

## Cow's Milk Anaphylaxis in Children First Report of Iranian Food Allergy Registry

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### ABSTRACT

Cow's milk anaphylaxis is the most common food-induced anaphylaxis in Iranian children. The clinical and laboratory findings of cow's milk anaphylaxis are evaluated in this study. All children who had experienced cow's milk anaphylaxis and had been referred to Immunology, asthma and allergy research center during a 5-year period were considered. After fulfilling a questionnaire, patients underwent measurement of total IgE and cow's milk-specific IgE by Immunocap test and Skin prick test (SPT) with cow's milk extract. Patients with a convincing history and one positive cow's milk-specific IgE test (SPT or Immunocap test) and patients with both positive tests were enrolled, in this study.

Out of 49 patients, 59.2% were male. Patients' mean age was 5 years old and their mean age at the time of first attack was 5.7 months (SD = 4.3). Most of the patients have experienced more than one episode of anaphylaxis (79.5%) and in 85.7% of all cases, first attack occurred during the first year of life. Severity grading 1-5 were 2%, 6.1%, 18.4%, 69.4%, 4.1% respectively. Most common manifestations were cutaneous 98%, Respiratory 91.8%, Gastrointestinal 55.1%, Cardiovascular 46.9% and neurologic 46.9% signs and symptoms respectively. Twenty four patients showed positive SPT. Mean total IgE was  $239.6 \pm 3.3$  (IU/mL) and mean cow's milk-specific IgE was  $19.28 \pm 27.2$  (IU/mL). Most patients showed reactions only after ingestion of cow's milk or after dairy foods (81.6%).

It is concluded that cow's milk anaphylaxis may happen early in life. Regarding the severity of attacks and remarkable number of patients with several attacks, poor knowledge about this disorder is evident.

**Keywords:** Food Allergy; Food Anaphylaxis; Immediate Hypersensitivity; Milk Allergy

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## INTRODUCTION

Food allergy is an ongoing disorder which affects 2% to 8% of children and less than 2% in adults. Its most common triggers are nuts, peanuts, cow's milk, wheat, soy, egg, fish and shellfish.<sup>1,2</sup> Cow's milk allergy is the most prevalent food allergy in the first year of life and may affect 2% to 6% of infants and 0.5% to 1% of adults.<sup>3</sup> There is a wide spectrum of manifestations for food allergy from mild local to severe systemic reactions called anaphylaxis. Anaphylaxis is a serious allergic reaction which happens rapidly and can cause death.<sup>4</sup> In a recent study based on available epidemiological evidence, the lifetime incidence of food anaphylaxis has been estimated 50 to 2000 episodes in a population of 10000 persons.<sup>5</sup> It may have different triggers but in children, adolescents and young adults, foods are the most common elicitors.<sup>5,6</sup> Food-induced anaphylaxis is an IgE-mediated hypersensitivity. In a previous research in Iran, it was revealed that cow's milk (CM) and wheat flour represent main causes of anaphylaxis in Iranian children.<sup>7</sup> Although allergy to cow's milk is usually seen in children, it has been reported in adults as well.<sup>8</sup> Diet, race and methods of food preparation vary in different countries. These factors may affect the prevalence and clinical features of specific food allergies and consequently food-induced anaphylaxis. On the other hand, there is a deep lack of information about clinical features and severity of cow's milk anaphylaxis in Iranian children. Accordingly, it is very necessary to determine the clinical aspects of cow's milk anaphylaxis in Iranian children.

## PATIENTS AND METHODS

All children (<18 years old) who had been diagnosed as having experienced cow's milk anaphylaxis and had been referred to IAARI (Immunology, Asthma and Allergy Research Center) during the year 2005 (Jan)-2010 (Sep) were considered. The diagnosis of cow's milk anaphylaxis had been established by physicians on the basis of clinical features and physical examination of patients. In fact, these patients had been referred to IAARI in order to verify the diagnosis by means of paraclinical tests and performing complementary workup and to be visited by subspecialist of immunology and allergy. After taking

informed consent from the parents regarding study participation and undergoing Skin prick test (SPT) and specific IgE testing, a detailed questionnaire (containing demographic data, personal and familial history of atopy, number of episodes and clinical manifestations) was filled out for each patient by a physician. Then, allergy workup was conducted. This work up included:

- Skin prick test (SPT) with cow's milk allergen extract
- Determination of cow's milk specific IgE level
- Determination of some common food allergens (wheat, soy, egg, tree nuts, peanuts) specific IgE levels
- Determination of Serum total IgE level
- Eosinophil count
- Stool sample examination

The basis of SPT is the evaluation of production of cow's milk specific IgE in patients who had been formerly subjected to cow's milk. These antibodies combine to the Fc IgE receptors on the surface of the mast cells which present in the skin and when small bit of cow's milk extract is applied on the volar side of the forearm with a lancet, these mast cells will be exposed. Then, a wheal and erythema reaction will appear. In this test, a negative control (normal saline) and a positive control (histamine 1mg/ml) were also used. The SPT responses for histamine and allergens were read at 10 and 20 minutes respectively. If the diameter of wheal for histamine was at least 5 mm and the diameter of the wheal for cow's milk extract was at least 3mm larger than the reaction to the negative control or if the erythema diameter was larger than 10 mm, the test was considered positive for cow's milk.<sup>9,10</sup> SPT was performed at least 4-6 weeks after patient's last anaphylactic attack, If he showed negative cow's milk specific IgE.<sup>11</sup> The extracts were obtained from Dome Holister Stier (miles, Canada). Serum total IgE was measured using a commercial enzyme Immunoassay (Genesis Diagnostics, Cambridshire, England). After determining the total serum IgE level, the results were compared with the normal value of serum total IgE for their age in Iranian children.<sup>12,13</sup> Cow's milk specific IgE and specific IgE for other common food allergens (peanuts, tree nuts, egg, wheat flour, soy) were measured with Immunocap system (laboratory substances from Phadia AB; Uppsala, Sweden). The results were read by Immunocap 100. The results of specific IgE were categorized in seven grades (0-6+).<sup>14</sup> The results equal to 1+ or more were considered positive.

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**Table 1. The criteria of differential diagnosis of anaphylaxis**

<b>Skin:</b> acute generalized urticaria, urticaria pigmentosa, mastocytosis, hereditary angioedema
<b>Respiratory:</b> asthma, COPD, pulmonary edema, smoke or toxin inhalation, aspiration of foreign body, croup, bronchiolitis, vocal cord dysfunction
<b>Gastrointestinal:</b> congenital obstruction (eg, pyloric stenosis, malrotation), acquired obstruction (eg, intussusceptions), scombroid poisoning, monosodium glutamate
<b>Neurologic:</b> seizure, trauma, stroke, increased intracranial pressure, post-ictal phase
<b>Cardiovascular:</b> faintness, chest pain, dysrhythmia, myocardial infarction
<b>Shock:</b> septic, cardiovascular, hypovolemic
<b>Flush syndromes:</b> perimenopause, carcinoid syndrome, red man syndrome, autonomic epilepsy
<b>Metabolic disorder</b>
<b>Sudden infant death syndrome</b>
<b>Others</b>

Collected from references <sup>15-17</sup>

To do this test, 2-3 mL of whole blood was taken and the serum was reserved at -20° for measuring specific IgE. In this study, a blood cells count was done with Sysmex (KX21) and an eosinophil count of more than 450 cells/ $\mu$ L was considered as eosinophilia. Moreover in all patients stool exam was done to rule out the parasitic infection.

In this study, the differential diagnosis of anaphylaxis was considered (Table 1) to exclude suspected cases.<sup>15-17</sup>

Besides, a grading system was used to determine the severity of anaphylaxis (Table 2).<sup>18</sup> In order to fulfill the criteria of grading system, along with the clinical history, we used patients' medical records which had been noted by the physicians who had visited the patients at the time of anaphylaxis. Since the patients whose medical records were not accessible had cutaneous, gastrointestinal or mild respiratory symptoms, we determined the grading by taking a careful clinical history.

**Table 2. Grading of food-induced anaphylaxis according to severity of clinical symptoms**

Grade	Skin	GI Tract	Respiratory Tract	Cardiovascular	Neurological
1	Localized pruritus, flushing, urticaria, angioedema	Oral pruritus, oral tingling, mild lip swelling			
2	Generalized pruritus, flushing, urticaria, angioedema	Any of the above, nausea and/or emesis	Nasal congestion and/or sneezing		Change in activity level
3	Any of the above	Any of the above plus repetitive vomiting	Rhinorrhea, marked congestion, sensation of throat pruritus or tightness	Tachycardia (increase >15 beats/min)	Change in activity level plus anxiety
4	Any of the above	Any of the above plus diarrhea	Any of the above, hoarsness, barking cough, difficulty swallowing, dyspnea, wheezing, cyanosis	Any of the above, dysrhythmia and/or mild hypertension	Light headedness, feeling of pending doom
5	Any of the above	Any of the above, loss of bowel control	Any of the above, respiratory arrest	Severe bradycardia and/or hypertension or cardiac arrest	Loss of consciousness

Adopted from reference <sup>18</sup>

Table 3. Some characteristics of patients with cow's milk anaphylaxis

Topics	Variable	Percent
Severity	Grade 1	2%
	Grade 2	6.1%
	Grade 3	18.4%
	Grade 4	69.4%
	Grade 5	4.1%
Number of attacks	One episode	24.5%
	Two episodes	16.3%
	Three episodes	18.4%
	Four episodes	6.1%
	Five episodes	18.4%
	Over five episodes	16.3%
Time between allergen(cow's milk) contact and beginning of symptoms	0-15 min	85.7%
	16-30 min	6.1%
	31-45 min	2%
	46-60 min	6.1%
Cow's Milk specific IgE	1+,2+	36.7%
	3+,4+	46.9%
	5+,6+	16.3%
Positive prior history of atopic disease		<b>53.06%</b>
	Atopic dermatitis	48.1%
	Asthma	40.7%
	Rhinitis	18.5%
	Drug allergy	11.1%
Positive prior familial history of atopic diseases		<b>59.2%</b>

Finally, the patients who satisfied the clinical diagnostic criteria of anaphylaxis and were compatible with one of the following criteria were enrolled:<sup>19</sup>

1-Patients with a convincing history of cow's anaphylaxis and one milk positive cow's milk specific IgE test (SPT or Immunocap test)

2-Patients with an unconvincing history or with anaphylaxis due to an unknown origin but with both positive cow's milk specific IgE tests (SPT and Immunocap test)

This study has satisfied the requirements of IAARI ethics committee.

## RESULTS

Out of 49 patients with mean age of 5 years old, their male to female ratio was 59.2% to 40.8% respectively. Their mean age at the time of first

anaphylactic attack was 5.7 months (SD=4.3) and in 85.7% of all cases, first attack occurred before one year old. Majority of them showed reactions within the first quarter of hour after contacting with the allergen (Cow's milk and dairy foods). Most patients (98%) were habitants of urban areas. Almost half of them had past histories of atopic diseases and more than half of them had positive familial history of atopy (Table 3). Most patients' parents did not have university degrees. 69.4% of mothers and 63.3% of fathers had low educational attainment but there was no significant relation between number of anaphylactic attacks and parents' education level ( $p>0.05$ ). Most of the patients experienced more than one episode of anaphylaxis. Also most of the patients showed reactions only after ingestion of cow's milk or dairy foods (81.4%).

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**Table 4. Symptoms and signs of patients with cow's milk anaphylaxis**

Organ involved	Symptoms and signs	Percent
<b>Cutaneous</b>		<b>98%</b>
	Urticaria	66.6%
	Pruritus	70.8%
	Erythema	39.5%
	Flushing	45.8%
	Conjunctivitis	35.4%
	Periorbital oedema	50%
	Angioedema	31.2%
	Maculopapular rash	35.4%
<b>Respiratory</b>		<b>91.8%</b>
	Dyspnea	80%
	Tachypnea	40%
	Cough	60%
	Wheeze	68.8%
	Rhinitis	28.8%
	Dysphonia	22.2%
	Cyanosis	24.4%
	Accessory respiratory muscle utilization	6.6%
	Oral mucosal swelling	40%
<b>Gastrointestinal</b>		<b>55.1%</b>
	Vomiting	81.4%
	Nausea	70.3%
	Diarrhea	14.8%
	Abdominal pain	33.3%
	Dysphagia	7.4%
	Difficulty handling of oral secretion	18.5%
<b>Cardiovascular</b>		<b>46.9%</b>
	Hypotension	13.04%
	Tachycardia	60.8%
	Palpitation	8.6%
<b>Neurologic</b>		<b>46.9%</b>
	Irritability	56.5%
	Lethargy	26%
	Drowsiness	21.7%
	Loss of consciousness	8.6%
	Headache	17.3%
	Seizure	4.3%

However, some patients (14.6%) had reactions either after ingestion of cow's milk or after dermal contact with it. One patient showed anaphylaxis attack only after dermal contact with cow's milk (2%) and another patient showed reaction after smelling boiling cow's milk (2%).

Most common clinical manifestations in descending order were: cutaneous, respiratory, gastrointestinal, cardiovascular and neurologic signs and symptoms

(Table 4). Only 16.3% of all cases have had other allergies except cow's milk allergy and these in descending order were: wheat-allergy, egg-allergy, tree nuts-allergy and peanut-allergy. Mean cow's milk specific IgE level was  $19.28 \pm 27.2$  (IU/mL) and mean total IgE was  $239.6 \pm 3.3$  (IU/mL). Among all cases, 56.4% showed normal total IgE level for their age and the rest had elevated total IgE levels. Twenty-four patients showed positive SPT. Mean wheal diameter

was  $6.5 \pm 3.09$  mm and mean erythema diameter was  $14.16 \pm 14$  mm. Some characteristics of patients with cow's milk anaphylaxis are demonstrated in table 3.

## DISCUSSION

Although any type of food has the potency to induce food anaphylaxis, the most common triggers of it in children are cow's milk, egg, wheat flour, soy, peanut and fish.<sup>20-23</sup> The most frequent allergens varies in different nations, for example, sea foods (fish or crustacean) and peanut are the most common triggers in Hong-Kong and the US respectively.<sup>24-26</sup> In Iran, a study had showed that cow's milk allergy is the most current elicitor of anaphylaxis in Iranian children.<sup>7</sup> Although some studies indicate that food anaphylaxis happens equally in both sexes but according to the most studies, there is gender preference and in adults it's predominant in women but among the children it's predominant in boys.<sup>27-29</sup> In this study, 29 patients out of 49 were male (59.2%).

Most patients showed clinical manifestations of cow's milk allergy before one year old, though it can be seen at any age.<sup>30-32</sup> In this study, most patients (95.5%) experienced the first attack of anaphylaxis before one year of age and 79.5% showed reactions before 6 months. Since the immune system and gastrointestinal tract are immature in infancy, penetration of cow's milk protein into the breast milk with early introduction of cow's milk in infants' diet may be the reasons of early development of cow's milk allergy and consequently cow's milk anaphylaxis.<sup>30,33</sup>

In this study 55.1% of patients had positive prior history of allergic diseases and the most frequent allergy in these children was atopic dermatitis (48.1%). These results confirm that food allergy is more common in children with other allergic diseases. Besides, atopy is a common problem in patients with anaphylaxis and it may be due to the existence of extracellular cytokine which may results in the increased risk of anaphylaxis.<sup>29,34</sup>

Since near 60% of patients had a family background of atopy, it implies that genetic predisposition to atopy plays a remarkable role in anaphylactic response.<sup>33,36</sup>

In some studies, wheal diameter in SPT and CM specific IgE which are 95% predictive for a clinical cow's milk allergy were 8mm and 15(IU/mL) respectively and in young infants (under 2 years old) these diagnostic decision points of CM specific IgE are

lower. The sizes of wheal by SPT and specific IgE levels in the serum are associated with a clinically relevant allergy.<sup>37-39</sup> In our study mean wheal diameter was 6.5 mm and mean CM specific IgE was  $19.28 \pm 27.2$  (IU/mL) showing a higher CM specific IgE in comparison with the result of the previous studies. It might be predicted because all of our patients had experienced cow's milk anaphylaxis as opposed to the cases of previous reports who did not have necessarily experienced anaphylactic reactions. Moreover, mean age of 24 patients who underwent SPT was 15 months and it may be it is reasonable that their wheal diameter in SPT being lower than the diagnostic point which has been defined before.

Only 8 patients had any other food allergies in addition to cow's milk allergy and it seems that other food allergies in patients with history of cow's milk anaphylaxis is not common and it appears also that severe allergen (foods other than cow's milk or dairy foods) avoidance, is not really necessary only because of having the prior history of cow's milk anaphylaxis unless other food allergies have been proved by appropriate methods and tests.

According to other studies, the most common route of exposure to the food allergens which may induce allergic reactions is ingestion, but as it has been mentioned in several cases reports that in some allergic patients severe systemic reactions may develop through dermal contact or even inhalation of the offending food allergen.<sup>40-42</sup> In this study it was revealed that ingestion of cow's milk or dairy foods and dermal contact with them are the most common routes of exposure to the allergen, though there has been one patient who had shown anaphylactic reaction after inhalation in the vicinity of places where the cow's milk was boiling so it is necessary to warn the patients and their parents upon the potential danger of other routes of allergen exposure other than dermal contact and inhalation.

In this study it was revealed that organs which are mainly involved in cow's milk anaphylaxis are the skin, respiratory tract, gastrointestinal tract, cardiovascular and central nervous system respectively and this is in agreement with the results of previous studies on anaphylaxis.<sup>35</sup>

In this study most patients (79.5%) had experienced more than one episode of anaphylaxis and also most of the patients (85.7%) had shown reactions following ingestion of cow's milk or dairy foods. So it seems that education of cow's milk allergic patients regarding

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avoidance of cow's milk or dairy foods is not sufficient. Since the cornerstone of prevention of anaphylaxis is avoidance of the causal foods, the patients and their parents should be informed on cow's milk or dairy foods avoidance and understanding food labels. They also should be given balanced diet consisting of suitable food substitutes for preventing malnutrition.

In this study, most patients (85.7%) showed reactions within the first quarter of hour after exposure to the allergen (cow's milk), so the necessity of patients' families educating about primary management of anaphylaxis is evident and the clinicians should prescribe adrenaline auto-injectors for patients and inform their parents on correct administration of it.

To be brief, it was understood that cow's milk anaphylaxis as the most common type of anaphylaxis in Iranian children is severe enough and the most common clinical manifestations are dermal and respiratory. Considering the frequency of anaphylactic attack that 79.5% of patients had experienced more than one attack, it is necessary to inform the patients' families and clinicians on diagnosing, managing and prevention of cow's milk anaphylaxis.

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