The Allergic Diseases Commonly Associated with Cow Milk Protein Sensitization: A Retrospective Study (Jeddah – Saudi Arabia)

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Abstract

Background: Cow milk allergy (CMA) is the clinical presentation of cow milk protein (CMP) sensitization. CMA is a prevalent morbidity worldwide especially in children.

Objective: To identify common allergic diseases associated with CMP sensitization.

Methods: This was a retrospective chart review conducted. Data from 83 patients were included in the study. Patients included in this study were those diagnosed with CMA at the allergy clinics of Laluna, a private medical center in Jeddah, Saudi Arabia. All in vitro tests of 83 CMA cases were performed retrospectively in 2018 utilizing a RIDA® system panel, which contains 30 common food sensitizers unique to Saudi Arabia. CMPs and other food sensitizations were determined based on the clinical allergic disease diagnoses taken from a local database in Laluna clinic.

Results: SIgE food allergy tests for 83 patients were evaluated. Gender distribution was 51 females (61.5%) and 32 males (38.5%). The most common CMP sensitizations, order were alpha lactalbumin, 59 (71%); casein, 48 (58%); milk, 38 (46%); beta lactoglobulin, 29 (35%); and assorted cheeses mix 13 (16%). Allergic diseases associated with CMP sensitization were atopic dermatitis, 40 (48%); allergic rhinosinusitis, 36 (43%); asthma, 26 (31%); allergic conjunctivitis, 12 (14%); urticaria and angioedema, 10 (12%). As for the most common associated food sensitizers, in the category of nuts, cashews and peanuts caused the most severe reaction. In the category of grains, wheat was also implicated in severe reactions, and egg in the protein category.

The severity of CMP sensitizations are as follows, in descending order: alpha lactalbumin (94.3); casein (58.54); milk (51.19); beta lactoglobulin (29.11) and assorted cheeses mix.

Conclusion: Alpha lactalbumin and casein, followed by milk are the most common sensitizers and also cause the most severe allergic reactions. Atopic dermatitis and allergic rhinosinusitis, followed by asthma are the most common clinical allergic diseases associated with CMP sensitization. Cashew, peanut, wheat and egg were the most common food sensitizers associated with CMP sensitization. It should be noted that the most severe food sensitizer of all associated with CMP sensitization is cashew.

Key words: allergic diseases,
Cow Milk Protein Sensitization

Introduction

Cow's milk (CM) is primarily composed of water (88%). The other components are carbohydrates (5%), fat (3%), proteins (3%), and trace minerals and vitamins. Proteins represent a small percentage of CM, but they are the chief allergenic component, and are implicated in triggering allergic reactions. Casein is the main cow milk protein (CMP) and represents 80% of all proteins. It is composed of similar proteins which can be divided by pH. Whey is the second most common CMP, and consists primarily of alpha-lactalbumin and beta-lactoglobulin, which can only be separated by heat. These are the main CMPs responsible for inducing clinical allergies caused by intake of cow's milk. Other trace protein enzymes have little to no role in the causation of allergic disease.

The prevalence of cow's milk allergy (CMA) is increasing worldwide, particularly in infants' first year of life. In developed countries, 3% of the population struggles with CMA. Many cases of CMA can improve over time with the complete avoidance of cow milk.

The specific immunoglobulin E (sIgEs) to CMPs are considered a significant prognostic tool for evaluation of improvement, so they should be measured regularly. It was found that the earlier the increase in sIgEs relative to CMPs occurs, the more likely the CMA disease will persist and the allergy morbidities will continue (1).

Adverse reactions to CMPs can be divided into immune and non-immune responses. Immediate reactions are type 1 hypersensitivity reactions, dependent on sIgE responses against CMPs, and identified as CMAs. Delayed reactions are non-immune, immunoglobulin G (IgG) mediated, and are called CM intolerance (CMI).

Both forms of reactions primarily manifest in infancy. Symptoms typically involve skin, gut and lungs. Diagnosis of sIgE immune reactions is made by history, followed by allergy testing to detect sIgEs against CMPs. In vivo skin prick test (SPT) and in vitro sIgE blood tests (RAST) are used to determine that. However, definitive diagnosis is made by complete elimination of CM and, the CM oral challenge (2).

Parental presence (or other primary caretaker) during the consultation is crucial for providing relevant history for accurate diagnosis. During CM elimination, the patient is monitored for symptomatic improvement. Improvement of symptoms is highly suggestive, and definitive diagnosis is then made by CM oral challenge and carefully observing for recurrence of the symptoms (3).

Feeding formulas used for the prevention of CMAs are different from those used for CMA treatment. CMA prevention should be prioritized in high risk infants with a positive family history of allergies in one or both of their parents. Mothers' milk is the first line of prevention followed by partially hydrolyzed formulas (pHFs). Treatment of established CMA cases begins by eliminating CM and other dairy products as dietary mainstays, and replacing them with alternatives, such as extensively hydrolyzed formulas (eHFs). However, in severe cases of CMA, amino acid formulas (AFs) may be used (4).

Methods

This study was a retrospective chart review conducted throughout the year 2018. Data from 83 patients were included in the study. Patients included in this study were those diagnosed with CMAs at the allergy clinics of Laluna, a private medical center in Jeddah, Saudi Arabia. Data collected included the in vitro sIgE results of common food allergy triggers. Additionally, the diagnoses of allergic diseases for each sIgE result were also extracted. Data were recorded in Microsoft Excel spreadsheets.

The food sIgEs list panel utilized in this study was the RIDA® system, composed of 30 single and separate allergens. These food allergens were chosen carefully to represent those most common in Saudi Arabia. Allergens in this panel are separate from each other, and not mixed, like in the (Unicap® system). Severity of sensitization for each allergen was scored from 1 to 6. A score of zero was considered a negative sensitization. Roughly, mild sensitization is scored 1 and 2, moderate is 3 and 4, while severe is 5 and 6. Food allergen families in the (RIDA® system) are CMPs, nuts, fruits, vegetables, egg, seafood, grains, meat and plants (like cacao and mustard).

CMPs included in the (RIDA® system) panel are milk, casein, lactalbumin, lactoglobulin and cheese mix. The RIDA® system is considered to be a practical and inexpensive way to diagnose CMAs. However it may sometimes give false positive or negative results. Therefore, clinical correlation is needed. It is worth noting that the most accurate sIgE system is (Unicap®) which has a reputation for being exact and precise. Accordingly, this system carries a greater financial burden for patients, especially those with no health insurance.

Results

SIgE food allergy tests for 83 patients were evaluated. Of these, 52 were adults (62.6%). There were also 31 pediatric patients (37.4%). Gender distribution was 51 females (61.5%), and 32 males (38.5%). Patients ranged in age from 1 month to 75 years (mean 27 years and median 30 years).

Allergic diseases associated with positive sensitization to CMPs are demonstrated in Table 1. By ranking, they are atopic dermatitis, 40 (48%); allergic rhinosinusitis, 36 (43%); asthma, 26 (31%); allergic conjunctivitis, 12 (14%); and urticaria and angioedema, 10 (12%). (Table 1).

Frequency of CMP sensitization differed from one type of protein to another. By ranking, the frequency of positive sensitization to CMPs are alpha lactalbumin, 59 (71%); Casein, 48 (58%); milk, 38 (46%); beta lactoglobulin, 29 (35%); and cheese mix, 13 (16%) (Table 2).

The sum of severity classes of CMP sensitization varied from one protein to another. The order of the sum of CMP severity classes appear in the following succession: alpha lactalbumin, (94.3); casein, (58.54); milk, (51.19); beta lactoglobulin, (29.11), and cheese mix, (17.8) (Table-3).

Results of positive sensitization to other allergenic foods associated with CMP sensitization were recorded opposite in (Table 4). Cashew, egg, wheat and peanut were the most commonly occurring sensitizations (Table 4).

Severity classes of food sensitizations other than CMPs differed from one to another. Cashew, egg white, wheat and egg yolk were the most severe sensitizers (Table 5).

Table 1: Clinical allergic diseases associated with CMP sensitization

	No. of positive results	Percentage/83 cases
Atopic dermatitis	40	48
Allergic rhinosinusitis	36	43
Asthma	26	31
Allergic conjunctivitis	12	14
Urticaria, Angioedema	10	12

Table 2: Frequency of positive sensitization to each CMP

	No. of positive sensitizations	Percentage/83 cases
Alpha lactalbumin	59	71
Casein	48	58
Milk	38	46
Beta lactoglobulin	29	35
Cheese mix	13	16

Table 3: The sum of severity classes to CMPs

	Sum of severity classes / 83 cases
Alpha lactalbumin	94.3
Casein	58.54
Milk	51.19
Beta lactoglobulin	29.11
Cheese mix	17.8

Table 4: Other food sensitizations associated with CMP sensitization

	Number of positive sensitizations /83 cases	%
Cashew nut	40	48
Egg white	37	44.5
Egg yolk	29	35
Wheat flour	29	35
Peanut	23	28
Carrot	23	28
Honey	21	25
Shrimp	18	22
Sesame seed	17	20
Orange	16	19
Kiwi	16	19
Banana	16	19
Pecan nut	15	18
Strawberry	14	17
Codfish	13	16
Mango	12	14
Soy bean	12	14
Walnut	12	14
Cocoa	12	14
Date	11	13
Onion	10	12
Mussel	9	11
Tomato	8	10

Table 5: Other severity classes of food sensitizations associated with CMP sensitization

	Sum of severity classes / total 83 cases
Cashew nut	97
Egg white	62.88
Wheat flour	51.61
Egg yolk	44.44
Honey	36.5
Peanut	31.45
Shrimp	29.2
Carrot	28
Pecan nut	24.5
Sesame seed	22
Codfish	19.6
Cocoa	18
Kiwi	17
Orange	14.9
Walnut	14.5
Banana	11.43
Mango	10.55
Date	10.5
Strawberry	10.38
Soy bean	8
Onion	7
Mussel	7
Tomato	5.5

Summary of Results

- AD and ARS were the most common allergic diseases associated with CMP sensitization, followed by asthma. Conversely, AC, urticaria and angioedema were rarely associated. This means that any patient complaining of AD, ARS or asthma should have allergy testing to exclude CMP sensitization.
- Alpha lactalbumin and casein were the most common causes of CMP sensitization, whereas milk and beta lactoglobulin CMPs were less so. Cheese was the least common cause of CMP sensitization.
- The most severe CMP classes were alpha lactalbumin, followed by casein and milk, whereas both beta lactoglobulin and cheese CMPs were the least severe.
- Other food sensitizations associated with CMP sensitization were cashew, egg (white, yolk), wheat, peanut, carrot and honey. The least commonly associated foods in this spectrum were shrimp, sesame, orange, kiwi, banana, pecan, strawberry, codfish, mango, soybean, walnut, cocoa, date, onion, mussel and tomato.
- The most severe food sensitization class was cashew, followed by egg white, wheat and egg yolk. However, the least severe food sensitizers were honey, peanut, shrimp, and carrot.

Discussion

The morbidity of AD is higher in children consuming CMPs than in those who do not. CMPs can be found not just in milk but in other dairy products such as yoghurt, cheese and butter. However, the most common sources of CMPs for children are chocolate, Nutella® hazelnut spread, Kinder® chocolate candy and ice cream. Total IgE and eosinophil counts are higher in children with AD who consume CM or other dairy products on a regular basis than in children who do not (5).

An unusual and surprising finding in this study was that ARS is the second most common allergic disease associated with CMP sensitization, after AD. This is unusual because it differs from previously reported findings. This raises the possibility of geographical variations between Saudi Arabia and, for example, the United Kingdom. New cases of ARS should be referred for sIgE measurements in vitro or in vivo, especially for children (6).

British Society of Allergy and Clinical Immunology (BSACI) guidelines show that the most common systems affected by CMA are the skin and gastrointestinal tract, while the respiratory system is less commonly affected. The cardiovascular system is rarely affected (7).

Asthma and wheezy chest in children are diseases that can be triggered by CMPs. Additionally, CMPs can induce poor control in asthmatic children. Identification of sIgEs to CMPs in children with poor asthmatic control is indicated. Moreover, allergy testing should be done at each clinic visit. Evidence has shown that serial in vitro CMP sIgE measurements for each visit are a viable way to track asthma improvement (8).

Worldwide, alpha lactalbumin and casein are the most common CMPs capable of inducing elevations of sIgE levels. Alpha lactalbumin is most prevalent in Southeast Asia, while casein prevails in the West. Beta lactoglobulin CMPs have almost the same prevalence as casein. sIgE levels are higher in children with atopic dermatitis, indicating that children with eczema should undergo in vivo or in vitro sIgE allergy testing for CMPs (9).

The cashew nut is a main cause of anaphylaxis, especially in children. A recent pediatric food challenge study on cashew sensitized children showed that most of them react to the lowest dose of cashew. A third of the children sampled reacted with anaphylaxis. Gastrointestinal and skin symptoms predominate. Parents of children with cashew allergies should remain alert, because the onset of a reaction can be sudden and serious (10).

The risk of introducing artificial milk early tends to be underestimated. This practice increases the possibility of CMAs in those who are at risk of developing future clinical allergies. For that reason, new mothers should prioritize breast feeding and avoid supplementary CM formulas. Similarly, hospital nurseries and new parents should avoid giving newborns artificial milk formulas (11).

In children, CMAs can present with gastrointestinal symptoms such as diarrhea and hematochezia which are unresponsive to treatment. In infants less than six months of age with gastrointestinal symptoms unresponsive to treatment, workup should include allergy testing. Pediatricians, family physicians, general practitioners and nurses should be very knowledgeable about this presentation of CMAs and act accordingly. (12).

Ruling out CMAs in infants as early as possible is crucial in avoiding future morbidities. Medical professionals should have an established protocol for any suspected cases of CMA that includes a detailed history from parents or primary caretakers, and in vitro or in vivo sIgE tests for CMPs. Very few cases require the CM oral challenge. While such a protocol will not rule out all CMA cases, it can adequately identify most of them. The cost of allergy testing, should not be allowed to become an obstacle because the lifelong morbidities of CMA diseases are more expensive (13).

Investigations for CMA diagnoses used in allergy clinics are in vitro (sIgE) levels or in vivo (SPT). SPT is more sensitive and specific. Nonetheless, results may sometimes be unreliable which is why it is advisable to use them as confirmatory tests for each other when one of them comes back negative. The most reliable methods for CMA diagnosis, considered the gold standard, are an oral open CMP challenge, and a detailed history from patients (14).

Although more research is needed, early evidence indicates that a milk patch test (MPT) may have a valid role in CMA diagnosis. A MPT can diagnose type IV hypersensitivity, but not an immediate type I hypersensitivity. However, some studies have found that MPT can diagnose early CMA before other tests can detect it (SPT, sIgEs and histamine release test). Nonetheless, the best way to diagnose CMA is still CM elimination for 1 month followed by observation after gradual CM re-introduction (15).

Infant breastfeeding (BF) is considered a treatment for CMA. For best results, feeding should be limited to BF only without any artificial formulas. Research has shown that BF alone induces a state of hyposensitization which raises the levels of protective cytokines like interleukin 10 (IL-10) and decreases the level of total IgE. Adding pharmacologic drugs and immunologic sublingual immunotherapy to BF creates an effective triad of CMA treatment (16).

Another treatment for CMA is immunotherapy. Immunotherapy employs subcutaneous injections, which have the side effect of sudden anaphylaxis. Sublingual shots have less severe reactions because they are initiated with a very low dose, and can be built up slowly and gradually. Results of immunotherapy to CMA are impressive, with a good level of improvement. However much the improvement, though, CMA patients should always carry auto injector adrenalin pens with them (17).

It is common for parents of children with CMAs to frequently ask when CM can be re-introduced. Patients' tolerance to CM must be measured to answer such a question. There is evidence that a continuous, gradual decrease in sIgE levels to CMPs on regular clinic visits can give an impression that the child has developed a good level of tolerance. However, the main test before re-introducing CM is the milk challenge (18).

The question of whether CMA morbidities can appear in infants of exclusively BF mothers is an interesting one. Seemingly, the only way that can happen is through the passage of CMPs into breast milk. Initial research shows that may happen in 0.5% of infants, but it remains a controversial issue. To confirm that, one would have to identify CMPs in breast milk, and perform allergy tests such as in vivo, in vitro and milk challenge tests. The ideal way to prove this theory is to do a CM elimination from mothers, then monitor the infants. Mothers should not take this step as a preventive measure (19).

Conlusion

Atopic dermatitis and allergic rhinosinusitis, followed by asthma are the most common clinical allergic diseases associated with CMP sensitization. Alpha lactalbumin and casein, followed by milk CMPs are the most common sensitizers and the most severe classes. Cashew, egg, wheat and peanut are the most common food sensitizers associated with CMP sensitization. The most severe class food sensitizer associated with CMP sensitization is cashew.

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