

Growth Pattern Investigation in Cow's Milk Allergic Proctocolitis in Those Who are Under Elimination Diet

Mohadese Khakpour¹, *Nasrin Moazzen², Ali Khakshour¹, Samaneh Norouzi Asl³, Saeedeh Talebi⁴, Hamidreza Kianifar⁵

¹Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran. ²Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. ³Department of Pediatric Endocrinology, Mashhad University of medical sciences, Mashhad, Iran. ⁴Clinical Research Development Unit of Akbar Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ⁵Department of Pediatric Gastroenterology, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background

Cow's milk allergy is one of most prevalent food allergies worldwide. Due to elimination diet it can impair growth in infants. In this study we evaluate growth disorders in Non-immunoglobulin E mediated cow's milk allergy named allergic proctocolitis.

Materials and Methods: Forty-nine patients were included in this longitudinal study. The study was launched from February 2018 to February 2019 in Akbar hospital, Mashhad-Iran. Cow's milk allergy was diagnosed according to the clinical presentation and Challenge test. All participants were breastfed during the course of study. Mothers were received 1000 mg calcium and infants 400 IU Vitamin D daily, as routine. The cow's milk was eliminated from the diet of both mother and infant. Infants were followed up for 9 months with 3 month intervals. Growth patterns were evaluated by measuring height, weight and head circumference z-scores every 3-months. Serum level of Calcium, Vitamin D, PTH and phosphorus were evaluated before and after the follow-up period.

Results: The mean age of the study participants was 4.57 ± 2.41 month. There was a statistical significant difference between weight and height Z score ($p=0.028$) ($p=0.001$), respectively, at baseline and 9 months after treatment. However, no significant difference was found in head circumference Z-score at baseline and 9 months after treatment ($p=0.564$). The increase in Vitamin D and PTH along with the decrease in calcium, phosphorus was significant during the study period ($p<0.01$).

Conclusion

It seems that elimination diet in infants with cow's milk allergy would not suppress growth parameters and might even improve it, especially weight gain.

Key Words: Allergy, Children, Cow's Milk, Growth, Proctocolitis.

*Please cite this article as: Khakpour M, Moazzen N, Khakshour A, Norouzi Asl S, Talebi S, Kianifar H. Growth Pattern Investigation in Cow's Milk Allergic Proctocolitis in Those Who are Under Elimination Diet. Int J Pediatr 2020; 8(11): 12455-460. DOI:10.22038/IJP.2020.47183.3829

*Corresponding Author:

Nasrin Moazzen, MD, Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: moazzenn@mums.ac.ir

Received date: Feb.14, 2020; Accepted date: Jul. 22, 2020

1- INTRODUCTION

In recent decades, prevalence of food allergies is increasing. There is not any accurate estimation of food allergies, maybe because of different diagnostic tools. In the United States, its prevalence rate is 1 -2%, and in some studies, 10% is estimated (1-4). One of the most common food allergies is cow's milk allergy with prevalence rate of 0.1- 4.2% in different countries. Although there is not any unique diagnostic approach (5, 6). Cow's milk allergy (CMA) is defined as an immune mediated reaction to proteins in cow's milk (7). The major allergen of cow's milk is casein that is a potent inducer of allergy. Another allergen is whey that is water soluble, with fast absorption and can produce severe systemic reaction (8). Allergic reaction to these proteins can be induced by direct use of them by infant or sometimes infants are restrictively breast fed but allergen by passing of mother's milk can cause allergy (9).

These allergic reactions are categorized to pure IgE mediated, non-IgE mediated and mixed (IgE and non- IgE) reactions. Therefore, clinical manifestations can be very different. Definite diagnosis can be achieved by double blind placebo controlled food challenge (DBPCFC) (7). In this study we evaluate non-IgE mediated cow's milk allergy named allergic proctocolitis. This food allergy usually occurs in young infants that are frequently breast fed. They have blood-streaked stools or sometimes only have hem-positive stool. Otherwise they appear healthy. Most common food proteins that are implicated in proctocolitis are cow's milk and soy. Forty percent of patients have hypersensitivity reaction to both cow's milk and soy. Diagnosis is made by disappearance of clinical manifestation after 72 hours of elimination of cow's milk in infant and his/her mother's diet (10). According to national protocol every infant aged below 2 years old, should

receive 400 IU vitamin D every day. But due to the restriction of milk in these allergic infants, they may be susceptible to calcium and Vitamin D deficiency and then rickets and growth retardation may occur (11). The aim of this study is investigation of growth parameters in infant with proctocolitis induced by cow's milk who have restriction of milk and dairy product in their diet, but are administered vitamin D supplement as routine.

2- MATERIALS AND METHODS

In this longitudinal study from February 2018 to February 2019, forty-nine infants aged between 1-12 months with cow's milk allergy referring to Akbar pediatrics gastroenterology clinic were enrolled. CMA was diagnosed according to the clinical presentation and Challenge test (10). Their diagnosis was confirmed by pediatric gastroenterologist and after resolution of clinical manifestation with 72 hours' elimination of cow's milk. Children with multiple food hypersensitivities and those with corticosteroid use during the study were excluded. All participants were breastfed during the course of study. Mothers and infants received 1000 mg calcium and 400IU Vitamin D daily (based on national protocol), respectively.

The cow's milk was eliminated from the diet of both mother and infant. Infants were followed up for 9 months with 3 month intervals. Growth patterns were evaluated by measuring height, weight and head circumference z-scores every 3 months by just one person that was a pediatrician. For each infant, weight measurements with Seca weight scaler, height measurement with Seca infantometer and head circumflex measurement with non-flexible meter were done three times. The formula used for calculating z-score: $Z = (x-\mu)/\sigma$, where x is the raw score, μ is the population mean, and σ is the population standard deviation.

Five-milliliter blood was collected from each infant and Serum level of Calcium, Vitamin D, PTH and phosphorus were evaluated before and after the follow up period in reference laboratory. Normal ranges of the above-mentioned parameters are in **Table.1**.

Table 1: Normal range of evaluated parameters (10).

Parameters	Normal range
Z-score	<-2: abnormal -2 to +2: normal ≥ +2: abnormal
Calcium (mg/dl)	8.6-10.3
Phosphor (mg/dl)	4-7
Alkaline phosphatase (mg/dl)	80-1200
Vitamin D3 (mg/dl)	Deficiency: 0-10 Insufficient: 10-30 Sufficient: 30-150 Toxic: more than 150
Parathyroid hormone (mg/dl)	14.5-87

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences and an informed consent was obtained from each participant prior to study entrance (Code:

IR.mums.fm.REC.1395.471). Statistical analysis was performed by the statistical package for social sciences (SPSS) software version 16.0 (IBM Inc., Chicago, IL, USA). The quantitative variables were checked for normal distribution using WHO growth charts (Kolmogrof-Smironove). Weight, height and head circumference were described using mean, standard deviation (SD), median and first and third quartiles. Categorical data were presented as frequency and percentage. Paired sample T-test was used to compare quantitative variables at first and third visits. The trend of changes was analyzed by repeated measures ANOVA. All tests were two-tailed and significance level was set at $P < 0.05$.

3- RESULTS

Forty-nine participants with mean age of 4.53 ± 2.39 months were enrolled the study. There were 27 female (55%) infants. Weight, height and head circumflex Z-score before and after study are reported in **Table.2**.

Table-2: Changes in weight, height and head circumference before and after nine months follow-up.

Variables	Baseline treatment	9 th month	Change	P-value
Weight Z- score	-0.08 ± 0.68 (0.0, -0.5 – 0.5)	0.42 ± 0.80 (0.3, 0.0 – 1.1)	0.51 ± 0.92	0.028
Height Z- score	0.50 ± 0.89 (0.4, -0.35 – 1.0)	-0.54 ± 0.84 (-0.4, -1.2 – 0.1)	-1.04 ± 1.18	0.001
Head circumflex Z- score	0.05 ± 1.10 (0.0, -0.8 – 0.4)	-0.09 ± 0.82 (-0.1, -0.6 – 0.2)	-0.14 ± 1.10	0.564

Data is represented as mean \pm standard deviation (median, 1st quartile, 3rd quartile).

With paired t-test, there was a statistical significant difference between weight Z-score ($p=0.028$), and height Z-score ($p=0.001$), at baseline and 9 months after treatment. However, no significant difference was found in head circumference Z-score at baseline and 9 months after treatment ($p=0.564$). With

repeated measure ANOVA test, weight Z-score changes in four time points had a statistical significant increasing trend ($p=0.022$), height Z-score had a statistical significant decreasing trend ($p=0.002$). However, head circumference had a relatively steady pattern ($p=0.069$) (**Figure.1**).

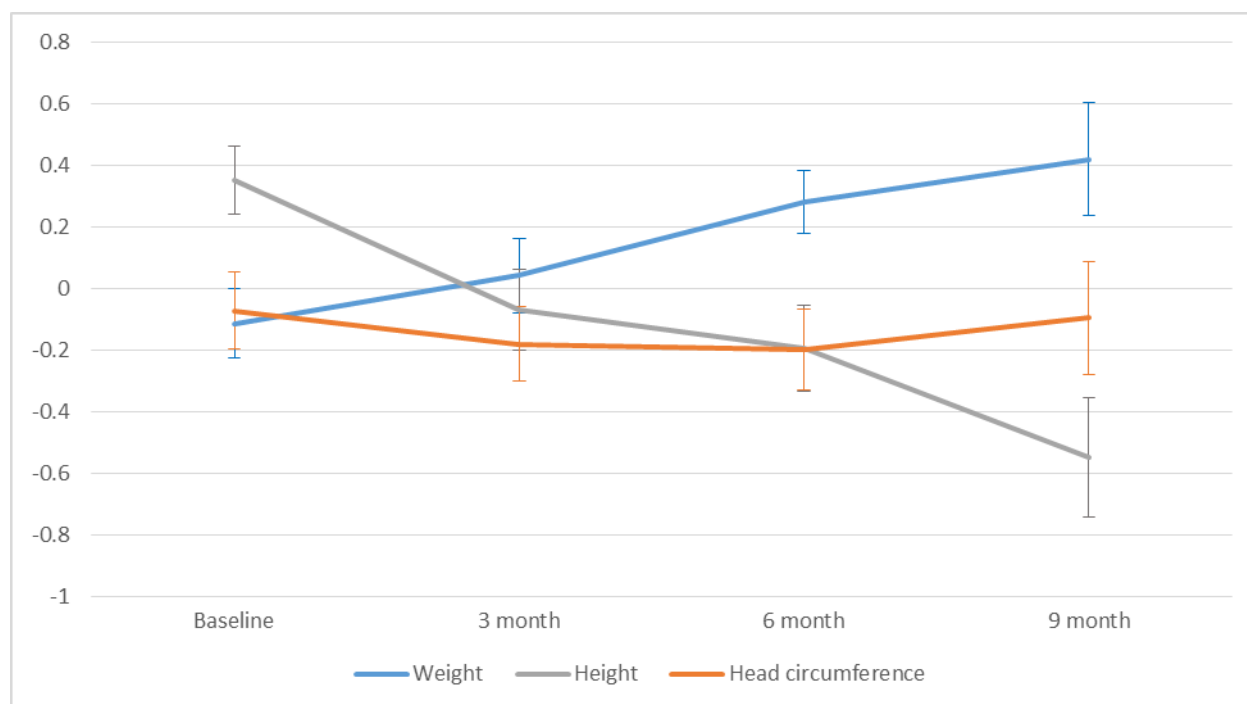


Fig.1: The trend of growth parameters during a 9 month follow up (Error bar=1 SE).

These laboratory data were measured at time of enrollment in the study, and after nine months of supplement intake, and then compared with paired sample T-test,

the increase in Vitamin D and PTH alongside with the decrease in calcium, phosphorus was significant during the study period (**Table.3**).

Table-3: Laboratory data comparison before and after treatment.

Parameters	Baseline treatment	9 th Month	P-value
Calcium (mg/dl)	9.80 ±0.59	9.54 ±0.60	0.003
Phosphor (mg/dl)	5.17 ±0.53	4.84 ±0.39	<0.001
Alkaline phosphatase (mg/dl)	493.69 ±268.02	511.35 ±202.20	0.524
Vitamin D (mg/dl)	33.02 ±15.61	37.14 ±13.06	0.020
Parathyroid hormone (mg/dl)	24.87±12.17	26.75 ±10.39	0.010

Data represented as mean ± standard deviation.

4- DISCUSSION

Prevalence of allergic diseases, especially food allergies, is increasing worldwide. There is some concern about their impact on normal growth. Cow's milk allergy induced proctocolitis usually occurs in otherwise healthy infants and without growth abnormalities (10, 12, 13). However, due to elimination diet there is

some concern about weight gain and other growth parameters. Here we investigate growth pattern in infants who are under cow's milk elimination diet because of proctocolitis. In our study, mean age of participants was 4.53±2.39 months, there was a statistical significant difference between weight Z-score (p=0.028), and height Z-score (p=0.001), at baseline and 9 months after treatment. However, no

significant difference was found between head circumflex Z-score at baseline and 9 months after treatment ($p = 0.564$). With repeated measure ANOVA test, weight Z-score changes in four time points had a statistical significant increasing trend ($p = 0.022$), height z score had a statistical significant decreasing trend ($p = 0.002$). However, head circumference had a relatively steady pattern ($p = 0.069$) (Figure.1). Decreasing pattern of height in this study is probably due to genetics, constitutional short statures are presented after 6 months. Effect of nutrition on height decreases with increase in age and genetic background becomes prominent. In Camargo et al.'s study performed in Brazil, forty-four infants with allergic proctocolitis were enrolled the study. Patients have received two therapeutic diets, one group exclusive breastfeeding with elimination of six allergens from their mother's diet, and the other only used hypo allergic formula without breastfeeding. Infants were followed for six months and the study revealed that anthropometric evaluation were normal in both groups (14).

In agreement with this study, monitoring of weight Z-score of our patients did not show any impairment and even there was significant improvement after restricted diet and supplement therapy. In another study that was performed in Italy by Diaferio et al., the aim of study was evaluation of cow' milk hypersensitivity in infants with failure to thrive (FTT) and growth catch up after elimination of cow's milk from diet. Forty-three infants were enrolled in the study, 23% were diagnosed to have gastroesophageal reflux disease (GERD), and the others (77%) presented with cow's milk allergy disorders. Ninety-three percent of the former group had manifestation of non IgE-mediated cow's milk allergy and after four to eight weeks of elimination diet their growth percentiles increased (15). The results of this study are

in agreement with our data and both show that elimination diet in infant with non IgE-mediated cow's milk allergy like proctocolitis can improve growth pattern. The increase in Vitamin D and PTH along with the decrease in calcium, phosphorus was significant during our study period (Table 3). In one study by Ercan et al. in Turkey, among fifty-six cow's milk allergic children < 2 years old, there was no statistically significant difference between their vitamin D level and that of healthy infants (16). In Paganus et al.'s study in 1992, nineteen children (range 0.64-4.1 years) with cow's milk allergy were followed during their elimination diet for nine months, and growth parameters and nutritional indices like calcium and vitamin status were monitored. Although all of them had some other food allergies. During the study, calcium supplement was given to them. Height monitoring remained relatively steady, but weight decreased significantly. Two of the children had high alkaline phosphatase serum level. However, there was no correlation between nutritional status and dietary intake (17). Decreasing status of their weight gain is not consistent with our result, however, it may be because of multiple food allergies in the Paganus study participants.

4-1. Study Limitations

It seems that vitamin D supplement in cow's allergic infants could be helpful in weight gain, although if there was a control group of healthy infants, the results would be more reliable.

5- CONCLUSION

Based on this study, authors conclude that elimination diet in infants with cow's milk allergy does not induce growth abnormality and even it can improve growth parameters especially weight gain.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

The authors thank Majid Khadem Rezaiyan and Zahra Abbasi Shaye for their help with the statistical analysis.

8- REFERENCES

1. Dunlop, J.H. and C.A. Keet, Epidemiology of food allergy. *Immunology and Allergy Clinics*, 2018. 38(1): 13-25.
2. Sicherer, S.H. and H.A. Sampson, Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *Journal of Allergy and Clinical Immunology*, 2014. 133(2): 291-307. e5.
3. Ataee P, Zoghali M, Nikkhoo B, Ghaderi E, Mansouri M, et al. Diagnostic Value of Fecal Calprotectin in Response to Mother's Diet in Breast-Fed Infants with Cow's Milk Allergy Colitis, *Iran J Pediatr*. 2018 ; 28(4):e66172. doi: 10.5812/ijp.66172.
4. Flom, J.D, S.H. Sicherer, Epidemiology of Cow's Milk Allergy. *Nutrients*, 2019; 11(5): 1051.
5. Ahanchian H, Nouri Z, Jafari SA, Moghiman T, Amirian MH, Ezzati A, et al.. Synbiotics in children with cow's milk allergy: a randomized controlled trial. *Iranian journal of pediatrics*, 2014; 24(1): 29.
6. Sackesen C, Assa'ad A, Baena-Cagnani C, Ebisawa M, Fiocchi A, Heine RG, Von Berg A, Kalayci O. Cow's milk allergy as a global challenge. *Curr Opin Allergy Clin Immunol*. 2011 Jun;11(3):243-8. doi: 10.1097/ACI.0b013e328346566f.
7. Flom, J.D. and S.H. Sicherer, Epidemiology of Cow's Milk Allergy. *Nutrients*, 2019. 11(5).
8. O'Hehir, R.E., S.T. Holgate, and A. Sheikh, *Middleton's Allergy Essentials E-Book*. 2015: Elsevier Health Sciences.
9. Järvinen, K.M., H. Suomalainen, Development of cow's milk allergy in breast-fed infants. *Clinical & Experimental Allergy*, 2001; 31(7): 978-87.
10. Kliegman, R., Nelson W. Nelson textbook of pediatrics. 2016, Philadelphia: Elsevier Saunders.
11. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C. Peak bone mass. *Osteoporos Int*. 2000;11(12):985-1009. doi: 10.1007/s001980070020. PMID: 11256898.
12. Burks, A.W., et al., *Middleton's Allergy E-Book: Principles and Practice*. 2019: Elsevier Health Sciences. eBook ISBN: 9780323546980
13. Moazzen, N., Ahanchian, H., Jabbari Azad, F., Mohammadi, M., Farid, R., Nikpoor, A., Salehi, M., Khoshkhui, M. Subcutaneous Immunotherapy and Synbiotic Combination Shift T-Helper 1 and Cytotoxic T Cells in Allergic Rhinitis. *International Journal of Pediatrics*, 2020; 8(1): 10731-742. doi: 10.22038/ijp.2019.14040
14. Camargo, L.S., Et Al., Allergic Proctocolitis in Infants: analysis of the evolution of the nutritional status. *Arquivos de gastroenterologia*, 2016; 53(4): 262-66.
15. Diaferio, L., et al., May Failure to Thrive in Infants Be a Clinical Marker for the Early Diagnosis of Cow's Milk Allergy? *Nutrients*, 2020; 12(2): 466.
16. Ercan N, Bostanci İB, Ozmen S, Tekindal MA. Is there an association between vitamin D levels and cow's milk protein allergy at infancy? *Arch Argent Pediatr*. 2019 Oct 1;117(5):306-313. English, Spanish.
17. Paganus, A., K. Juntunen-Backman, and E. Savilahti, Follow-up of nutritional status and dietary survey in children with cow's milk allergy. *Acta Paediatr*, 1992; 81(6-7): 518-21.