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Original Article

# Cow milk protein allergy: clinical phenotype and risk factors

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## ABSTRACT

Our study aimed to analyze the clinical data of a cohort of Egyptian children with cow's milk protein allergy (CMPA) to explore the epidemiological, clinical characteristics, and risk factors of CMPA. A prospective, multi-center observational cross-sectional study was conducted by assessing the clinical data of infants with CMPA. A total of 317 infants met inclusion criteria, including 175 males (55.2%); the mean age at presentation was 4.2 ± 3.2 months. In our series, artificial feeding was found in 48% of patients, breastfeeding in 22.7%, and 29.3% of infants were mixed fed. 83.6% of patients with CMPA have mild to moderate disease, and 16.4% have severe disease. The most prevalent symptoms were mainly of gastrointestinal tract (GIT) origin, which include diarrhea (57.7%), hematochezia (39.7%), vomiting (30%), and constipation (5%). Skin manifestations included eczema (25.8%) and urticarial (8.2%). Chest wheezes and oral allergy syndrome were found in 7.9% and 4.4%, respectively. Family history of atopy and parent's and/or sibling's allergy were found in 60.5% and 27.7%, respectively. Finally, failure to thrive was found in 22.4% of our patients. The multivariate logistic regression analysis of risk factors for CMPA showed that parent's food allergy ($p < 0.001$), cesarean section ($p < 0.01$), and the use of weaning food before four months of age ($p = 0.02$) were independent risk factors for CMPA. On the other hand, exclusive breastfeeding ($p = 0.001$) and weaning food after six months ($p = 0.03$) were protective factors for CMPA. Gastrointestinal symptoms were the main manifestations of CMPA. The incidence of malnutrition, anemia, low total protein, and hypoalbuminemia was significantly higher in children with severe CMPA. In our locality, the history of parent's food allergy, cesarean section, and the use of weaning food before four months of age were independent risk factors for CMPA. On the other hand, exclusive breastfeeding and weaning food after six months were protective factors for CMPA.

**KEYWORDS:** cow milk, protein, allergy, infants, gastrointestinal symptoms.

## INTRODUCTION

Cow's milk protein allergy (CMPA) is the most common food allergy of children, affecting 2-6% of infants [1]. It results from an immunological reaction to one or more milk proteins. It can be divided into three types: immunoglobulin E (IgE)-mediated, non-IgE-mediated, and mixed-mediated with the involvement of two systems [2, 3]. CMPA reactions have a rapid onset in IgE-mediated, where manifestations may occur within hours, and slow

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onset in non-IgE mediated, where symptoms take days to present [4]. It is well established that a food allergy is a global health problem that significantly reduces the quality of life, not just for children but for the entire family. Everything becomes more difficult with a food allergy. There are also significant costs related to food allergy management [3]. Also, there are multiple concerns regarding dietary sufficiency, the increased prevalence in difficult feeding behaviors, and, for IgE-mediated allergy, the constant fear of anaphylaxis, which can be fatal [4]. Typically, CMPA starts within the first three months of life and usually before six months. The manifestations appear a few days or weeks after cow's milk ingestion. The symptoms can vary from mild GIT problems to life-threatening anaphylaxis [5]. CMPA clinical manifestations are complex and diverse, mainly involving the GIT, cardiovascular and respiratory tracts, and skin. The clinical manifestations of CMPA with gastrointestinal symptoms as the primary manifestation lack specificity and are easy to be misdiagnosed and mistreated [5-7]. It is difficult to detect the exact prevalence of cow's milk allergy due to a lack of precise diagnostic criteria [8]. Our study aimed to analyze the clinical data of 307 Egyptian children with CMPA to explore the epidemiological and clinical characteristics of CMPA and assess the risk factors.

## PATIENTS AND METHODS

The Ethical Scientific Committee at Assiut University Hospital, Assiut, Egypt approved this study. It was conducted following the code of Ethics of the Declaration of Helsinki for humans' experiments. Caregivers of all the participants gave their informed written consent under Ethical Committee guidelines (Assiut University, Egypt). The study was conducted in three tertiary Hospitals from June 2014 to May 2019.

### Patients

The prospective, multi-center cross-sectional, observational study included all CMPA infants attending pediatrics outpatient clinics at three tertiary hospitals in Egypt. We excluded any patients with one or more of the following diseases: immunodeficiency diseases, genetic and metabolic diseases, chronic renal, hepatic, and cardiac diseases. Besides, we excluded children with organic and chronic GIT diseases such as inflammatory bowel disease, gastroesophageal reflux disease, lactose intolerance, and obstructive GIT lesions.

### Methods

### Clinical assessment

Detailed medical history and physical examination were made for all patients, including the personal and family history of allergic diseases and a list of any suspected foods. Medical history, including demographic, anthropometric data (weight, length, and BMI), details of feeding history, and pregnancy are reported.

We registered all manifestations of CMPA, including rapid onset manifestation, e.g., flushing, hives (urticaria), angioedema, wheezy chest, laryngeal edema, itching, cough, dyspnea, and anaphylactic reactions. Besides, we reported other systematic manifestations, including abdominal pain, vomiting, diarrhea, colic, constipation, and hematochezia.

There is no specific test to detect CMPA. The diagnosis is primarily dependent on infants' diagnostic protocol for suspected cow's milk allergy [9-11]. The diagnostic criteria for CMPA in our cohort depended on the following:

1. Skin prick test: The extract of cow's milk allergen was prepared from lyophilized milk plus lyophilized solution containing 50% glycerin and 5% NaCl as previously described [12-14]. One drop of this extract was applied to the infant's forearm with saline and Histamine diphosphate solutions as controls. We estimated the diameters of all wheal reactions after 15-20 minutes. All skin tests were done using a single-blind method. We used a wheal diameter of <3 mm for negative cases and ≥ 8mm for confirming the diagnosis [12-14].
2. Serum-specific IgE to CMPA: Specific IgE antibody titers for cow's milk were analyzed in all patients' serum samples. We used fluorescence enzyme immunoassay (CAP system, Uppsala, Sweden). Infants with specific IgE levels of more than 0.35 kU/L were considered positively sensitized [14].
3. Diet elimination: If CMPA was suspected, the infant received a cow's milk-free diet for one month. If symptoms are resolved, an oral food challenge is used to confirm the diagnosis.

4. Iron deficiency anemia: Initially evaluated by Complete blood count using an automated cell counter (automated ABX Pentra XL80 HORIBA ABX-France).
5. Biochemical markers: serum iron, total iron-binding capacity (TIBC), total serum proteins, and serum albumin were determined using COBAS C 311; serum ferritin was evaluated by enzyme-linked immunosorbent assay (ELISA) (Bio Check USA). Fecal occult blood test was done for all patients. The previous investigations were done to evaluate the complications of CMPA.

According to [15], patients with CMPA are categorized into two classes: severe CMPA and mild-moderate CMPA. Severe CMPA included patients presenting with one or more of the following:

i) GIT manifestations: failure to thrive due to chronic diarrhea and/or regurgitation, vomiting and/or food refusal.
ii) Iron deficiency anemia/pallor due to occult or macroscopic blood loss "blood-streaked stool".
iii) Protein-losing enteropathy and hypoalbuminemia.
iv) Dermatological manifestations: severe or exudative atopic dermatitis associated with hypoalbuminemia-anemia or iron deficiency anemia and failure to thrive,
v) Respiratory manifestations: laryngoedema or bronchospasm with dyspnea
vi) Systemic manifestations with anaphylactic shock.

Children who do not meet the above conditions were classified as mild to moderate CMPA [15].

### Statistical analysis

Data analysis was done by SPSS version 22. We used independent sample T-test and Chi-square test for evaluation of statistical difference between groups. Finally, a multi-factor logistic regression analysis was done to recognize the statistically significant risk factors associated with CMPA. A p-value of $\leq 0.05$ was considered significant.

## RESULTS

Table 1 shows all demographic data of CMPA patients in our study. A total of 317 infants met the inclusion criteria, including 175 males (55.2%); the mean age at presentation was 4.2 ± 3.2 months. In our series, artificial feeding was found in 48% of CMPA cases, breastfeeding in 22.7%, and 29.3% of patients were mixed fed. 83.6% of patients with CMPA have mild to moderate disease, and 16.4% have severe disease. Table 1 also shows the mode of delivery among all patients. All clinical manifestations of CMPA are listed in Table 1. The most prevalent symptoms were mainly of GIT origin, which includes diarrhea (57.7%), hematochezia (39.7%), vomiting (30%), food refusal (21.5%), and constipation (5%). Skin manifestations included eczema (25.8%) and urticarial (8.2%). Chest wheezes and oral allergy syndrome were found in 7.9% and 4.4%, respectively. Family history of atopy and parents and/or sibling's allergy were found in 60.5% and 27.7%, respectively. Finally, failure to thrive was found in 22.4% of our patients. Table 2 shows a comparison between different CMPA classes. The incidence of malnutrition, anemia, low total protein, and hypoalbuminemia was significantly higher in children with severe CMPA. Table 3 shows the multivariate logistic regression analysis of risk factors for CMPA. Parent's food allergy (OR = 8.81, 95% CI:4.48~20.89, $p < 0.001$), cesarean section (OR = 6.36, 95% CI:2.64~14.32, $p < 0.01$), and the use of weaning food before four months of age (OR = 1.66, 95% CI:1.49~9.77, $p = 0.02$) were independent risk factors for CMPA. On the other hand, exclusive breastfeeding (OR = -2.09, 95% CI:0.08~0.58, $p = 0.001$) and weaning food after six months (OR = -0.98, 95% CI:0.07~0.71, $p = 0.03$) were protective factors for CMPA.

## DISCUSSION

Over the past 20 years, the prevalence of food allergy has risen substantially to be one of the most critical health problems worldwide [16]. CMPA is the most common type of food allergy in infants and young children. This may be attributed to the increased use of infant formulae and early weaning food containing dairy products during early infancy [16]. Expanding rates of cesarean sections may also contribute to the global increase in the incidence of CMPA [1, 16]. CMPA usually affects multiple systems, with a wide range of manifestations. In our study, GIT manifestations were the most prevalent in infants with CMPA. The frequency of diarrhea was 57.7%, bloody stool (39.7%), vomiting (30%),

**Table 1.** Demographic data of all CMPA patients.

| **Parameter** | **(N = 317)** |
|---|---|
| • Sex: Male (N, %) | 175/55.2 |
| • Weight (mean ± SD, kg) | 6.1 ± 2.3 |
| • Age at presentation | |
| Range, month | 1-11 |
| Mean ± SD, month | 4.2 ± 1.7 |
| • Type of feeding | |
| Formula feeding (N, %) | 152 (48) |
| Mixed feeding (N, %) | 93 (29.3) |
| Breastfeeding (N, %) | 72 (22.7) |
| • Mode of delivery | |
| Vaginal delivery (N, %) | 174 (54.9) |
| Cesarean section (N, %) | 143 (45.1) |
| • Age of weaning foods | |
| Range, month | 3-10 |
| Mean ± SD, month | 5.7 ± 1.33 |
| • Clinical characteristics (N, %) | |
| Eczema | 82 (25.8) |
| Urticaria | 26 (8.2) |
| Oral allergy syndrome | 14 (4.4) |
| Wheezy chest | 25 (7.9) |
| Hematochezia | 126 (39.7) |
| Diarrhea | 183 (57.7) |
| Vomiting/ excessive reguirge | 95 (30) |
| Constipation | 16 (5) |
| Food refusal | 68 (21.5) |
| Failure to thrive | 71 (22.4) |
| • Classification (N, %) | |
| Mild/ moderate | 265 (83.6) |
| Severe | 52 (16.4) |
| • Family history of atopy (N, %) | 192 (60.5) |
| • Allergic disease in parents and or siblings (N, %) | 88 (27.7) |

and constipation (5%). A previous large study [17] reported skin reactions in 94% of infants with CMPA, followed by GIT symptoms in 33% and respiratory manifestation in 8%. Severe manifestations affected 32% of cases [17]. Furthermore, our results and a recent study [18] have comparable results. In our study, severe CMPA was found in 52 patients (16.4%). Failure to thrive, anemia, hypoproteinemia, and hypoalbuminemia were significantly higher in the severely allergic group. Other studies showed severe CMPA in 7.9% [18] and 11.4% [19] of their cohorts. This may be due to the difference between our patients' age groups and different ethnicity. Previous studies have pointed out that the probability of severe food allergies may increase gradually with age [19, 20]; however, we couldn't prove that in our study.

**Table 2.** Comparison between different CMPA classes.

| Parameter | Severe (*n* = 52) | Mild/ moderate (*n* =265) | p-value |
|---|---|---|---|
| • Sex: Male (N, %) | 28 (53.8) | 147 (55.5) | NS |
| • Preterm (N, %) | 8 (15.4) | 12 (4.5) | <0.05 |
| • Full-term (N, %) | 44 (84.6) | 253 (95.5) | <0.05 |
| • Mechanism of CMPA (N, %) | | | |
| IgE-mediated | 41(78.8) | 110 (41.5) | 0.02 |
| Non IgE-Mediated | 4 (7.7) | 126(47.5) | 0.01 |
| Mixed | 7 (13.5) | 29 (11) | NS |
| • Anemia (N, %) | 37 (71.1) | 18 (6.8) | <0.001 |
| • Failure to thrive (N, %) | 23 (44.2) | 33 (12.5) | <0.001 |
| • Low total protein (N, %) | 12 (23) | 6 (2.2) | <0.0001 |
| • Low albumin (N, %) | 22 (42.3) | 31 (11.7) | <0.001 |
| • Family history of atopy (N, %) | 33 (63.4) | 159 (60) | NS |
| • Allergic disease in parents and or siblings (N, %) | 15 (28.8) | 73 (27.5) | NS |

**Table 3.** Multivariate logistic regression analysis of the associated risk factors for CMPA.

| Risk factor | ß | OR | 95%CI | p-value |
|---|---|---|---|---|
| • **Parent's food allergy** | 0.78 | 8.81 | 4.48~20.89 | <0.001* |
| • **Cesarean section** | 2.30 | 6.36 | 2.64~14.32 | 0.01* |
| • **Exclusive breastfeeding**** | -2.09 | 0.32 | 0.08~0.58 | 0.001* |
| • **Mixed feeding**** | -0.55 | 0.69 | 0.26~1.48 | 0.32 |
| • **Weaning food > 6 months***** | -0.98 | 0.30 | 0.07~0.71 | 0.03* |
| • **Weaning food < 4 months***** | 1.66 | 5.31 | 1.49~9.77 | 0.02* |
| • **Constant** | -1.002 | 0.35 | -- | 0.09 |

*Significant, **Artificial feeding as a reference, ***4-6 months of age as a reference.

At present, the risk factors of CMPA are not fully understood. With the continuous in-depth studying of CMPA risk factors and epidemiological investigation, it has been found that a single factor cannot explain the exact cause of CMPA. However, it may be the result of a combination of multiple factors [21]. Our study used a multivariate logistic regression analysis to assess the possible risk factors for CMPA. We found that parent's food allergy is a risk factor for infants to develop CMPA. Studies have shown that family history, especially first-degree relatives of children with food allergies, is a risk for CMPA in more than 80% of cases. The correlation between mother's food allergies and baby food allergies is more robust [21-24]. Therefore, parent's history of food allergy is one of the most critical risk factors for CMPA [25].

The multivariate logistic regression analysis of this study found that exclusive breastfeeding can reduce the risk of CMPA. Our findings agreed with previous research [26], which reported that the risk of CMPA in cow milk formula-fed infants is four times higher than exclusive breastfeeding. Breastfeeding reduces CMPA by promoting the infant's GIT mucosal maturation, healthy development of the intestinal flora, immune regulation, and anti-inflammatory effects. Besides, Secretory

immunoglobulin A (sIgA) in breast milk exert a protective effect on the infant's intestines by preventing the penetration of potential allergens such as foreign proteins [27]. Other researchers [24] found that the longer the duration of breastfeeding, the lower the incidence of CMPA. Community health providers and nurses have an essential role in raising awareness about the benefits of exclusive breastfeeding in the first six months, using mass media, encouraging this practice, discouraging artificial feeding, and early introducing solid foods that are more likely to cause CMPA [27, 28].

Our findings showed that the early introduction of complementary foods before four months of age had a higher risk of CMPA. Our results were in line with previous studies [21, 29, 30]. This may be due to premature exposure to allergens, which disrupted the balance of intestinal mucosal cell transport. Also, the gut has increased permeability at this age, and the gastrointestinal colonization is not developed, resulting in an increased risk of CMPA. Therefore, most international guidelines for infant feeding suggest delaying the introduction of complementary foods (after four months of age) [31, 32].

Cesarean delivery was another significant risk factor linked to CMPA. Our results were in line with previous studies [21, 32]. However, this point has conflicting results [33-35].

Better awareness of the epidemiological risk factor linked to CMPA will guide pediatricians and community health efforts for the promotion of breastfeeding, early diagnosis, and prevention of short- and long-term complications of CMPA. The community health worker performs a key role in successful breastfeeding. They are the healthcare professionals next to mothers, working as an integrating link between healthcare staff and the community. Application of public health education campaigns encouraging young women to breastfeed is needed, especially before delivery, by all primary health care nurses. Furthermore, it is necessary to implement guidelines for avoiding CMPA risk factors, especially in children younger than two years.

## CONCLUSION

Our study showed that gastrointestinal symptoms were the main manifestations of CMPA. The incidence of malnutrition, anemia, low total protein, and hypoalbuminemia was significantly higher in children with severe CMPA. In our locality, the history of parent's food allergy, cesarean section, and the use of weaning food before four months of age were independent risk factors for CMPA. On the other hand, exclusive breastfeeding and weaning food after six months were protective factors for CMPA.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

## REFERENCES

1. Edwards, C. W. and Younus, M. A. 2020, Cow Milk Allergy. In StatPearls. StatPearls Publishing.
2. Carucci, L., Nocerino, R., Paparo, L., Di Scala, C. and Berni Canani, R. 2020, Front Pediatr., 8, 440.
3. Gupta, R., Holdford, D., Bilaver, L., Dyer, A., Holl, J. L. and Meltzer, D. 2013, JAMA pediatrics., 167(11), 1026.
4. Bock, S. A., Muñoz-Furlong, A. and Sampson, H. A. 2001, J. Allergy Clin. Immunol. Pract., 107(1), 191.
5. Caffarelli, C., Baldi, F., Bendandi, B., Calzone, L., Marani, M., Pasquinelli, P. and EWGPAG. 2010, Ital. J. Pediatr., 36, 5.
6. Kansu, A., Yüce, A., Dalgıç, B., Şekerel, B. E., Çullu-Çokuğraş, F. and Çokuğraş, H. 2016, Turk J.. Pediatr., 58(1), 1.
7. Martorell, A., Plaza, A. M., Boné, J., Nevot, S., García Ara, M. C., Echeverria, L., Alonso, E., Garde, J., Vila, B., Alvaro, M., Tauler, E., Hernando, V. and Fernández, M. 2006, Allergol Immunopathol. (Madr.), 34(2), 46.
8. Caffarelli, C., Santamaria, F., Di Mauro, D., Mastrorilli, C., Montella, S., Tchana, B., Valerio, G., Verrotti, A., Valenzise, M., Bernasconi, S. and Corsello, G. 2018, Ital. J. Pediatr., 44(1), 82.
9. Cuomo, B., Indirli, G. C., Bianchi, A., Arasi, S., Caimmi, D., Dondi, A., La Grutta, S., Panetta, V., Verga, M. C. and Calvani, M. 2017, Ital. J. Pediatr., 43(1), 93.
10. Caffarelli, C., Ricò, S., Rinaldi, L., Povesi Dascola, C., Terzi, C. and Bernasconi, S. 2012, Ann. Allergy Asthma. Immunol., 108(4), 285.

11. Høst, A. 2002, Annals of allergy, asthma and immunology, 89(6 Suppl. 1), 33.
12. Lauener, R., Roduit, C., Vuitton, D. A., von Mutius, E., Dalphin, J. C. and PASTURE Study Group. 2017, Allergy, 72(9), 1365.
13. Saad, K., Zahran, A. M., Elsayh, K. I., Abdelmoghny, A. and Aboul-Khair, M. D. 2018, Arch. Immunol. Ther. Exp. (Warsz)., 66(4), 307.
14. Kido, J., Hirata, M., Ueno, H., Nishi, N., Mochinaga, M., Ueno, Y., Yanai, M., Johno, M. and Matsumoto, T. 2016, Allergy and rhinology, 7(3), 139.
15. Vandenplas, Y., Koletzko, S., Isolauri, E., Hill, D., Oranje, A. P., Brueton, M., Staiano, A. and Dupont, C. 2007, Arch. Dis. Child., 92(10), 902.
16. Yang, M., Tan, M., Wu, J., Chen, Z., Long, X., Zeng, Y., Cai, H., Zhang, Y., Geng, L., Xiao, Y., Ke, H., Liu, Y., Rong, L., Fu, S., Wang, H., Wang, Y., Li, X., Chen, P., Li, K., Xie, J. and Gong, S. 2019, J. Parenter. Enteral. Nutr., 43(6), 803.
17. Martorell, A., Plaza, A. M., Boné, J., Nevot, S., García Ara, M. C., Echeverria, L., Alonso, E., Garde, J., Vila, B., Alvaro, M., Tauler, E., Hernando, V. and Fernández, M. 2006, Allergol. Immunopathol. (Madr), 34(2), 46.
18. Yang, Q. H., Zheng, B. S., Zhou, S. M. and Dai, D. L. 2019, Chinese journal of contemporary pediatrics, 21(3), 271.
19. Fleischer, D. M., Perry, T. T., Atkins, D., Wood, R. A., Burks, A. W., Jones, S. M., Henning, A. K., Stablein, D., Sampson, H. A. and Sicherer, S. H. 2012, Pediatrics, 130(1), e25.
20. Gupta, R. S., Springston, E. E., Warrier, M. R., Smith, B., Kumar, R., Pongracic, J. and Holl, J. L. 2011, Pediatrics, 128(1), e9.
21. Zhang, J. Y., Zhou, S. M., Wang, S. H., Sui, F. X., Gao, W. H., Liu, Q., Cai, H. B., Jiang, H. Y., Li, W. Y., Wang, L. T., Li, L., Zhao, W., Ying, J., Wu, Q. Z., Weng, B. X. and Zeng, Y. M. 2020, Chinese journal of contemporary pediatrics, 22(1), 42.
22. Kalach, N., Bellaïche, M., Elias-Billon, I., and Dupont, C. 2019, Arch Pediatr., 26(4), 226.
23. Koplin, J. J., Allen, K. J., Gurrin, L. C., Peters, R. L., Lowe, A. J., Tang, M. L., Dharmage, S. C. and Health Nuts Study Team. 2013, Int. J. Environ. Res. Public Health, 10(11), 5364.
24. Sardecka, I., Łoś-Rycharska, E., Ludwig, H., Gawryjołek, J. and Krogulska, A. 2018, Allergy Asthma Proc., 39(6), e44.
25. Vandenplas, Y., Abuabat, A., Al-Hammadi, S., Aly, G. S., Miqdady, M. S., Shaaban, S. Y. and Torbey, P. H. 2014, Pediatr. Gastroenterol. Hepatol. Nutr., 17(2), 61.
26. Goldsmith, A. J., Koplin, J. J., Lowe, A. J., Tang, M. L., Matheson, M. C., Robinson, M., Peters, R., Dharmage, S. C. and Allen, K. J. 2016, J. Paediatr. Child Health, 52(4), 377.
27. Amira A. El-Houfey, A. A., Saad, K., Abbas, A. A., Mahmoud, S. R. and Wadani, M. 2017, Int. J. Nursing Didactics, 7(11), 24.
28. Nies, M. A and Mcewen, M. 2019, Community Public Health Nursing Promoting the Health of Population, Maternal, Prenatal, and Newborn Populations, ch27, 9th ed, Saunders, 623.
29. Forsyth, J. S., Ogston, S. A., Clark, A., Florey, C. D. and Howie, P. W. 1993, BMJ, 306(6892), 1572.
30. Zutavern, A., Brockow, I., Schaaf, B., Bolte, G., von Berg, A., Diez, U., Borte, M., Herbarth, O., Wichmann, H. E., Heinrich, J. and LISA Study Group. 2006, Pediatrics, 117(2), 401.
31. Fewtrell, M., Bronsky, J., Campoy, C., Domellöf, M., Embleton, N., Fidler Mis, N., Hojsak, I., Hulst, J. M., Indrio, F., Lapillonne, A., and Molgaard, C. 2017, J. Pediatr. Gastroenterol. Nutr., 64(1), 119.
32. Chan, E. S., Cummings, C. and Canadian Paediatric Society, Community Paediatrics Committee and Allergy Section. 2013, Paed Child Healt., 18(10), 545.
33. Gil, F., Amezqueta, A., Martinez, D., Aznal, E., Etayo, V., Durá, T. and Sánchez-Valverde, F. 2017, Int. Arch. Allergy Immunol., 173(3), 147.
34. Sánchez-Valverde, F., Gil, F., Martinez, D., Fernandez, B., Aznal, E., Oscoz, M. and Olivera, J. E. 2009, Allergy, 64(6), 884.
35. Bager, P., Wohlfahrt, J. and Westergaard, T. 2008, Clin. Exp. Allergy, 38(4), 634.