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Cow Milk Sensitization in Allergic Children from Mumbai, India

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Abstract

Background: Cow milk allergy is common in younger children and, fortunately, many of these children outgrow it. But, during the time that these children have milk allergy, it is hard for them and their family. Aims and objectives: The prevalence of cow's milk allergy varies from region to region and there is, to date, no data on cow milk sensitization in the children from Mumbai. Hence, we carried out a retrospective study of the records of the children who attended our clinic for allergic symptoms. Study design and setting: Retrospective study of allergic children at our clinic. Subjects and methods: The detailed history and examination findings of these children were noted. Family history of atopy and the anthropometric measurements of these children were jotted down. All these children had blood allergen test done on them for 29 different allergens including cow's milk. Results: Out of 185 patients studied, 63 children were found to have milk sensitization. They were significantly younger in age compared to those who were not allergic to milk. The gender ratio, family history of allergy, anthropometric measurements, the number of systems involved with allergy, and types of systemic allergies were similar in the two categories of children. The total blood IgE levels did not differ in the two groups. However, children with cow milk sensitization also had higher sensitization to cheese, casein, soya, coconut, wheat, egg white, chicken meat, tuna, fungi, some weeds, corn, carrot, and banana. Conclusion: One-third of the allergic children attending our clinic had cow milk sensitization. They were younger in age and had co-existent other food allergies and some aero-allergies.

Keywords: Cow's milk allergy, IGE-mediated allergy, Food allergy, Prevalence.

INTRODUCTION

IgE-mediated cow milk protein allergy is prevalent in the world, mostly in infants and younger children [1]. It is a common type of food allergy and can lead to allergic symptoms involving the skin, eyes, nose, and lungs [2]. Anaphylactic reactions are also known and it could adversely affect the growth of the child [3]. This allergy is different from milk intolerance or hypersensitivity in which gut symptoms predominate and IgE immune system is not involved [4, 5]. The estimates of true cow milk protein allergy in general population have ranged from 0.5 to 3% in the developed countries [1, 2, 6, 7].

But when only allergic children from a specialized center are studied, this percentage is bound to be higher [8]. In a university skin department, cow milk sensitization was found to be present in 16% of the children suffering from moderate atopic dermatitis. And in children who had no other allergy except atopic dermatitis, it was higher at 37% [9, 10]. The proportion of children found to have cow milk allergy symptoms also depends on the study design and the type of test used to diagnose cow milk allergy [10]. Double blind, placebo-controlled oral milk challenge is the gold standard for diagnosis but it carries its own risks and is also time consuming, labor-intensive, and resource-intensive [11, 12]. Elimination of milk can be tried to see for ebbing of symptoms [11]. Skin-prick tests and serum-specific IgE levels (in vitro immunoassay) are relatively less accurate and tend to overestimate prevalence. But nonetheless, they are fairly reliable and safer for epidemiological studies [13, 14].

Allergy to various food and airborne substances is not uncommon in Mumbai and India but the data on it is limited. Cow's milk allergy is also encountered in smaller children but the epidemiological data on it are scarce. Therefore, we analyzed the records of children less than 18 years who attended our clinic

for allergic symptoms to estimate the proportion of children with sensitization to cow's milk and other dairy products.

SUBJECTS AND METHODS

For this retrospective study, we analyzed the medical records of allergic children less than 18 years of age who attended our clinic. Blood specific allergy tests were performed on them as part of their allergy workup. Each child's age, gender, detailed history and physical findings were noted. Family history of allergic tendency was also looked into. The height and weight of each child was jotted down. Their nutritional status was determined and as per their weight, these children were grouped into malnourished, normal, or overweight (CDC charts of weight for age) [15]. Height retardation, if any, was also assessed [16].

The studied children's total blood IgE values were recorded and the specific levels of IgE in their blood to food and aeroallergens were noted down. These tests were carried out by means of Phadiatop using immunoCAP technology of Pharmacia, Uppsala, Sweden [17]. Each of these children had specific IgE determination done on their blood to 29 different allergens (food allergens and air-borne allergens) including to cow's milk protein.

Children with specific IgE to cow's milk or other allergens of value 0.35 kUA/L and above were considered sensitized to that particular allergen [18]. These children were grouped into cow milk-sensitized and those who did not demonstrate any sensitivity to the protein. The demographic and anthropometric details of the two groups were compared for statistical difference, if any. Family history of allergy, organs of allergic involvement, mean total blood IgE levels, and IgE levels to other allergens were evaluated in the two categories of patients and the differences were tested for statistical significance.

Statistical Analysis

All data were subjected to statistical analysis. Mean of numerical values are expressed as mean ± SEM. Numerical data were assessed for statistically significant differences by application of Student's t test. Categorical data in the two groups were compared by means of Chi-square test [19]. P value of <0.05 was considered statistically significant.

RESULTS

There were 185 children in our study group. The medical records and investigations revealed that 122 children had no cow's milk sensitization while 63 (34.05%) children were found to have cow milk protein-specific IgE levels of 0.35 and above kUA/L. The mean age of the children who were milk non-sensitized was 5.09 ± 0.29 years (range of 8 months to 15 years) and it was 3.54 ± 0.28 years (range of 5 months to 9 years) in milk-sensitized group with a p value of 0.00071. Thus, children with milk allergy were found to be significantly younger in age compared to those who did not have such an allergy. There were 63 males and 59 females in the non-milk sensitized category (group 1) and 37 males and 26 females in those children who demonstrated milk sensitization (group 2). This difference was not found to be significant (p value of 0.35) (Table 1).

Family history of allergy was seen in 50% of children in group 1 and 57.14% of group 2; the difference being insignificant statistically. The body weights of the children in the two groups were comparable (Table 1). As regards the different types of allergies in the two groups (eyes, skin, nasal, and lungs), there was no statistical difference in cases of allergic conjunctivitis, allergic dermatitis, allergic rhinitis, and bronchial asthma/cough variant asthma (Table 1). In the non-milk sensitized group, one child had failure to thrive as the presenting symptom. Children with 1, 2, 3 or 4 systems involved with allergy were similar in the two groups. But 3 system involvements were significantly lesser in the milk-sensitized children (p=0.02). The mean system involvement was found to be 2.77 ± 0.09 in the group with no cow milk allergen sensitization and 2.86±0.60 in cow milk IgE-positive children (p=0.60).

The total blood IgE levels in the two groups of children did not differ significantly (p=0.99). Similarly, the percentage of children with higher for age total IgE levels was similar in the two categories (p=0.28). Children with cow's milk sensitization has significantly higher overall allergen score compared to those without such sensitization (11.56±1.01 vs 7.03±0.66 respectively, p=0.0001). The food allergen score in children with milk allergy was also higher than that in the non-milk sensitized group (7.02±0.56 vs 2.93±0.33 respectively, p<0.001). But the aeroallergen score in the two categories of children was similar (4.54±0.54 vs 4.11±0.38 respectively, p=0.51) (Table 2).

Children with cow milk protein allergen sensitization also had higher sensitivity to cheese, casein, soya, coconut, wheat, egg white, chicken meat, and tuna allergens (Table 2). Amongst the aeroallergens, children with milk allergy also had predominant allergy to fungi such as *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Candida albicans*, and weeds such as rye and velvet (Table 3). It was found also that children with milk sensitization had concomitant significantly higher corn, carrot, and banana sensitization. Allergen testing for parrot feathers, rabbit epithelium, mushroom, beef, cauliflower, spinach, pear, cashew, lemon, malt, melon, and onion was done in a relatively smaller sample size of children. None of these tested allergens had positive results. Also, sample size of children with specific-IgE levels done for tomato, green pea, or grape was small. Hence data of these allergens could not be compared for statistical significance in the two groups.

DISCUSSION

Cow milk allergy is common in infants and toddlers and majority of them outgrow it. The percentage of children affected with cow milk protein allergy varies in the world countries and regions. It is common in Europe, the UK, and the developed world. But significant number of cases are also reported from the developing world. There is to date no data on cow milk allergy from Mumbai, India. We performed this retrospective analysis of allergic children attending our clinic and found that around one-third (34.05%) of these allergic children had sensitization to cow

milk protein. These children, as expected, were younger in age and had allergy to multiple other food and aeroallergens.

Table 1: Demographic and clinical characteristics of the study group

Parameters	Cow milk IgE-negative group	Cow milk-sensitized group	p value
No. of allergic children	122	63	---
Mean age (years ± SEM)	5.09 ± 0.29	3.54 ± 0.28	0.00071
Females	59	26	0.35
Confirmed family history of allergy [n (%)]	61/122 (50)	36/63 (57.14)	0.35
Nutritional status: Normal, low, high for age [n (%)]	81 (66.39), 15 (12.29), 26 (21.31)	45 (71.43), 6 (9.52), 12 (19.05)	>0.05
Allergic conjunctivitis [n(%)]	51/122 (41.8)	32/63 (50.79)	>0.05
Allergic dermatitis [n(%)]	89/122 (72.95)	50/63 (79.36)	>0.05
Allergic rhinitis [n(%)]	89/122 (72.95)	45/63 (71.43)	>0.05
Bronchial asthma/cough variant asthma [n(%)]	68/122 (55.73)	40/63 (63.49)	>0.05
Number of systems involved with allergy [0, 1, 2, 3, 4] [n(%)]	1 (0.82), 17 (13.93), 23 (18.85), 49 (40.16), 32 (26.22)	0 (0), 11 (17.46), 12 (19.04), 15 (23.81), 25 (39.68)	For 0, 1, 2 p value was above 0.05, for 3, it was 0.02 and for 4 it was 0.06
Mean system involvement score (mean ±SEM)	2.77 ± 0.09	2.86±0.60	0.60

Table 2: Total IgE and food-specific IgE data of the two groups

Parameters	Cow milk IgE-negative group	Cow milk-sensitized group	p value
Total IgE IU/ml [mean ± SEM]	589.97 ± 101.66	591.54 ± 120.89	>0.05
Percentage of children with higher for age total IgE levels [n(%)]	44/121 (36.36)	26/58 (44.83)	>0.05
Mean total allergen score [mean ± SEM]	7.03±0.66	11.56±1.01	0.00017
Mean food allergen score [mean ± SEM]	2.93±0.33	7.02±0.56	<0.001
Mean aeroallergen score [mean ± SEM]	4.11±0.38	4.54±0.54	0.051
Cheese [n (%)]	0/89 (0)	17/45 (37.78)	<0.001
Casein [n (%)]	0/24 (0)	6/21 (28.57)	0.005
Soybean [n (%)]	5/117 (4.27)	13/59 (22.03)	0.0002
Almond [n (%)]	2/82 (2.44)	4/38 (10.53)	>0.05
Coconut [n (%)]	9/112 (8.04)	21/55 (38.18)	<0.001
Wheat [n (%)]	15/116 (12.93)	37/58 (63.79)	<0.001
Egg white [n (%)]	23/120 (19.17)	44/62 (70.97)	<0.001
Chicken meat [n (%)]	3/114 (2.63)	7/57 (12.28)	<0.001
Cod [n (%)]	2/52 (3.85)	2/22 (9.09)	>0.05
Shrimp [n (%)]	29/119 (24.37)	13/59 (22.03)	>0.05
Tuna [n (%)]	8/121 (6.61)	12/61 (19.67)	0.007
Salmon [n (%)]	3/59 (5.08)	4/26 (15.38)	>0.05
Peanut [n (%)]	2/26 (7.69)	3/11 (27.27)	>0.05
Corn [n (%)]	5/64 (7.81)	8/36 (22.22)	0.039
Potato [n (%)]	1/15 (6.67)	1/7 (14.29)	>0.05
Apple [n (%)]	4/64 (6.25)	6/34 (17.65)	0.07
Carrot [n (%)]	2/71 (2.82)	6/38 (15.79)	0.01
Cabbage [n (%)]	2/58 (3.45)	4/27 (14.81)	0.056
Banana [n (%)]	3/40 (7.5)	10/21 (47.62)	0.00027
Baker's yeast [n (%)]	2/30 (6.67)	1/15 (6.67)	1
Cocoa [n (%)]	0/27 (0)	1/10 (10)	>0.05
Mango [n (%)]	1/16 (6.25)	3/9 (33.33)	>0.05
Strawberry [n (%)]	1/8 (12.5)	1/2 (50)	>0.05
Orange [n (%)]	1/14 (7.14)	0/8 (0)	>0.05
Rice [n (%)]	0/6 (0)	2/7 (28.57)	>0.05

Table 3: Aeroallergens specific IgE in the two groups of allergic children

Parameters	Cow milk specific IgE-negative group	Cow milk specific IgE-positive group	p value
Cat epithelium [n (%)]	3/45 (6.67)	4/20 (20)	>0.05
Dog dander [n (%)]	4/39 (10.26)	6/18 (33.33)	0.03
Pigeon droppings [n (%)]	16/78 (20.51)	8/42 (19.05)	>0.05
Dermatophagoides pteronyssinus [n (%)]	67/122 (54.92)	28/62 (45.16)	>0.05
Dermatophagoides farina [n (%)]	65/122 (53.28)	29/61 (47.54)	>0.05
Cockroach [n (%)]	39/122 (31.97)	19/62 (30.65)	>0.05
House dust greer [n (%)]	51/117 (43.59)	25/58 (43.10)	>0.05
Cladosporium herbarum [n (%)]	0/48 (0)	2/23 (8.70)	>0.05
Aspergillus fumigatus [n (%)]	5/116 (4.31)	8/56 (14.29)	0.02
Candida albicans [n (%)]	9/116 (7.76)	14/56 (25)	0.0018
Sweet vernal [n (%)]	8/120 (6.67)	9/59 (15.25)	>0.05
Rye [n (%)]	12/99 (12.12)	23/56 (41.07)	<0.001
Velvet [n (%)]	8/118 (6.78)	10/59 (16.95)	0.03
Mugwort [n (%)]	11/115 (9.57)	10/59 (16.95)	>0.05
Bermuda grass [n (%)]	17/122 (13.93)	13/59 (22.03)	>0.05
Timothy grass [n (%)]	12/121 (9.92)	9/59 (15.25)	>0.05
Alder [n (%)]	2/43 (4.65)	2/18 (11.11)	>0.05
Birch [n (%)]	2/43 (4.65)	2/18 (11.11)	>0.05

We analyzed the allergen sensitization data of allergic children attending our clinic. This is the first of its kind study from Mumbai, India. Mumbai has a cosmopolitan population and being a congested metro city, it has a number of cases of respiratory illnesses with underlying allergic tendency. One hundred and eighty five children with complaints suggestive of allergy formed our study group. Nearly one-third of these had documented sensitization to cow's milk protein. We evaluated the specific IgE to cow's milk protein and other 28 allergens in these children. The gold standard for diagnosis of cow's milk allergy is double-blind, placebo-controlled oral challenge with milk. But this test needs special setups and is fraught with risk of anaphylaxis. It is also time-consuming [20]. The other alternatives are skin prick tests and determination of specific IgE to cow's milk and other allergens in the serum of these children (immunoassay test) [21, 22]. We resorted to the latter test at our clinic. It is a reliable and fairly accurate test with good sensitivity and specificity [23-25]. Usually, allergen-specific IgE levels with values of 0.35 and above kAU/L are considered as positive. But values in the range of 0.35 and < 0.70 kAU/L might be equivocal and of doubtful significance [18, 26]. For this study, we took values of ≥ 0.35 kAU/L to imply sensitization to that particular allergen [27]. This might detect higher percentage of children sensitized to this protein than the actual true clinical cow's milk allergy. This study provides an estimate of the proportion of allergic children with documented cow's milk sensitization in Mumbai. It can be used to compare the data with those available from international studies. The study can also form a basis for future studies for temporal comparison of values. In this study, the children had cow's milk allergen specific-IgE determination. The remaining 28 aero and food allergens tested in them were different in these children. It would be worthwhile to carry out a further study where the allergic children are tested for the same types of 29 allergens. Various reviews have confirmed that cow milk allergy resolves over the years in an individual [2, 28, 29]. The Consortium for Food Allergy Research (CoFAR) has also demonstrated that 53% of the children (3 to 15 months) with atopic dermatitis and positive tests for cow milk allergy developed tolerance at a mean age of 53 months [30]. In another study, 57% had shown tolerance development at 1 year follow-up [31]. We have not done long-term follow-up studies on these children to assess the natural history of cow milk allergy in them.

An estimated 34.05% of allergic children in our study had specific IgE in their blood to cow milk protein ≥ 0.35 kAU/L. In 2007, Rona *et al* carried out a meta-analysis of study articles on food allergy. They found that self-reporting studies revealed a prevalence of 1.2 to 17% and skin prick studies showed a prevalence of 0.2 to 2.5%. On the other hand, studies that utilized serum specific IgE estimation showed a percentage of 2 to 9% and food challenge studies showed this figure to be from 0 to 3% [32]. This prevalence is expected to be higher in allergic children in specialized clinics. Nwaru ***et al's*** systematic review of European studies on cow milk allergy revealed a point prevalence of 2.3% by self-reporting, 0.3% by skin prick test, 4.7% by specific IgE estimation and 0.6% by oral food challenge [33]. Similar to our study, this study also revealed that younger children were more affected. This fact was also confirmed by other studies including that of Liu *et al* [34]. Studies have also shown that male children have a 2-fold higher risk of allergy to cow milk protein but this undergoes a change in adults where women form 80% of the affected people [6]. In our study, we did not find any gender predominance in affliction. Cow allergy also leads to growth impairments [6]. None of the children in our study had any height retardation but 9.52% of children in cow milk-sensitized group had less weight for age. But this was not

significantly different from that in the cow milk-non-sensitized group (12.29%).

Cow milk has also been associated with severe reactions including anaphylaxis [35, 36]. Fortunately, we did not have any child with anaphylactic reaction to cow's milk in our study. In line with other studies, the children in our study also had multiple other food allergies [6]. Cow milk allergy can affect different systems of the body especially skin and respiratory. We found that 79.36% of the cow milk-hypersensitized children had atopic dermatitis, 71.43% had allergic rhinitis, 63.49% had lung allergy, and only 50.79% had allergic conjunctivitis. Thus, predominantly more of the children with cow milk sensitization had atopic dermatitis compared to eye allergy (p=0.0007).

A South Korean study showed that around 18.3% of cow milk allergic children also had co-existent soya milk allergy [37]. We report similar findings with 22.03% of our cow milk protein-positive children having associated soya protein hypersensitivity. Our study also showed that maximum number of children with cow milk allergy had sensitivity to egg white (70.97%). And the least allergy in this group was to baker's yeast (6.67%). None of the children with cow milk allergy had sensitization to oranges but the number of children tested for orange specific-IgE was less. Hence interpretation on this aspect would be difficult.

Amongst the aeroallergens, dust mite allergy was most common (47.54% had co-existent *Dermatophagoides farina* allergy and 45.16% had sensitization to *Dermatophagoides pteronyssinus*) in the cow's milk-sensitized group. Fewer children in this category had sensitization to *Cladosporium herbarum* (8.70%).

CONCLUSION

Thus, our study shows that in a clinic setup, cow milk sensitization may be as high as 34.03%. The children are in the younger age group and have multiple other food and airborne allergies; the common being that to egg white and house dust mite. This study could form a basis for geographical comparison and to know the temporal trends in prevalence of cow milk allergy in allergic children of Mumbai.

Conflict of Interest

There is no conflict of interest in this study.

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