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

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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 flatteringgrowth.
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) IgEforCow'sMilkprotein(CMP)forallpatients.Thegrowthandnutritionalstatusofthepatients wasassessedbasedon World Health Organization (WHO) growth charts and growth z-scores for weight-for-age, weight-for-height and height-for-age, in addition to laboratoryinvestigations.
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%)werediagnosedasImmediateIgEmediatedCMAwhiletheother63infants(87.5 %)wereconsidered delayed non-IgE mediated CMA. Twenty-five infant 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.

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Conclusion:Growthfalteringandnutritionalproblemsaremajorconcernsininfantswith CMA. Propermanagement 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 forCMA.

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 ~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).**

Forclinicalpractice,diagnosisofCMAisachallengingprocessthatrequiresintegrationofmedicalhistory andfoodchallengeprocedure,inadditiontolaboratorytests.Positiveskinpricktestand/orelevatedspecific IgEtoCow'sMilkProtein(CMP)areusefuldiagnostictestsindicatingsensitizationtoCMPandanon going 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 Helniski.

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 investigationsperformedincludedCompleteBloodPicture(CBC)withdifferentiationWBCs,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 usingcow'smilkallergenextract.Histaminedihydrochlorideandsalinesolutionswereusedaspositi veand negativecontrols,respectively.Thediametersofthewhealreactionsweredeterminedafter15minute s.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

Dataweretestedfornormaldistributionusingtheshapirowalktest.Qualitativedatawererepre sented asfrequenciesandrelativepercentages.Chisquaretest($\chi 2$)andfisherexactwasusedtocalculatediffe rence 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 mannwhitney 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 levelofp-value$\leq$0.05indicatessignificant,p<0.001indicateshighlysignificantdifferencewhile,p>0.05 indicates non-significantdifference.

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 familyhistoryoffoodallergy.Wealsofoundthat58.3%ofthemwerefromurbanareaswhile41.7%w ere from rural areas. (Table1)

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,while76.4%hadCutaneoussymptoms(Itching,flushingskinrashand/orswellingofthelips,f ace),
47.2 % of infants had respiratory symptoms (Cough and/or wheezing) and 1.4 % had anaphylaxis. (Table 3)

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In our study, 34.7% of infants suffer from faltering of growth in which 20.8% of infants had z score
<-2SDasregardweightforage,(9.7%)and(4.3%)hadzscore<-
2SDasregardheightforageandweight for height respectively. (Table4)

Regarding laboratory investigations, we found slight elevation in total leucocytic count with mean
9.57 ± 1.69 x10^3/µL and 30.5% on infants had eosinophilia. 37.5% of patients were positive for occult bloodinstooland36.2%sufferedfromirondeficiencyanemia(IDA)withhaemoglobin11.16±1.53g /dL, while 29.2% of infants showed hypoalbuminemia with serum albumin level (2.9 ±0.177) g/dl. (Table5)

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

		All patients (n=72)
Age (months) **Mean ± SD Range**		9.92 ± 5.853 2 – 24
Sex	**Male**	43 (59.7%)
	Female	29 (40.3%)
Positive family history for food allergy		52 (72.2%)
Residence	**Rural**	30 (41.7%)
	Urban	42 (58.3%)

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

All patients = 72	**N (%)**
Immediate IgE mediated CMA	9 (12.5%)
Delayed non-IgE mediated CMA	63 (87.5%)

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Table 3. Distribution of symptoms among CMA patients.

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

Table (4): Anthropometrics of CMA patients

All patients (n=72)	**Z score (Mean ± SD)**	**Deficit Z score< -2 SD**
Weight -for-age (kg)	-0.7 ± 1.33	15 20.8%
Height-for-age(cm)	-0.9 ± 1.82	7 9.7%
Weight-for-height(kg)	-0.4 ± 1.72	3 4.2%

Table 5. Laboratory parameters of CMA patients

Laboratory parameters	**All patients (n=72)**
Haemoglobin(g/dl) Mean ± SD Range	11.16 ± 1.53 8 – 14

TLC (10^3 /μL) Mean ± SD Range	 9.57 ± 1.69 7 – 11.3
Eosinophil count(cells/ul) Mean ± SD Range	 160-780
Eosinophilia	22 (30.5%)
Neutrophil (%) Mean ± SD	 50.06 ± 17.48
PLT (10^3 /μL) Mean ± SD Range	 227.3 ± 59.59 145 – 350
Serum albumin (g/dl) Mean ± SD Range	 2.96 ± 0.177 2.5 – 3.2
Total protein (g/dl) Mean ± SD Range	 7.24 ± 0.773 6 – 8.5
Positive occult blood in stool	27 (37.5%)
Iron deficiency anaemia	26 (36.2%)

4. DISCUSSION

CMA is the most common food allergy found in children under 3 years of age. It is defined as a reproducibleadversereactiontooneormoremilkproteinsmediatedbyoneormoreimmunemechanisms**. (6)**

Inthepresentstudy,weincluded72infantswithCMAconfirmedbyoralchallengeprocedure,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 ofCMPA.

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 dominationofmalegenderthan femaleby56/44%amongCMPAchildren.Thiscommonfindingtogether 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)** documentedthatmostoftheirpatientswereurban.Thiscouldbeexplainedbyadecreaseinbreastfeeding and an increased feeding with cow's milk-based formulas in urbanareas.

In addition, we found that 72% of the patients had positive family history for food allergy. **Hossny 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 presentationintoimmediateIgEmediatedallergyanddelayednon-IgEmediatedallergy**(2).**Weperformed 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 to2hourafteroralchallengetestand9patientsoutof72(12.5%)wereconsideredtohaveimmediateIgE mediatedCMA.

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 clinicalpresentationsandthelackofdefinitivelaboratorybiomarkersforCMA,speciallydelayednon-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 hypothesizedthatCMAcanleadtogrowthflatteringornutritionalproblemsandtriedtotestthishypothesis by clinical and laboratorymeasures.

In our study, 34.7% of case had flattering growth. Faltering growth (previously known as failure to thrive[FTT])isconsideredwhenthereisadropinweightof>1SDinweight-for-ageorweight-for-height growthcurveinthepast3monthsinachild<1yearofage,orthedownwardcrossingof2centilesifcentile 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 < -2SDrespectively.

The concern about growth in CMA was raised more than 20years 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 milkallergicinfantscomparedtohealthycontrols.Subsequently,severalotherstudieshavebeenpublished 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 infantshadWt/Htzscore<-2SD.Thisstudyshowspredominanceinweight-for-agedeficitasinourstudy.

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/Htz score< -2 SD respectively.

Weight usually declines from the baseline percentile before length does when Flattering growth is duetonutritionalinsufficiency.WhilelineargrowthdeclinesisrelatedtotheeffectofCMPonInsulin-like growth factor 1 and insulin**(17).**
Inourstudy,thelaboratoryfindingofstudiedgroupshowlowlevelofhaemoglobinwithmean(11.16 ± 1.53) g/dl and 36.1% of infants suffer from iron deficiency anaemia. This may be explained by occult bloodlossinstoolwhichwasdetectedin37%ofourcasesduetoinflammationofthegastrointestinaltract. In addition, anemia 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. Hypo albumenia 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)** reported84%ofinfantswithoccultbloodinstool.However**,LozinskyandMorais(23)** documented 43.8% of infants with esinophilia.

CMPA is a major health problem that affect the growth and nutritional status of infants. Definitive diagnosis of CMA is challenging. Therefore, growth flattering, iron deficiency anemia and hypoalbumineamia 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 flatteringgrowth, iron deficiency anaemia and/ or hypoalbuminemia physicians should include in their evaluation extensive search forCMA.

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