

Association of Cow's Milk Protein Allergy Prevalence With Socioeconomic Status in a Cohort of Chilean Infants

**María E. Arancibia, *†Yalda Lucero, *Isabel Miquel, ‡Pamela Marchant, *Lorena Rodríguez, *Francisco Alliende, *Gloria Ríos, and §Andrés Maturana*

ABSTRACT

Objectives: The aim of the study was to compare the cow's milk protein allergy (CMPA) prevalence in 2 cohorts of children from different socioeconomic strata.

Methods: Prospective birth cohort that included patients from 2 hospitals providing care for a low- and high-income population, respectively. Healthy newborns ≥ 34 gestational weeks were recruited and followed up to 12 months by a monthly telephone survey. If ≥ 2 predefined symptoms/signs suggestive of CMPA were detected, the patient was evaluated by a pediatric gastroenterologist. Diagnosis was confirmed by exclusion diet followed by open oral food challenge.

Results: Overall the prevalence of CMPA was 5.2%, with a 6 times higher prevalence in the high income cohort (9.2%) compared with the low-income group (1.5%; relative risk 6.2; 95% confidence interval 1.8–20.7; $P = 0.0005$). All the cases were non-immunoglobulin E-mediated with predominantly gastrointestinal symptoms. High-income cohort did have higher frequency of C-section, mother's previous chronic disease, mother's history of atopy/food allergy, older age, and higher educational level of parents. Parent smoking and presence of pets at home were more frequent in the low-income cohort. Multiple logistic regression showed that the high-income cohort did have older age and higher educational level of both parents.

Conclusion: In these cohorts the prevalence of CMPA was higher than reported previously in other developing countries and significantly higher in the high-income group. Our findings were associated with sociodemographic characteristics of the parents.

Key Words: atopy, cow's milk protein allergy, diversity, food allergy, sociodemographic determinants

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What Is Known

- Cow's milk protein allergy is the most frequent food allergy, with a prevalence of 1% to 5% in infants in developed countries.
- Genetic and environmental factors contribute to cow's milk protein allergy pathogenesis.
- The role of sociodemographic factors has not been completely established.

What Is New

- Overall the prevalence of cow's milk protein allergy in this cohort from a developing country was similar to that described in developed countries.
- Cow's milk protein allergy prevalence was 6 times higher in the high compared to the low socioeconomic status group.

Cow's milk protein allergy (CMPA) is the most frequent food allergy in infants. Most studies have been conducted in developed countries with a prevalence ranging from 0.5% to 4.9% (1,2). Few Latin American studies with limited design (2 retrospective and 1 prospective study with no food challenge confirmation) have been performed and estimate a lower prevalence than in developed countries, ranging from 0.7% to 1% (3–5).

CMPA is a multifactorial condition including genetic and environmental factors that hinder the induction of tolerance to food antigens (6). The effect of socioeconomic factors in the development of CMPA has not been completely elucidated and should be explored to identify variables potentially modifiable to prevent this condition.

The aims of this birth cohort study were to determine the CMPA prevalence in a cohort of infants from Chile, a developing country with high socioeconomic disparities, and to compare it between 2 groups, one recruited in a low-income area and the other in a high-income population.

PATIENTS AND METHODS

Study design

This prospective cohort study included patients from 2 tertiary health care centers in Santiago, the capital city of Chile. One was a public hospital (Hospital Padre Hurtado) located in San Ramón, a county with a per capita income of US \$270 and 17.7% of the population under poverty line. The other one was a private

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From the *Pediatric Gastroenterology Unit, Department of Pediatrics, Clínica Alemana de Santiago, Facultad de Medicina-Clínica Alemana, Universidad del Desarrollo, Santiago, Chile, the †Pediatric and Pediatric Surgery Department (Northern Campus), Faculty of Medicine, University of Chile, Santiago, Chile, the ‡Pediatric Gastroenterology Unit, Department of Pediatrics, Hospital Padre Hurtado, Santiago, Chile, and the §Neonatology Unit, Department of Pediatrics, Clínica Alemana de Santiago, Facultad de Medicina-Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

Address correspondence and reprint requests to María E. Arancibia, MD, Pediatric Gastroenterologist, Department of Pediatrics, Clínica Alemana de Santiago, Facultad de Medicina, Universidad del Desarrollo, Vitacura 5951, Vitacura, Santiago, Chile (e-mail: marancibia@alemana.cl).

M.E.A. and Y.L. contributed equally as co-first authors.

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hospital (Clínica Alemana de Santiago), located in Vitacura, a county with a per capita income of US \$1,915, and 0.1% of population under poverty line (7). Both populations were urban and had similar access to sanitation (>97% of access to basic sanitation according to the last national socioeconomic survey) (7) differing mainly in per capita income. After informed consent by the parents, healthy newborns ≥ 34 weeks of gestational age, born between September 2013 and June 2014 were enrolled during their first 3 days of life and followed up to 12 months of age. Newborns with Apgar score < 7 at 5 minutes and/or any chronic concomitant pathology were excluded. The protocol was approved by the local institutional review boards.

Procedures

In the first visit, a sociodemographic survey was completed by the parents. After that, monthly telephone calls to the mothers asking a structured questionnaire to screen for signs or symptoms (digestive, cutaneous, respiratory, and systemic) suggestive of CMPA were conducted by 2 trained nurses until the infants were 12 months of age. All patients that screened positive for ≥ 2 signs or symptoms were evaluated by 1 of 7 pediatric gastroenterologists with experience in CMPA diagnosis, and who performed a pre-designed survey asking symptoms and signs suggestive of CMPA, anthropometry, and physical examination.

Patients with a clinical suspicion of CMPA by the pediatric gastroenterologist were prescribed a cow's milk protein elimination diet. In breast-fed infants, the diet was given to the mother using a written guide, verbally explained by one of the study pediatric gastroenterologists. Those who were bottle fed had their formula replaced by extensively hydrolyzed or amino acid-based formula according to severity of the clinical presentation. After 4 to 6 weeks of exclusion diet the patients were re-evaluated by pediatric gastroenterologist and if they were in complete remission of the symptoms, an open oral food challenge (OFC) was indicated to confirm the diagnosis, introducing cow's milk protein to the diet of the mother and/or the infant. OFC was considered positive if symptoms suggestive of CMPA reappeared during the following 4 weeks after reintroduction of cow's milk protein.

In cases clinically suggestive of immediate hypersensitivity, cow's milk protein-specific immunoglobulin E (IgE) was requested, considering as positive a value ≥ 0.7 kU/L. If the tests were positive, a hospital-based OFC was performed.

Statistical Analysis

Categorical variables were described by percentages and compared between groups using the Chi-squared or Fisher exact test; continuous variables were described by median and interquartile range and compared using a nonparametric test. The relative risk of the association between recruitment in 1 center and sociodemographic factors was calculated. Univariate and multivariate analyses were performed by using Stata 15. A P value ≤ 0.05 was considered statistically significant. For sample size calculation, based on previous reports, we considered an estimated prevalence of 0.7% in the low-income and 5.6% in the high-income group, with an alpha error of 5% and power of 80%.

RESULTS

In the high-income center, 200 infants were enrolled and 184 (92%) completed follow-up. In the low-income center, 211 infants were recruited and 199 (94%) completed follow-up. Table 1 compares the baseline characteristics of both cohorts. In the univariate analysis C-section, previous chronic disease in the mother, mother's

history of atopy, and food allergy were significantly more frequent in the high-income center. The median age of both parents and their educational level were significantly higher in the high-income center compared with the low-income setting. Smoking habit in both parents and presence of pets at home were more frequent in the low-income center. After multiple logistic regression age of the mother/father and mother/father's educational level were significantly different between both centers.

Overall 20 confirmed CMPA cases were diagnosed (5.2%). In addition 2 cases with clinical suspicion of CMPA that improved after exclusion diet did not undergo the OFC and remained on the exclusion diet until 12 months of age. One case had undernutrition, and OFC was contraindicated until the age of 12 months. In the other case, parents rejected OFC due to a bad experience with a previous child with severe CMPA. Including these cases, the overall prevalence was 6.0%. In the high-income center the prevalence of CMPA during the first year of life was 9.2%, whereas in the low-income center the prevalence was 1.5% (RR 6.2; 95% confidence interval 1.8–20.7; $P = 0.0005$).

The median age at the beginning of symptoms in the confirmed cases was 20 days of life (range 3–150 days), and the median age at diagnostic confirmation was 113 days (range 30–300 days). Table 2 summarizes the clinical presentation of the 20 confirmed cases. All patients presented with > 2 symptoms suggestive of CMPA, predominantly from the digestive tract. Only 1 case presented with symptoms suggestive of immediate hypersensitivity; specific IgE for cow's milk was requested, and the result was negative.

DISCUSSION

This is the first study of CMPA prevalence based on general population and confirmed by OFC in Latin America. It is also one of the few studies that explored differences between a clinic in a low compared with high socioeconomic status area. Overall, the prevalence (5.2%) was higher than what has been previously reported in other developing countries. European series with diagnosis confirmed by OFC have reported a prevalence between 0.7% and 3.5% with a predominance of IgE-mediated cases (2,8,9). A study performed in an underdeveloped area from China reported 1.3% of OFC-confirmed CMPA in children younger than 1 year of age (10). A cohort study performed in a low-income suburbs area from Cartagena, Colombia, including 326 mother-infants pairs followed up during 2 years, reported a 0.7% of children with symptoms attributable to CMPA. These cases were, however, not confirmed by OFC (3). A retrospective birth cohort study performed in Buenos Aires, Argentina, reported a 0.8% of CMPA prevalence in infants (4). Finally, Gonçalves et al (5) conducted a retrospective series of Brazilian infants and reported a prevalence of 1%. The higher prevalence found in our cohort may be attributable at least in part to the active search of cases since newborn and close follow-up. It also could be related to a selection bias in the high socioeconomic level group, because the parents of patients with higher risk for CMPA may be more inclined to participate.

The cases were confirmed by open OFC supervised by a pediatric gastroenterologist which is the standard of diagnosis. In cases of subjective symptoms such as irritability or colic, the diagnosis could be overestimated. This is, however, a practice recommended for clinical setting by international guidelines (11), and all the cases in our study with irritability or colic did have also other more objective signs such as bloody or mucoid stools.

Notably, the prevalence differed between the 2 clinics representing diverse social strata, with a 6-fold higher frequency in the highest socioeconomic level. Although we did not include

TABLE 1. Sociodemographic and perinatal characteristic of newborns enrolled in 2 hospitals with different socioeconomic level

	High socioeconomic level center n = 200	Low socioeconomic level center n = 211	RR (95% CI)	P
Male, n (%)	102 (51)	107 (51)	1.006 (0.83–1.22)	0.48
Weight at birth, median in g (IQR)	3335 (3053–3610)	3390 (3118–3665)		0.20
Height at birth, median in cm (IQR)	49.8 (48.4–50.5)	50.0 (48.0–51.0)		0.71
C-section, n (%)	63 (32)	47 (22)	1.41 (1.02–1.96)	0.017
Preterm delivery (34–36 wk), n (%)	16 (8)	10 (5)	1.69 (0.78–3.63)	0.09
Rural residency, n (%)	2 (1)	1 (0.5)	2.11 (0.19–23.09)	0.48
Hospitalization, n (%)	2 (1)*	7 (3.3) [†]	0.30 (0.06–1.43)	0.10
Formula during newborn period, n (%)	10 (5)	19 (9)	0.56 (0.26–1.16)	0.058
Mother's age	33.5 (31–35.8)	24 (20–30)		< 0.0001
Mother's educational level, n (%)				< 0.0001
Graduate complete	197 (99)	17 (8)	12.22 (7.75–19.29)	
Graduate incomplete	3 (1)	13 (6)		
High school complete	0	104 (49)		
High school incomplete	0	49 (23)		
No education	0	28 (13)		
Number of siblings, median (IQR)	2 (1–2)	2 (1–2)		0.004
Mother's previous chronic disease	43 (22)	21 (10)	2.16 (1.33–3.50)	0.0006
Mother's atopy, n (%)	53 (27)	32 (15)	1.75 (1.18–2.59)	0.002
Mother's food allergy	17 (9)	2 (1)	8.98 (2.10–38.32)	0.0001
Mother's smoking habit, n (%)	24 (12)	96 (46)	0.26 (0.17–0.39)	< 0.0001
Father's age	33.5 (31–35.8)	24 (20–30)		< 0.0001
Father's educational level, n (%)				< 0.0001
Graduate complete	199 (99.5)	27 (13)	7.77 (5.47–11.06)	
Graduate incomplete	1 (0.5)	7 (3)		
High school complete	0	99 (47)		
High school incomplete	0	45 (21)		
No education	0	33 (16)		
Father's previous chronic disease, n (%)	18 (9)	12 (6)	1.58 (0.78–3.20)	0.10
Father's atopy, n (%)	28 (14)	31 (15)	0.95 (0.59–1.53)	0.42
Father's food allergy	4 (2)	0		0.055
Father's smoking habit, n (%)	44 (22)	98 (46)	0.47 (0.35–0.63)	< 0.0001
Pets, n (%)	61 (31)	138 (65)	0.47 (0.37–0.59)	< 0.0001

CI = confidence interval; IQR = interquartile range.

*2 Hyperbilirubinemia.

[†]6 Hyperbilirubinemia + 1 sepsis.

TABLE 2. Clinical presentation of 20 cases of confirmed cow's milk protein allergy

	N (%)
Number of symptoms presented by patient	
Two symptoms	3 (15)
Three or more symptoms	17 (85)
Symptoms	
Perianal erythema	13 (65)
Regurgitation/vomiting	11 (55)
Atopic dermatitis	10 (50)
Mucous stools	10 (50)
Colic	9 (45)
Bloody stool	6 (30)
Abdominal distension	4 (20)
Food refusal	3 (15)
Failure to thrive	2 (10)
Constipation	2 (10)

economic variables in the baseline survey of the recruited families, we consider that the socioeconomic parameters described for the county where the hospitals were located at least partially reflect the strata of the population treated in these centers. Access to the public hospital was restricted to the population of an assigned district that included the county where it was located. Conversely, access to the private hospital is theoretically open, but in reality is restricted to individuals who can pay for the high costs of its services. In contrast, previous studies have not clearly shown socioeconomic deprivation by itself to be a protective factor for asthma and other atopic conditions, including food allergy (3,12). Interestingly, anticipated protective factors, such as low hygienic conditions, do not confer protection in poor and overcrowded communities, where a high prevalence of asthma and early infections concur. Our findings may be associated to some sociodemographic features that also differed between both populations as higher educational level in the parents, older age from the parents, higher frequency of C-section, lower frequency of smoking, and pets in the high socioeconomic level compared to the lower socioeconomic group.

A study performed in Hong Kong reported a 2-fold higher prevalence of food allergy in children born and raised in Hong Kong

compared with those born in mainland China and raised in Hong Kong (4.8% and 2.4%, respectively). As these populations have the same genetic background, environmental factors early in life have been suggested to explain this difference (13). In Chile, the socioeconomic level is associated with educational level, ethnic origin, dietary habits, among other factors that could affect the risk of CMPA. Leung et al (13) in Hong Kong and Sardecka et al (14) in Poland reported higher risk of developing CMPA in children from parents with higher educational level and older age. In a population-based study performed in Canada with self-reported food allergy, higher educational level was associated to higher risk of food allergy (specifically for tree nuts (15)), which is consistent with other series describing this risk factor for atopy in general (16,17). Given that a higher educational level may be associated with changes in family lifestyle (15,17), the hygiene hypothesis may at least partially account for these findings. Consistent with the hygiene hypothesis, smaller family size, decreased exposure to pets and livestock, fewer infections during infancy, increased use of antibiotics and vaccinations, and improved sanitation may decrease microbial burden and lead predominantly to a type 2 T-helper (Th2) cell response that can be responsible for triggering allergic disorders (6,15).

Alternatively, C-section was more frequent in the high socioeconomic level population, and this factor has been associated by itself to changes in the microbiota of the newborns and infants, with a decreased diversity and a profile favoring the development of Th2 pathway also (18). This finding has been associated to the subsequent development of atopy and other chronic nontransmissible diseases (19).

We believe that a detection bias for symptoms in the lower income population attributable to the parent's lower educational level would be minimal since the signs and symptoms were clearly defined and sought by the same research team in both populations.

Educational level could, however, impact recruitment, because the process was voluntary and in the high socioeconomic level parents of children with higher risk to develop CMPA may be more prone to participate in the study.

Although the registry did not include any concomitant use of antibiotics or other medications, it is improbable that this influenced our results since the definition of CMPA in this study was based on improvement with exclusion diet and recurrence with OFC.

In this cohort no case of IgE-mediated CMPA was identified, in contrast to the findings of studies performed in Western developed countries (20). A study performed in Poland reported a predominance of non-IgE cases (14). In Israel, a report including >13,000 infants; 50% of the cases with CMPA confirmed by OFC (0.5%) did have a non-IgE-mediated form (16). The finding of our group is probably because the study was performed by gastroenterologists with careful evaluation of non-IgE-mediated symptoms that could be underestimated in other series (7).

In conclusion, the prevalence of CMPA in this cohort of infants from a developing country was high (5.2%), mainly as a non-IgE-mediated form, and had a 6-fold higher prevalence in the higher-income center compared to the lower-income one.

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REFERENCES

1. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;69:992–1007.
2. Schoemaker AA, Sprickelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children—EuroPrevall birth cohort. *Allergy* 2015;70:963–72.
3. Acevedo N, Sánchez J, Zakzuk J, et al. Particular characteristics of allergic symptoms in tropical environments: follow up to 24 months in the FRAAT birth cohort study. *BMC Pulm Med* 2012;12:13.
4. Mehaudy R, Parisi C, Petriz N, et al. Prevalence of cow's milk protein allergy among children in a university community hospital. *Arch Argent Pediatr* 2018;116:219–23.
5. Gonçalves LCP, Guimarães TCP, Silva RM, et al. Prevalence of food allergy in infants and pre-schoolers in Brazil. *Allergol Immunopathol (Madr)* 2016;44:497–503.
6. Iweala OI, Burks AW. Food allergy: our evolving understanding of its pathogenesis, prevention, and treatment. *Curr Allergy Asthma Rep* 2016;16:37.
7. Ministry of Social Development and Family. CASEN Survey 2017 [Internet] [cited October 28, 2019]. <http://observatorio.ministeriode-sarrollosocial.gob.cl/casen-multidimensional/casen>.
8. Venkataraman D, Erlewyn-Lajeunesse M, Kuruklaarachy RJ, et al. Prevalence and longitudinal trends of food allergy during childhood and adolescence: Results of the Isle of Wight Birth Cohort Study. *Clin Exp Allergy* 2018;48:394–402.
9. Koletzko S, Heine RG. Non-IgE mediated cow's milk allergy in EuroPrevall. *Allergy* 2015;70:1679–80.
10. Chen J, Hu Y, Allen KJ, et al. The prevalence of food allergy in infants in Chongqing, China: the prevalence of food allergy. *Pediatr Allergy Immunol* 2011;22:356–60.
11. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(6 suppl):S1–58.
12. Ardura-García C, Garner P, Cooper PJ. Is childhood wheeze and asthma in Latin America associated with poor hygiene and infection? A systematic review. *BMJ Open Respir Res* 2018;5:e000249.
13. Leung TF, Yung E, Wong YS, et al. Parent-reported adverse food reactions in Hong Kong Chinese pre-schoolers: epidemiology, clinical spectrum and risk factors. *Pediatr Allergy Immunol* 2009;20:339–46.
14. Sardecka I, Łoś-Rycharska E, Ludwig H, et al. Early risk factors for cow's milk allergy in children in the first year of life. *Allergy Asthma Proc* 2018;39:e44–54.
15. Ben-Shoshan M, Harrington DW, Soller L, et al. Demographic predictors of peanut, tree nut, fish, shellfish, and sesame allergy in Canada. *J Allergy* 2012;2012:858306.
16. Pawlinska-Chmara R, Wronka I, Muc M. Prevalence and correlates of allergic diseases among children. *J Physiol Pharmacol Off J Pol Physiol Soc* 2008;59(suppl 6):549–56.
17. Dom S, Droste JHJ, Sariachvili MA, et al. The influence of parental educational level on the development of atopic sensitization, wheezing and eczema during the first year of life. *Pediatr Allergy Immunol* 2009;20:438–47.
18. Shao Y, Forster SC, Tsaliqi E, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature* 2019;574:117–21.
19. Musso P, Chiappini E, Bernardini R. Human microbiome and allergic diseases in children: pathogenetic role and therapeutic options. *Current Pediatric Reviews* 2019;15:1315666191025110849.
20. Peters RL, Koplin JJ, Gurrin LC, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017;140:145.e8–53.e8.