effect of cow's milk avoidance was evaluated in patients with uncontrolled asthma who had not responded to standard treatment based on GINA guideline [10]. This was associated with a significant improvement in asthma control in 82% of participants.

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Table 3. C-ACT score in patients with positive and negative results in either skin prick test or in vitro who underwent an elimination diet

Positive skin prick test patients	Before elimination diet number (%)	After elimination diet number (%)
ACT score >19	0 (0%)	17 (100%)
ACT score ≤19	20 (100%)	3 (15%)
Chi square test results		<i>P</i> value = 0.02
Negative Skin prick test	Before elimination diet number (%)	After elimination diet number (%)
ACT score >19	0 (0%)	13 (72%)
ACT score ≤19	18 (100%)	5 (28%)
Chi square test results		<i>P</i> value = 0.04

Table 4. A summary of patients' responses to an elimination diet based on ACT score

ACT score	Before elimination diet number (%)	After elimination diet number (%)
>19	0 (0%)	58 (82%)
≤19	71 (100%)	13 (18%)

Before initiating the elimination diet in these patients, the C-ACT was 19 or less, which increased after completion of the study in all except 18% of the patients, who still had a C-ACT score less than or equal to 19. Even in these patients, we attribute treatment failure mainly to non-adherence to the elimination diet.

The natural history of atopic manifestations characterized by a typical sequence of allergic events that may appear early in life and persist over years has been defined as an atopic march. Therefore, a patient with food allergy in infancy may later develop asthma at school-age. However, a causal link between food allergy and asthma has rarely been discussed in previous studies. It is also noteworthy that most studies have addressed a link between IgE-mediated food allergies and asthma rather than non-IgE mediated food allergies [15]. Although any association between immediate food allergy and isolated respiratory symptoms has been considered rare, there is a strong tendency that foods may trigger respiratory symptoms in 4 to 8% of asthmatic children [16-18]. This suggests that sensitization to egg, cow's milk [19], peanut, soy, fish, shellfish, and tree nuts could be risk factors for the development of asthma later in life [15]. Also, infants with

documented IgE-mediated milk allergy at 7 months of age confirmed by an oral food challenge, have shown an increased risk of bronchial hyper-responsiveness at 8 years of age [20, 21], and cow's milk sensitization has been shown to be associated with an increased airway hyper-reactivity and a lower expiratory flow rate even before the clinical onset of respiratory features [22].

Despite the suggested association between IgE-mediated food allergies, particularly occurring

with cow's milk and egg proteins sensitization in up to 45% of these patients leading to the development of increased bronchial hyper-responsiveness and asthma, there has been not such a report indicating a causal relationship between non-IgE-mediated food allergies and later the development of asthma. In other words, this association is justified only in the context of IgE-mediated reactions and atopic conditions [13, 14]. However, some studies have assessed the significance of non-IgE-mediated food allergies in the subsequent development of increased airway hyper-responsiveness in a subset of food-allergic children despite the absence of acute symptoms after eating the culprit allergens [23].

Bock studied 410 children with food-induced respiratory reactions, of whom 279 (68%) reported food-induced asthma [24]. Vega et al. also demonstrated that asthma may severely deteriorate after ingestion of small amounts of food to which the patient is allergic [25]. Some authors highlight the specific role of food allergy in all patients with severe refractory asthma [2]. Friedlander et al. emphasized that having asthma and a food allergy together may increase the risk of morbidities [24].

Agerkhedkar et al. also reported their observations regarding better asthma control in 70% (significant improvement in 58 out of 71) of their patients by specific elimination diets, lending support to our results in the present study [26].

Brown et al. reported a group of asthmatic patients with severe uncontrolled asthma, who were managed with a "few foods diet", which

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was introduced to their usual regimen for 2 or 3 weeks. This dietary modification caused subjective and objective improvements in their asthma control, peak flow rates, and quality of life, even though the major sensitizing allergen was house dust mite in these patients [6]. In another report published by Virdee et al. a substantial relief of asthma symptoms was reported after initiating an elimination diet for two patients [12]. The efficacy of elimination diets in asthmatic children has also been analyzed by Yusoff et al. who reported significant improvements in asthma control and peak-expiratory flow rates in children following an elimination diet compared to those who followed a free diet [27]. Of note, sensitivity to food allergens in infants is more common than aeroallergen sensitization [5].

Atopic march involves IgE-mediated food allergies, while gastrointestinal manifestations of non-IgE-mediated food allergies, which mostly have a delayed manifestation and present as GERD, Eosinophilic Gastrointestinal Disorders (EGID), Food Protein-Induced Enterocolitis Syndrome (FPIES), Food protein-induced enteropathy, and Food protein-induced allergic proctocolitis, are not considered as a part of the atopic march, but it seems that they are somehow reciprocally related [28].

Among these gastrointestinal food allergies, the upper GI allergic diseases including Eosinophilic esophagitis and GERD mostly affect the respiratory tract. GERD is estimated to accompany asthma in 77% of patients [29].

Given the above, we present the case for a complete rethinking of how non-IgE mediated gastrointestinal food allergy and asthma may be interrelated by suggesting the following reasons; firstly, the proximity of the gastrointestinal tract with the respiratory system; secondly, the common pattern of immunological mechanisms involving the same inflammatory cells and cytokines; and finally, the direct effect of food allergens on both organs.

To the best of our knowledge, this is the first study presenting the case for the probable effect of non-IgE-mediated food reactions and their causal impact on later developing asthma. Therefore, the present study is an evaluation of a novel hypothesis regarding the elimination of cow's milk protein as the most prevalent and

best-known food allergen in order to better control asthma. The children in this study were evaluated as a whole population and were not categorized into different age groups because the purpose of our study was to demonstrate the role of cow's milk allergy as a risk factor for uncontrolled asthma in all age groups. A significant number of our patients in this study were under the age of six years which makes spirometry an infeasible investigation tool because of the lack of essential cooperation needed to perform this evaluation. Therefore, in order to have a standardized interpretation of the patients' responses to the elimination diet, we used the Childhood Asthma Control Test (C-ACT). Cow's milk protein removal from the patients' diets resulted in a significant rise in the ACT scores to above 19. We explained airway hyperreactivity in non-immediate food allergies, as respiratory consequences of gastrointestinal tract involvement, such as occurs in gastroesophageal reflux, which also has been previously suggested by Haveman et al. in 2007 [7].

Our results indicate that children with signs and symptoms of airway inflammation expressed as childhood asthma may suffer from a hidden food allergy that may implicate its role by the following mechanism: an underlying hidden allergic gastroesophageal reflux as a comorbidity of asthma, through which the food may enter the airway with subsequent stimulation of airway mast cells together with vagal stimulation inducing a lower airway reaction. Considering GERD as a highly prevalent condition, signs and symptoms of airway reactivity in these patients are due to extra-gastroesophageal (respiratory) manifestations of GERD which is entirely a clinical diagnosis requiring no more paraclinical and laboratory investigations to be performed in the absence of others.

According to 2018 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN/ESPAGAN) [30] and ESPGHAN [9] guidelines, a challenge-proven food allergy is the underlying cause in the majority of children with GERD. Therefore, 2 to 4 weeks of an extensive hydrolysate protein-based or amino-acid based formula is recommended as the non-pharmacological treatment of severe GERD,

which demonstrates an accepted interrelationship between cow's milk allergy and GERD [31, 32]. NICE also suggested that GERD may be a clinical presentation of non-IgE-mediated food allergy [33].

Overproduction of specific cytokines and the recruitment of Th2 cells as well as eosinophils which is typical for eosinophilic digestive disease (EDD) as a chronic and non-IgE mediated food allergy, shares many features with bronchial asthma [1, 13], which may demonstrate that these two maladies are regarded as two clinical expressions of one disease in two separate anatomical sites [34] with similar pathogenesis, pathology and treatment policies.

Other possible underlying mechanisms are; increased intestinal permeability after re-exposure to an allergen to which the patient has previously been sensitized, and finally, absorption of allergenic proteins from the skin or intestine which may induce the release of inflammatory mediators acting indirectly on the lower respiratory tract with a greater risk of inducing asthma [8]. These sequential events may eventually lead to bronchial hyper-responsiveness [35].

Measurement of total serum IgE in patients showing delayed forms of food allergies is not a valid test. Also, specific serum IgE, and skin prick tests do not appear helpful. However, performing these tests on 41 (51%) patients demonstrated cow's milk protein and egg white as the two most common food allergens, respectively.

Therefore, in all those patients who lack an appropriate response to the conventional asthma treatment, a trial of an elimination diet seems rational. Given the fact that the study period was short, compromising growth and development was not a concern.

However, some limitations should be noted: Firstly, the lack of a control group of patients with asthma being managed with an identical standard treatment but without dietary restrictions; secondly, the short duration of the study; thirdly, the small sample size of patients participating in the study; and lastly, lung function measurements which were relatively difficult to perform in our patients who were mostly under the age of six, and therefore, were replaced by C-ACT scores.

To conclude, the results were surprisingly promising, demonstrating that a cow's milk protein (as the most common food allergen) elimination diet is a prudent approach in the management of patients with recalcitrant asthma, and can be considered as the missing link in asthma treatment. We also suggest further studies with more appropriate sizes, needed to validate the use of this intervention in order to better control asthma.

Disclosure of conflict of interest

None.

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