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ORIGINAL RESEARCH

Children with Delayed-Type Cow's Milk Protein Allergy May Be at a Significant Risk of Developing Immediate Allergic Reactions Upon Re-introduction

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Background: Cow's Milk Protein Allergy (CMPA) is the most common food allergy in children. The reaction is classified into IgE-mediated immediate reaction and delayed-onset, according to the underlying immune mechanism, and hence, the timing of the symptoms. Case reports suggest that children, with delayed CMPA reactions on elimination diet, may develop severe immediate reactions on reintroduction.

Aim: The objective of this study was to evaluate the incidence and the risk factors of developing immediate reactions to milk and dairy products in children with CMPA whose initial presentations were of delayed type.

Methods: A retrospective chart review of children, aged 0–12 years, presented with delayed type CMPA reactions to the allergy-clinical immunology clinics, was performed. The diagnosis was made clinically, and with appropriate allergy tests when indicated.

Results: Sixty children were included. Males:female ratio was 1.7:1. Family history of atopy was in 72%, and 57% had personal history of atopy. Sixty percent were not breast fed. The most common concomitant food allergy was egg. The most common initial presentation was diarrhea without protein loss or bleeding followed by exacerbation of atopic dermatitis upon exposure to dairy products. Immediate reactions developed in 21.6% upon re-exposure. There were significant associations with concomitant food allergy (OR 56.6 (3.15–1016.1) P<0.0001), especially eggs (OR 12.85 (3.09–53.5) P<0.01).

Conclusion: Children with CMPA, who present with delayed-type allergic reactions, may be at a significant risk of developing immediate reactions upon reintroduction. Evaluation of possible IgE-mediated allergic reactions before reintroduction may be advisable.

Keywords: atopy, cow's milk protein allergy, food allergy, proctocolitis, eczema, allergy

Introduction

The prevalence of food allergy has increased in recent decades, affecting around 6% of children.[1–4] Cow's milk protein allergy (CMPA) is the most common cause of food allergy in children, with an estimated prevalence of 1.8–7.5%.[4,5] CMPA may be defined as a reproducible adverse reaction of an immunological nature induced by cow's milk protein.[5] Both IgE and non-IgE mediated CMPA exist.[1,4,5] Typically, IgE-mediated reactions are immediate with a wide spectrum of clinical severity ranging from urticaria to anaphylaxis. Delayed-type reactions are non-IgE-mediated or mixed clinical signs and symptoms involving the gastrointestinal tract (GI), respiratory system or the skin appearing 6–48 hours after ingestion.[5,8] The GI symptoms of non-IgE mediated CMPA are variable and affect the entire GI tract. These include well-defined syndromes such as food protein-induced enterocolitis, proctocolitis and enteropathy or non-specific GI symptoms, including vomiting, diarrhea, constipation, colic, gastroesophageal reflux disease (GERD).[4,5,8]

The natural history of CMPA is favorable, as most children, 80–90%, outgrow their allergy during childhood.[5,9] With regard to proctocolitis, most infants tolerate cow's milk by the age of 1 year.[7,8] In general,

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non-IgE mediated reactions tend to resolve more rapidly than IgE-mediated reactions. Risk factors for persistence of CMPA are concomitant food allergy, especially eggs and the presence of comorbidities, such as asthma and allergic rhinitis. Reactivity to baked milk is associated with less favorable outcome.[5] It is crucial that physicians can recognize children at risk of developing immediate reactions upon re-exposure, as this affects the treatment plan in terms of injectable epinephrin prescription, emergency action plan distribution, avoidance strategies and whether milk protein re-introduction can be offered at home.

Few reports suggest that children, with non-IgE mediated CMPA on elimination diets, may develop immediate reactions on accidental exposure or reintroduction, which may be as severe as anaphylaxis and death.[6,10–12] Given such risk, these patients may benefit from epinephrin autoinjectors prescription and supervised milk reintroduction.

The aim of this study is to systematically study the incidence and the risk factors of developing immediate reaction to cow's milk protein in children with CMPA whose initial presentations were of delayed type.

Methods

A retrospective chart review of children, aged 0–12 years, with CMPA reactions presented to the pediatric allergy clinics, between Jan. 2017-Jan. 2020, was performed. We included children diagnosed with delayed type CMPA in the pediatric allergy clinics in Amiri and Mubarak AL Kabir Hospitals, which serve as secondary/tertiary refer centers. Demographic and clinical data were collected.

Children whose presentation was of type I hypersensitivity reactions or unclear or their records were incomplete, or those who lost follow-up, were excluded.

Delayed type CMPA reactions were defined as non-IgE or mixed-type reactions that occur 6–48 hours after ingestion.[6] These include both gastrointestinal or cutaneous symptoms that improve with exclusion and reappear with reintroduction of cow's milk. We included patients presented with food protein-induced allergic proctocolitis, diarrhea or non-specific GI symptoms such as emesis, GERD, colic, irritability with feeds, constipation, or refusal to feed, and patients who presented with atopic dermatitis.

In the current study, food protein-induced allergic proctocolitis (FPIAP) was defined as a benign transient condition, characterized by blood-streaked stools in otherwise healthy, thriving infants.[7,8] The diagnosis was made clinically based on the response to elimination diet and the resolution of symptoms, with the exclusion of other causes of rectal bleeding in infants. Proctocolitis and FPIAP will be used interchangeably in this manuscript.

The diagnosis of food-induced atopic dermatitis (AD) was made clinically by allergists, with appropriate supportive allergy tests,[6] when indicated. These children had poorly controlled, severe atopic dermatitis despite optimal topical corticosteroid treatment, and had subsequent significant clinical improvement in dermatitis after CMP elimination diet as assessed by the treating allergists.

Breast fed infants' mothers were instructed to strictly avoid milk and dairy products. Children on formulas were prescribed extensively hydrolyzed formulas or amino acids-based formulas (AA formulas), while few were switched to soy or other non-dairy formulas. Dietary advice on weaning food introduction were given to caregivers, with the instruction to avoid milk and dairy products. No consistent instructions about baked dairy products were unified, as this study is retrospective.

Information on the symptoms of allergy on milk reintroduction after 12 months of age was obtained. Acquisition of tolerance was defined by the absence of allergic symptoms after reintroduction of cow's milk. For most children, the reintroduction was done at home.

Data was analyzed using IBM SPSS Statistics version 28, analysis was performed using Chi-squared test and the Fisher's exact test. Alternate Welch's *t*-test was used to calculate Mean Age. Odds Ratio (OR) was calculated with 95% Confidence Interval (CI). P values of 0.05 or less were considered as statistically significant.

Ethical approval was obtained from the Health Sciences Center Committee for the Protection of Human Subjects in Research, College of Medicine, Kuwait University (Reference number: VDR/EC/3330), and from The Ethics Committee, Ministry of Health, Kuwait (number: 2018/926). Informed consent was obtained from the study participants' parents/legal guardians at the time of follow-up visits during the planning of the study. The study complies with the declaration of Helsinki.

Results

A total of 60 patients were included. Male: female ratio was 1.7:1. The mean age at presentation was 4.3 ± 4.1 months. The majority of the patients (72%) had family history of atopy such as eczema, allergic rhinitis or asthma. Around 57% had personal history of atopy, atopic conditions other than that for which they were included in the study. Sixty percent were not breast-fed. Half the sample was on AA-based formulas. The most common concomitant food allergy was egg allergy; however, 53% did not have other food allergies. Table 1 outlines the demographic and clinical characteristics of the sample.

The most common initial presentation was diarrhea without protein loss or bleeding in 38.2% of the sample, followed by atopic dermatitis in 35%. Twenty percent presented with FPIAP while 6.7% presented with non-specific GI symptoms, such as colic, GERD and constipation.

Immediate reactions developed in 13 children (21.6%), whose initial reactions were of delayed type, upon cow's milk re-introduction.

On further analysis assessing the risk factors for the development of immediate reactions, there was significant associations with concomitant food allergy (OR 56.6 (3.15–1016.1) P<0.0001), especially eggs (OR 12.85 (3.09–53.5) P<0.01), as shown in Table 2

Table 1 Demographic and Clinical Data of the Patients

Variables	Total n=60 (%)
Gender	
Male	38 (63.3)
Female	22 (36.7)
Mean age at presentation (months)	4.3 ± 4.1
Family history of Atopy	
No	17 (28.3)
Yes	43 (71.7)
Personal history of Atopy	
No	26 (43.3)
Yes	34 (56.7)
Breast feeding	
No	36 (60)
Yes	24 (40)
Type of Formula	
Extensively Hydrolyzed formula	20 (33.3)
Amino Acid-based formula	31 (51.7)
Extensively Hydrolyzed formula	20 (33.3)
Other formulas*	9 (15)
Baked products tolerance	
No	28 (46.7)
Yes	32 (53.3)
Strictly avoiding dairy products	
No	26 (43.3)
Yes	34 (56.7)
Concomitant food allergy	
No	32 (53.3)
Yes	28 (46.7)
Type of food allergy	
No	32 (53.3)
Eggs	16 (26.7)
Others**	12 (20.0)

Notes: *Other formulas include soy and non-dairy formulas. **Others include tree nut, peanut, wheat, soy, sesame and others.

Table 2 Risk Factors for the Development of Immediate Reactions to Dairy Products in Patients with Delayed-Type Reactions at Presentation

Variables	Patients With Immediate Reaction N=13 (21.7%)	Patients Without Immediate Reaction N=47 (78.3%)	OR (95% CI)	P value
Gender				
Male	7(53.8)	29(61.7)	0.72(0.20–2.50)	0.75
Female	6(46.2)	18(38.3)	1.38(0.39–4.76)	0.75
Mean age (months)	3.8 ± 2.2	4.43 ±4.4	-	0.48
Family history of atopy				
No	10(76.9)	33(70.2)		
Yes	3(23.1)	14(29.8)	0.70(0.16–2.96)	0.74
Personal history of atopy				
No	3(23.1)	23(48.9)		
Yes	10(76.9)	24(51.1)	3.19(0.77–13.1)	0.12
Breast feeding				
No	8(61.5)	28(59.6)		
Yes	5(38.5)	19(40.4)	0.92(0.26–3.24)	1.00
Type of formula				
Extensively-Hydrolyzed formula	3(23.1)	17(36.2)	0.52(0.12–2.19)	0.51
Amino Acid-based formula	9(69.2)	22(46.8)	2.55(0.68–9.47)	0.21
Others	1(7.7)	8(17.0)	0.40(0.04–3.58)	0.66
Baked products tolerance				
No	7(53.8)	21(44.7)		
Yes	6(46.2)	26(55.3)	0.69(0.20–2.37)	0.75
Strictly avoiding dairy products				
No	6(46.2)	20(42.6)		
Yes	7(53.8)	27(57.4)	0.86(0.25–2.97)	1.00
Concomitant food allergy				
No	0(0)	32(68.1)		
Yes	13(100)	15(31.9)	56.6(3.15–1016.1)	<0.0001
Types of concomitant food allergy				
Eggs	9(69.2)	7(14.9)	12.85(3.09–53.5)	<0.01
PN	1(7.7)	2(4.3)	1.87(0.15–22.48)	0.52
TN	2(15.4)	2(4.3)	4.09(0.51–32.36	0.20
Soy	1(7.7)	0(0)	11.4(0.43–29.41)	0.21
Wheat	0 (0)	4(8.5)	0.35(0.02–7.08)	0.56

Interestingly, the ability to tolerate baked dairy product, type of formula or the extent of dietary restriction did not correlate with the risk of the development of immediate reactions later in life. In addition, there were no significant associations with other demographic or clinical parameters studied in this report (Table 2).

Discussion

Our study sought to determine the incidence of the development of immediate reactions in patients with non-IgE mediated CMPA, who presented with FPIAP, diarrhea, non-specific GI symptoms or AD, and to identify the risk factors for the development of type 1 food allergy upon reintroduction or accidental exposure to the culprit protein. We identified that 21.6% of children, who never had immediate reactions to cow's milk and avoided milk protein because of food-triggered AD or delayed GI symptoms, developed type 1 allergic reactions upon reintroduction. The reactions were mostly of cutaneous manifestations; however, the details of these reactions were not available for all patients; therefore, we elected not to include these details in our analysis.

The recommended treatment for non-IgE mediated CMPA is to avoid cow's milk protein with suitable alternative formulas, or maternal dietary restriction for breast-fed infants, with reassessment at around 12 months of age and onward for tolerance.[5] The reintroduction of milk in these cases is usually done at home. Therefore, the ability to identify infants at risk of severe immediate reactions upon re-exposure is critical. This affects the treatment plan in terms of parent counselling, injectable epinephrin prescription, emergency action plan distribution, avoidance strategies and whether milk protein re-introduction can be offered at home.

Multiple studies, mostly on food-triggered AD, have demonstrated the increased risk of developing immediate severe allergic reactions after prolonged periods of elimination diet, especially in the absence of confirmed diagnoses and unnecessary avoidance.[6,10–12]

Chang et al reported that 19% of children with food-triggered AD and no previous immediate reactions developed new immediate food reactions after a period of an elimination diet; with 30% developed anaphylaxis.[6]

Moreover, there are multiple similar reports.[10–12] In a study involving 11 children with AD, who avoided cow's milk protein, eight developed severe acute allergic reactions after accidental ingestion. However, all of them experienced acute reactions following DBPCFC in the clinic.[10] In the aforementioned study, the elimination diet was continued for a median of 2.3 years despite the inaccurate diagnosis and the lack of improvement with it. In another study involving 80 patients with AD, four developed anaphylactic shock after reintroduction of a single food (soy, corn, chicken, and cow's milk). None of them had immediate reactions before the elimination started.[11]

Given such risk on accidental exposure or planned reintroduction, these patients may benefit from epinephrin autoinjectors prescription and supervised milk reintroduction. Moreover, unnecessary prescription of exclusion diets may inadvertently lead to loss of tolerance. Hence, the precise diagnosis of food allergy and the careful prescription of elimination diet is essential.

Our study has shown that the risk factors for the development of immediate reactions were concomitant food allergy, especially eggs. Contrary to what we expected, the ability to tolerate baked dairy product, type of formula or the extent of dietary restriction did not correlate with the risk of the development of immediate reactions later in life. However, studies have shown conflicting results.

There is a debate around the proper use of AA formula and tolerance induction.[13] It was found that the use of EHF with probiotics was associated with lower incidence of atopic manifestation and greater rate of tolerance acquisition, compared to other formulas, including AA-based formulas.[14] Recent evidence suggests that the hydrolysate formulas are capable of reducing intestinal permeability, thus improving barrier function and decreasing antigen uptake. Furthermore, there is evidence that the hydrolyzed peptides have an active role in modulating the immune system in children with CMPA and in those at risk of developing CMPA.[16–18] These immunomodulatory mechanisms include increasing the regulatory cytokines, such as IL-10; and reducing the inflammatory mediators, including IL-8.[16,19] On the other hand, it was found that early introduction of cow's milk protein may prevent CMPA.[15]

It was demonstrated that the AD does not seem to influence the achievement of tolerance in CMPA in children.[20] In our sample, personal history of atopy did not affect the induction of tolerance.

Limitations of the present study include the fact that it is a retrospective chart review. The details of the immediate reactions, the amount of milk consumed, and the patients' disposition were not precisely documented for all the patients included. The study was carried out in two major tertiary referral centers; therefore, the sample might represent a subgroup of patients with severe forms of allergies, and that they are at a higher risk of persistent food allergy. Comparison of our findings with studies including patients seen in the primary care would be interesting.

In conclusion, significant number of children with CMPA, who presented with delayed-type allergic reactions, may be at risk of developing immediate reactions upon reintroduction. Therefore, evaluation of these children for possible IgE-mediated reactions may be advisable before cow's milk protein reintroduction. Further studies exploring the characteristics of those children and the risk factors of decreased oral tolerance are warranted.

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Disclosure

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