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Cross reactivity between Cow's and Camel's milk in the infant population of Saudi Arabia.

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Abstract

Objective: One of the most common types of allergy in the early childhood is cow's milk allergy (CMA). Patients suffering from CMA may show severe allergic responses and therefore they have to follow a strict diet. Camel's milk is different in protein composition as compared to cow's milk and could be used as its substitute. Thus, in the present study we tried to identify patients with CMA and camel milk allergy and their cross reactivity in the Saudi Arabian infant population.

Method: The patients below 2 years of age and diagnosed with CMA were recruited from two different hospitals of Saudi Arabia. Also demographic data were collected for all the patients. Electronic chart were reviewed for food allergy, milk allergy and anaphylaxis shock using the International Classification of Diseases (ICD) coding process.

Results: A total of 112 patients were recruited for the study with male to female ratio of 1:33. The clinical presentations showed by the participants were atopic dermatitis (24%), chronic diarrhea (21%), anaphylaxis (16%), poor weight gain (16%), chronic vomiting (11%) and urticaria (5%). 108 patients showed positive results for Cow milk's skin prick test and 2 patients showed positive Camel milk skin prick test. The cross reactivity between CMA and camel milk was low i.e., 108 to 2 prospectively. The Cow's milk specific IgE was positive in 92% of participants with 25 ± 34 KU/L.

Conclusion: If we can confirm positive CMA and confirm negative camel allergy by oral challenge, the results will be more reliable, and possibly we can determine the safety for suggesting camel milk for children suffering from CMA.

Keywords: Cow's milk, Camel's Milk, Cross reactivity, Infants, Saudi Arabia.

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Introduction

From infancy to early childhood, the most common type of food allergy is Cow's milk allergy (CMA), which is considered as a challenge for patients, and their families [1]. The allergy may present as an IgE or non-IgE-mediated disease. The patients with CMA are at a risk of developing severe allergic responses and thus they must follow a strict diet [2]. The diagnosis of CMA depends on skin prick tests (SPT) and specific IgE measurements. Atopic patch test can help in selecting patients with CMA, but the diagnosis must always be correlated with clinical symptoms, which is often determined by standardized food challenges [3]. Currently the only practice for dealing with CMA patients is total elimination of cow's milk and its products and substituting it with elemental formula or soy-based formulas. Although their nutritional value is almost similar to cow's milk but their high cost and unpleasant taste for some children limit the use of extensively hydrolysed formulas. For these reasons, there has been a continuous search for other non-bovine, mammalian milks as a replacement of cow's milk. These trials included milk of goat, sheep, and buffalo.

Camel's milk is different in protein composition as compared to cow's milk. Casein is the major protein in camel milk constituting around 52 -87% of total protein. Out of the total, β-casein is 65%, αs1 casein is 22%, αs2 casein is 9.5% and k-casein is 3.5%. Whey protein is the second principal fraction of camel milk protein which constitutes 20 to 25% of the total protein. The camel milk is deficient in beta-lactoglobulin (β-Lg) which is similar to human milk [4,5] whereas in the cow's milk, whey proteins and beta-lactoglobulin (β-Lg) are the major components (55%) followed by α-La (20%). The αs1 is the predominant casein causing protein allergy. The human casein does not contain the αs1-fraction, but cow's milk contains larger amount of αs1 casein i.e., 38.4%. The β-Lg is another major protein allergen but human milk is free of β-Lg which is similar to camel milk. On the contrary, β-Lg is a major whey protein in cow's milk [6]. As the camel milk has low amount of αs1 casein and β-Lg, it may act as a better protein source for the nutrition of children who are allergic to cow's milk. Camel milk can be used both in the raw form as well as a modified formula [5].

Thus in our study, we tried to identify the patients with CMA and camel milk allergy and their cross reactivity in infant population of Saudi Arabia.

Materials and Methods

Study design

The study was conducted at two different hospitals (Blinded for Review) in Saudi Arabia. Patients diagnosed with Cow's milk allergy (CMA) between December 2013 and December 2016 were recruited for the study, however, only the patients who were under 2 years of age were considered for study. Chart review of all the patients who were referred to the Pediatric Allergy-Immunology clinics of both the hospitals was recorded. All the data was collected from the medical record only.

Inclusion and exclusion criteria

The inclusion criterion for this study was history of the patient suggestive of Cow's milk allergy. Also, the criteria included patient with elevated cow milk protein specific IgE ≥0.35. The patient showing positive skin prick test to cow milk protein and fresh pasteurized camel milk were also considered for the study. The exclusion criteria for this study only for demographic skin testing.

Chart review

Electronic charts were reviewed using the International Classification of Diseases (ICD) coding process. Review was done for all the patients showing food allergy, milk allergy, and anaphylaxis shock. Skin testing was done routinely in the allergy clinic for almost all the patients with history of allergy. Demographic details and clinical presentations of all the enrolled patients were collected for the study. Informed consent was obtained from the participant's legal guardian after explanation of the procedure.

Statistical analysis

The test of 'between-subjects' effects was done to determine whether either of the two independent variables or their interaction is statistically significant.

Results

Demographic details

A total of 230 patients were enrolled for the study. All the patients were labelled with Cow's milk allergy. After applying the criteria on all the 230 patients, only 112 fitted the inclusion criteria. The basic demographic data for all the 112 patients is shown in Table 1. Out of the total, 64 were male and 48 were female with male/female ratio of 1.33. Family history of allergy showed that the maximum number (34%) of the patients had atopic dermatitis. All the patients were breast fed between 0-24 months.

Table 1. *Basic demographic characteristics of the enrolled patients for the study (N=112).*

Variables	CMA patients
Age (months, median)	20 months
Sex (Male/Female)	1.33
Male	64
Female	48
Family history of allergy	
Allergic rhinitis	24%
Asthma	26%
Atopic dermatitis	35%
Duration of breast feeding	
0-6 months	8%
7-12 months	34%
13-18 months	35%
19-24 months	23%

Clinical presentation

The CMA patients showed variable clinical presentations ranging from cutaneous manifestations to severe anaphylaxis. The percentage of different clinical presentations is shown Table 2. Majority of the patients showed symptoms of atopic dermatitis (24%) followed by chronic diarrhoea (21%). Only 5% of the patients showed the symptom of Urticaria and 7% showed other symptoms.

Tests for allergy

All the 112 patients included in the study underwent certain blood tests including complete blood count (CBC), eosinophil count, total IgE, cow's milk specific IgE, skin prick test for cow's milk and fresh pasteurized camel milk. The tests were conducted in the microbiology department of Umm Al-Qura University. The results of these investigations are represented in Table 3. 108 patients showed positive results for Cow's milk skin prick test and 2 patients showed positive results for camel milk skin prick test.

Table 2. *Clinical presentations of the enrolled patients.*

Variable Clinical presentations	CMA children
Anaphylaxis	16%
Atopic dermatitis	24%
Chronic diarrhoea	21%
Chronic vomiting	11%
Poor weight gain	16%
Urticaria	5%
Others	7%

Table 3. *Investigations and other test of the enrolled patients.*

CMA children	Variable
Range: 0.51 -2.5 celles/UL (80% positive)	Eosinophiles (Absolute)
425 ± 1100 (52% positive)	Total IgE (IU/ml)
108 Positive SPT	Cow milk prick test
2 positive SPT	Camel milk skin test
25 ± 34 (92% positive)	Cow's milk specific IgE (KU/L)

Tests of between-subjects effects

The tests of between-subjects effects were performed for the cow and camel milk skin test, IgE, age and clinical presentations (Table 4). The p-value for both cow and camel

milk skin test were found to be statistically significant (p-value <0.05). Also, the p-value for age was calculated to be .011 and thus is statistically significant (p-value <0.05). On this basis, we can conclude that the age of participants is a significant factor in severity of the symptoms in case of cow milk skin test. In case of the clinical presentation, p-value of urticaria was calculated to be 0.033 for Cow milk and .018 for Camel milk. Since p-value was less than 0.05, urticaria can be considered as a prominent factor for both groups. The p-value for anaphylaxis was calculated to be .016 in case of cow milk group only.

Discussion

CMA has been considered as a prototypic food allergy by paediatricians since several centuries. It is an established fact that the only therapy for this at present is complete elimination of cow's milk protein from the diet and use of any other substitute. The clinical use of animal non-bovine milk as a substitute has been evaluated by many studies including camel, buffalo, sheep, and goat. But unfortunately, it has been demonstrated by several studies that due to similarity between the natures of mammalian milk proteins to cow milk, children with CMA can also develop allergy to other substitute mammalian milk proteins. The Food and Agriculture Organization stated that the camel produces nutritious milk for human consumption and therapeutics use whose benefits are comparable with human milk [7]. Camel's milk differs from the cow's milk with respect to its protein composition.The major protein in camel milk is casein (52-87%) followed by whey protein (20-25%) and similar to human milk, is deficient in α-lactalbumin (α-La) and beta-lactoglobulin (β-Lg) However, in cow's milk beta-lactoglobulin (β-Lg) is the main component (55%) followed by α-La (20%)4-6. In the present study, the cross reactivity between Cow's and camel's milk was studied in 112 paediatric subjects below the age of two years at two different hospitals in Saudi Arabia. The participants were tested for different types of allergy including the presence of cow or camel milk allergy and their cross reactivity.

Table 4. *Tests of between-subjects effects.*

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Cow milk	1.245a	22	0.057	1.927	0.017
	Camel milk	.334b	22	0.015	0.828	0.684
Intercept	Cow milk	1.892	1	1.892	64.461	0
	Camel milk	3.377	1	3.377	184.315	0
Cow milk IgE	Cow milk	0.054	1	0.054	1.845	0.178
	Camel milk	0.023	1	0.023	1.271	0.263
Total IgE	Cow milk	0.102	1	0.102	3.475	0.066
	Camel milk	0.019	1	0.019	1.017	0.316
Eosinophil	Cow milk	0.063	1	0.063	2.134	0.148
	Camel milk	0.009	1	0.009	0.487	0.487
Age	Cow milk	0.196	1	0.196	6.69	0.011
	Camel milk	0.011	1	0.011	0.6	0.441
Gender	Cow milk	0.013	1	0.013	0.435	0.511
	Camel milk	3.53E-05	1	3.53E-05	0.002	0.965
History	Cow milk	0.237	7	0.034	1.156	0.336
	Camel milk	0.064	7	0.009	0.499	0.833
AD	Cow milk	5.42E-05	1	5.42E-05	0.002	0.966
	Camel milk	0.002	1	0.002	0.098	0.755
Diarrhea	Cow milk	1.72E-05	1	1.72E-05	0.001	0.981
	Camel milk	0.014	1	0.014	0.774	0.381
Vomiting	Cow milk	0.001	1	0.001	0.033	0.857
	Camel milk	0.002	1	0.002	0.13	0.719
FTT	Cow milk	0.005	1	0.005	0.171	0.68
	Camel milk	0.005	1	0.005	0.278	0.599
Urticaria	Cow milk	0.138	1	0.138	4.713	0.033
	Camel milk	0.106	1	0.106	5.793	0.018
Feeding	Cow milk	0.095	4	0.024	0.806	0.525
	Camel milk	0.016	4	0.004	0.222	0.926
Anaphylaxis	Cow milk	0.176	1	0.176	6.002	0.016
	Camel milk	0.002	1	0.002	0.102	0.75
Error	Cow milk	2.613	89	0.029		
	Camel milk	1.631	89	0.018		
Total	Cow milk	124	112			
	Camel milk	442	112			
Corrected Total	Cow milk	3.857	111			
	Camel milk	1.964	111			
a. R Squared = .323 (Adjusted R Squared = .155)						
b. R Squared = .170 (Adjusted R Squared = -.035)						

The αs1 protein is a predominant casein which acts as a protein allergen. The cow's milk contains large amount of αs1 casein (38.4%) as compare to human casein which does not have any αs1-protein in it [8-10]. Also, the β-Lg is another major protein allergen which is absent in both human milk and camel milk. On the other hand, β-Lg is a major whey protein in cow's milk [11]. Since camel milk contains lower amount of αs1 casein and β-Lg, it may be considered as a new protein source for nutrition of children allergic to cow's milk and can be used as such or in a modified form. A series of CMA in children showed a probability that it might be present both as IgE mediated type or a non-IgE-mediated type allergy. Thus, diagnosis of allergy depends on both IgE tests such as SPT (mention full form) or serum specific IgE antibody level to cow's milk measurement, and regular food tests [12,13]. In our study, 108 participants showed positive Cow milk prick test and only two patients showed positive Camel milk prick test. Further cow's milk specific IgE was found to be positive in 92% of the participants. Understanding of SPT and specific IgE tests are most of the time hampered by patients sensitized to cow's milk in the absence of clinical symptoms. Many of the researches gave a cut-off values for SPT or specific IgE values. The author Sampson et al., reported a specific IgE value in the serum of 15 kU/l to be 95% predictive of CMA with children predominantly suffering with atopic dermatitis [14]. Recently, a study which included over 500 participants and suffering

mostly with atopic dermatitis found cut-off value of 88.8 kU/l [15]. Our present study showed Cow's milk specific IgE as 25 ± 34 KU/L which is lower than the previously reported studies. Thus it is obvious that these values depend on a given populace including the age and type of symptoms which must be interpreted accordingly.

In the absence of positive tests in non-IgE mediated CMA, the preliminary diagnosis basically depends on the suggestive history. Our present study showed the family history of allergic rhinitis, asthma and atopic dermatitis in the participants. Children in whom a non-IgE-mediated CMA is suspected and who are suffering with atopic dermatitis, atopy patch tests may play a helpful role as a diagnostic tool. The study participants presented with clinical symptoms of anaphylaxis, atopic dermatitis, chronic diarrhea, chronic vomiting, poor weight gain, urticaria including others. Most of the time infants may show non-specific gastrointestinal signs such as chronic vomiting and diarrhea or failure-to-thrive which is attributed to cow's milk. Statistical analysis by tests of between-subjects effects showed urticaria as significant clinical presentation for both Cow milk and Camel milk as p-value was less than 0.05. Although anaphylaxis is a significant indicative of severity, it was found to be statistically significant only in case of CMA group. In such patients, the diagnosis depends on avoidance of milk diet and clinical relapses after re-use to cow's milk proteins.

Conclusion

In conclusion, skin testing and specific IgE to cow's milk are not the gold standard for diagnosis of true CMA, and negative skin testing for camel milk could not rule out false negative camel milk allergy. Also, the cross reactivity between CMA and camel milk are not high according to our results i.e., 108 to 2 prospectively. As it is known that double blinded placebo oral challenges is the gold standard for diagnosing food allergy, but it is not done in most of those patients. Thus in our study, it was not clear if the participants tested negative for camel milk were able to tolerate camel milk in their diet despite the physicians recommendations to replace it with cow's milk, especially for families who already had camel milk as a part of their regular diet. Also, very few studies are done on the cross reactivity of the Cow's milk and Camel's milk till now. Thus, if we can confirm positive CMA and a negative camel allergy by oral challenge, the results will be more reliable and possibly we can determine the safety of suggesting camel milk for children suffering from CMA.

As CMA represents significant burden for infants, the care managers, patient's families, and healthcare system plays a major role. The primary health care practitioners are usually placed to address the gap in service provision for CMA as shown by previous studies [16]. Also, international consensus guidelines were developed to support primary care system for recognizing, diagnosing and management of CMA. The author Ciccone et al. showed in his study that there is unanimous agreement for positive impact on patient's health and its management due to collaboration between the care managers, physicians and family of patient [17]. One of the limitations of the present study is relatively small number of study sample and its retrospective nature as only recorded data was used for analysis. This may have resulted in selection bias and information bias of the analyses. Thus, further studies need to be done with large sample size for better outcomes and conclusions.

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