Clinical and Laboratory Evaluation of Faltering Growth in Infants with Cow’s Milk Protein Allergy

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The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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Abstract
Background: Cow's Milk protein Allergy (CMA) is a serious and potentially life-threatening problem for an estimated 2.5 % of children. Infants with CMA are at risk of growth faltering, however, data are still limited.

Objectives: The aim of the study was to assess growth and nutritional status in infants with CMA and to evaluate the implications of CMA in infants with flattering growth.

Methods: This cross sectional study was performed in the period from April 2019 to September 2019 in Pediatrics Department of Zagazig University Hospitals. The study included 72 patients with CMA diagnosed by oral challenge test after elimination diet. Allergy work up included skin prick test and measuring specific (Immunoglobulin E) IgE for Cow's Milk protein (CMP) for all patients. The growth and nutritional status of the patients was assessed based on World Health Organization (WHO) growth charts and growth z-scores for weight-for-age, weight-for-height and height-for-age, in addition to laboratory investigations.

Results: Data from 72 infants (43 male and 29 female) with age of 9.92 ± 5.853 months indicated that 9 out of 72 infants (12.5%) were diagnosed as immediate IgE mediated CMA while the other 63 infants (87.5%) were considered delayed non-IgE mediated CMA. Twenty-five infants out of 72 (34.7%) suffered from faltering of growth. We found that 20.8% of infants had z score < -2SD as regard weight for age while (9.7%) and (4.3%) had z score < -2 SD as regard height for age and weight for height respectively. We also, found that 36.1% of infants suffered from iron deficiency anaemia with haemoglobin (11.16 ± 1.53) g/dl, while 29.2% of infants showed hypoalbuminemia with serum albumin level (2.9 ±0.177)g/dl.
Conclusion: Growth faltering and nutritional problems are major concerns in infants with CMA. Proper management of infants with CMA, including specialist dietetic advice and regular growth monitoring, is mandatory to avoid these concerns. When evaluating an infant with flattering growth, iron deficiency anaemia and/or hypoalbuminemia physicians should include in their evaluation extensive search for CMA.

1. INTRODUCTION

Cow's milk is one of the most common and often the first food introduced into the infant diet, even during breastfeeding. Cow milk protein allergy (CMA) affects approximately 2.5% of children and may occur early in life, even during the neonatal period (1). The immunological mechanisms that lead to the development of CMA have not been clarified, yet. There are two main described mechanisms contributing to the pathogenesis of this disease referred to as immediate Immunoglobulin E (IgE) mediated and delayed non-IgE mediated mechanisms (2). There is no one symptom pathognomonic of CMA; it can present with an array of symptoms affecting different organ systems typically the skin, respiratory and gastrointestinal tracts with many infants developing symptoms in more than one organ system (3). For clinical practice, diagnosis of CMA is a challenging process that requires integration of medical history and food challenge procedure, in addition to laboratory tests. Positive skin prick test and/or elevated specific IgE to Cow's Milk Protein (CMP) are useful diagnostic tests indicating sensitization to CMP and an ongoing IgE-mediated immunological process; however, their results must be interpreted in the context of medical history and food challenge procedure (4).

Infants with CMA are at risk of growth faltering due to increased energy requirements from inflammation (skin/gut), disrupted sleep, reduced nutrient absorption, vomiting, diarrhea, and reduced intake while on elimination diets (5).

The aim of this study is to assess the nutritional status of infants with CMA and evaluate the implications of CMA in infants with flattering growth.

2. PATIENT AND METHODS

This cross sectional study was performed in the period from April 2019 to September 2019 in Pediatrics Department of Zagazig University Hospitals. This study included 72 patients with CMA. Inclusion criteria were male and female infants with any manifestations suggesting allergy including eczema, bronchial asthma and/or chronic diarrhea. Diagnosis was established in accordance to patients' history and positive food challenge test. Infants with known cause of flattering growth were excluded.

Written informed consent was taken from the patients' guardians to participate in the study. Approval for performing the study was obtained from Pediatrics and Medial Microbiology and Immunology Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. The study was performed in accordance with the Declaration of Helsinki.

All patients were subjected to detailed history taking include age, sex, history of any...
diseases and presence of allergic manifestations with the introduction of cow's milk. Full general examination was performed including measurement of the body weight and length to assess growth retardation. Laboratory investigations performed included Complete Blood Picture (CBC) with differentiation of WBCs, total proteins and albumin levels, stool analysis and occult blood in stool. Special investigations to assess sensitization to CMP were performed. SPT was performed for all patients using cow's milk allergen extract. Histamine dihydrochloride and saline solutions were used as positive and negative controls, respectively. The diameters of the wheal reactions were determined after 15 minutes. All tests with a wheal diameter of > 3 mm elicited by the extract and valid controls were considered positive tests for sensitisation to CMP. Specific IgE for CMP was measured by Immune blot assay (AllergyScreen test, UK) Allergy Screen Panel 1 (MEDIWISS Analytic GmbH, Hanover, Germany) according to the manufacturer’s instructions. The result was stated in iU/ml (range 0.35 – 100iU/ml).

Statistical analysis
Data were tested for normal distribution using the shapiro-wilk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test (χ2) and fisher exact test was used to calculated difference between qualitative variables as indicated. Quantitative data were expressed as mean ± sd (standard deviation) for parametric and median and range for non-parametric data. Independent t test and mann whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. All statistical comparisons were two tailed with significance level of p-value ≤ 0.05 indicates significant, p < 0.001 indicates highly significant difference while, p > 0.05 indicates non-significant difference.

3. RESULTS
In our study, we examined 72 infants (43 male and 29 female) with cow’s milk protein allergy confirmed with oral challenge test with mean age 9.92 month. We found that 72.2% of them had positive family history of food allergy. We also found that 58.3% of them were from urban areas while 41.7% were from rural areas. (Table 1)

Only nine case out of 72 (12.5%) had positive skin prick test to CMP and/or elevated levels of specific IgE to CMP. (Table 2)

The study shows great variability in symptoms of cow’s milk allergy where all infants (100%) had gastrointestinal manifestations, in the form of diarrhea, constipation, emesis, abdominal bloating and/or reflux, while 76.4% had cutaneous symptoms (Itching, flushing, skin rash and/or swelling of the lips, face), 47.2% of infants had respiratory symptoms (Cough and/or wheezing) and 1.4% had anaphylaxis. (Table 3)
In our study, 34.7% of infants suffer from faltering of growth in which 20.8% of infants had z score $<-2SD$ as regard weight for age, (9.7%) and (4.3%) had z score $<-2SD$ as regard height for age and weight for height respectively. (Table 4)

Regarding laboratory investigations, we found slight elevation in total leucocytic count with mean $9.57 \pm 1.69 \times 10^3/\mu L$ and 30.5% on infants had eosinophilia. 37.5% of patients were positive for occult blood in stool and 36.2% suffered from iron deficiency anemia (IDA) with haemoglobin $11.16 \pm 1.53 g/dL$, while 29.2% of infants showed hypoalbuminemia with serum albumin level $(2.9 \pm 0.177) g/dl$. (Table 5)

Table 1. Demographic distribution of the studied patients (n=72)

<table>
<thead>
<tr>
<th>Demographic Distribution</th>
<th>All patients (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (months)</strong></td>
<td><strong>Mean ± SD Range</strong></td>
</tr>
<tr>
<td>9.92 ± 5.853</td>
<td>2 – 24</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
</tr>
<tr>
<td>Male</td>
<td>43 (59.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (40.3%)</td>
</tr>
<tr>
<td><strong>Positive family history for food allergy</strong></td>
<td>52 (72.2%)</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td>Rural</td>
</tr>
<tr>
<td>Rural</td>
<td>30 (41.7%)</td>
</tr>
<tr>
<td>Urban</td>
<td>42 (58.3%)</td>
</tr>
</tbody>
</table>

Table 2. Classification of patients into immediate IgE mediated CMA and delayed non- IgE mediated CMA

<table>
<thead>
<tr>
<th>All patients = 72</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate IgE mediated CMA</strong></td>
<td>9 (12.5%)</td>
</tr>
<tr>
<td><strong>Delayed non-IgE mediated CMA</strong></td>
<td>63 (87.5%)</td>
</tr>
</tbody>
</table>
Table 3. Distribution of symptoms among CMA patients.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>All patients (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous symptoms</td>
<td>55 (76.4%)</td>
</tr>
<tr>
<td>(Itching, flushing skin rash and swelling of the lips, face)</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>34 (47.2%)</td>
</tr>
<tr>
<td>(Cough and wheezing)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>72 (100%)</td>
</tr>
<tr>
<td>(Diarrhea, constipation, emesis, abdominal bloating, reflux)</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

Table (4): Anthropometrics of CMA patients

<table>
<thead>
<tr>
<th>All patients (n=72)</th>
<th>Z score (Mean ± SD)</th>
<th>Deficit Z score&lt; -2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight -for-age (kg)</td>
<td>-0.7 ± 1.33</td>
<td>15</td>
</tr>
<tr>
<td>Height-for-age(cm)</td>
<td>-0.9 ± 1.82</td>
<td>7</td>
</tr>
<tr>
<td>Weight-for-height(kg)</td>
<td>-0.4 ± 1.72</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 5. Laboratory parameters of CMA patients

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>All patients (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl) Mean ± SD Range</td>
<td>11.16 ± 1.53</td>
</tr>
<tr>
<td></td>
<td>8 – 14</td>
</tr>
</tbody>
</table>
CMA is the most common food allergy found in children under 3 years of age. It is defined as a reproducible adverse reaction to one or more milk proteins mediated by one or more immunological mechanisms. (6)

In the present study, we included 72 infants with CMA confirmed by oral challenge procedure, which is the gold standard for diagnosis of food allergies. The age of patients ranged from 2 to 24 months, with a mean ± SD of 9.92 ± 5.853 months which represented the common age of CMPA.

Among the 72 infant with CMA there were 43 males (59.7%) and 29 females (40.3%) with male dominance at a ratio of 1.4:1. In accordance with our study, Teymourpour et al.
(7) found that of 49 patients, male to female ratio was 59.2/40.8%, respectively. Also, Vandenplas et al. (8) reported the domination of male gender than female by 56/44% among CMPA children. This common finding together with the male predominance of food allergies in general at young age could be explained by X-linked recessive traits associated with allergic disease that would be un-masked in males (9).

We noted that in our study, about 58% of the patients were urban. Similarly, Schoemaker et al. (6) documented that most of their patients were urban. This could be explained by a decrease in breastfeeding and an increased feeding with cow’s milk-based formulas in urban areas.

In addition, we found that 72% of the patients had positive family history for food allergy. Hosny et al. (10) found that 100% of the patients with positive family history for food allergy. This goes with the genetic predisposition for allergy (i.e., atopy) which is known to increase susceptibility to CMA.

Cow’s milk allergy is classified according to the underlying immune mechanism, timing of presentation into immediate IgE-mediated allergy and delayed non-IgE-mediated allergy (2). We performed SPT using CMP allergen extract and measured specific IgE to CMP by immunoblot assay and the results were interpreted in accordance to patients' history and rapid development of symptoms within minutes up to 2 hours after oral challenge test and 9 patients out of 72 (12.5%) were considered to have immediate IgE-mediated CMA.

Regarding the clinical presentation of our cases, we found that 76.4% of the patients had cutaneous symptoms, while gastrointestinal symptoms were found in 100% of the patients and respiratory symptoms were found in 47.2% of the patients, and only one patient had anaphylaxis. The marked variability in the clinical presentations and the lack of definitive laboratory biomarkers for CMA, specially delayed non-IgE allergy makes the diagnosis a great challenge (11).

Cow’s milk is a major provider of macro- and micronutrients in childhood. In addition, it forms part of a more varied diet where other foods also contribute essential nutrients, in later childhood (12). We hypothesized that CMA can lead to growth faltering or nutritional problems and tried to test this hypothesis by clinical and laboratory measures.

In our study, 34.7% of case had flatterin growth. Faltering growth (previously known as failure to thrive [FTT]) is considered when there is a drop in weight > 1 SD in weight-for-age or weight-for-height growth curve in the past 3 months in a child < 1 year of age, or the downward crossing of 2 centiles in the percentile charts used (13). We noted in our study among 72 infants, 15 (20.8%) infants had weight/age z score < -2SD, 7 (9.7%) and 3 (4.2%) infants had height/age and weight/height z score < -2SD respectively.
The concern about growth in CMA was raised more than 20 years ago in a study by Isolauri et al 1998 (14) where the mean SD for height-for-age and weight-for-height was significantly lower in cow's milk allergic infants compared to healthy controls. Subsequently, several other studies have published to report similar findings. For example, Flammarion et al (15) (10) documented that among 96 infants with food allergy, (9.3%) had Wt/Age z score < -2SD, (7.2%) had height/age z score < -2SD and (5.3 %) of infants had Wt/Height z score < -2SD. This study shows predominance in weight-for-age deficit in our study.

However, Meyer et al (16) studied 97 infants with food allergy most commonly to CM and found that (11.1%), (8.5%) and (3.7%) of infants had Ht/Age, Wt/Age and Wt/Height z score < -2 SD respectively.

Weight usually declines from the baseline percentile before length does when Flattering growth is due to nutritional insufficiency. While linear growth decline is related to the effect of CMP on insulin-like growth factor 1 and insulin (17). In our study, the laboratory finding of studied group showed low level of haemoglobin with mean (11.16 ± 1.53) g/dl and 36.1% of infants suffer from iron deficiency anaemia. This may be explained by occult bloodloss in stool which was detected in 37% of our cases due to inflammation of the gastrointestinal tract. In addition, anaemia could be attributed to inhibition of non-heme iron absorption by calcium and casein in cow's milk (18).

There is also decrease in serum albumin level with mean (2.9±0.177) g/dl. Hypoalbumenia may be due to mucosal inflammation and protein losing enteropathies (19).

We also found slight elevation in total leucocytic count with mean (15.34 ± 7.22) 10^3 /μL. eosinophilia in 30.5% which can be attributed to the allergic inflammatory reaction (20).

In consistency with our study, Yang et al. (16) studied 12 infants with milk protein induced enterocolitis and found that they all had hypoalbuminemia with mean serum albumin (2.13 ± 3.5) g/dl. Most of them had elevated leucocytic count (≥12.5 × 10^3 /μL). They also reported 33.3% of infants with iron deficiency anaemia. Similar to our finding, Lai and Yang (21) found that 57% of the patients had occult blood in stool and 29% with eosinophilia. In addition, Concha and Cabalin (22) reported 84% of infants with occult blood in stool. However, Lozinsky and Morais (23) documented 43.8% of infants with eosinophilia.

CMPA is a major health problem that affects the growth and nutritional status of infants. Definitive diagnosis of CMA is challenging. Therefore, growth flattering, iron deficiency anaemia and hypoalbuminemia may represent red flags for a paediatrician to investigate the possibility of CMP as a cause.
5. CONCLUSION

Growth faltering and nutritional problems are major concerns in infants with CMA. Proper management of infants with CMA, including specialist dietetic advice and regular growth monitoring, is mandatory to avoid these concerns. When evaluating an infant with flattering growth, iron deficiency anaemia and/or hypoalbuminemia physicians should include in their evaluation extensive search for CMA.

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