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ORIGINAL

Knowledge and practice of pediatricians and nutritionists regarding treatment of cow's milk protein allergy in infants

Conhecimento e prática de pediatras e nutricionistas sobre o tratamento da alergia às proteínas do leite de vaca em lactentes

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ABSTRACT

Objective

This study evaluated the knowledge and practices of pediatricians and nutritionists about cow's milk protein allergy in infants, with an emphasis on issues related to the exclusion diet and nutritional status.

Methods

A cross-sectional, descriptive study was performed with a convenience sample of 204 pediatricians and 202 nutritionists randomly invited in scientific events in the city of *São Paulo*, from November 2014 to March 2016.

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Results

Between 1.5% and 21.0% of respondents indicated inadequate products for the treatment of cow's milk protein allergy, including goat's milk, beverages or juices based on soy extract, lactose-free milk formula and partially hydrolyzed formula. The daily calcium recommendation for children between zero and 36 months of age was correctly indicated by 27.0% of pediatricians and 46.0% of nutritionists (p=0.001). Additionally, 96.1% of pediatricians and 82.7% of dietitians (p<0.001) provided guidance on about labels of industrialized products.

Conclusion

Pediatricians and nutritionists present gaps in knowledge about cow's milk protein allergy treatment in infants and educational strategies that increase the knowledge of the professionals are important for the management of cow's milk protein allergy.

Keywords: Cow's milk allergy. Infant. Knowledge attitude and practice. Pediatricians. Nutritionists.

RESUMO

Objetivo

Este estudo avaliou o conhecimento e práticas de pediatras e nutricionistas sobre alergia às proteínas do leite de vaca em lactentes, com ênfase em questões relacionadas à dieta de exclusão e ao estado nutricional.

Métodos

Estudo transversal, descritivo, realizado com uma amostra de conveniência de 204 pediatras e 202 nutricionistas, convidados aleatoriamente em eventos científicos na cidade de São Paulo, de novembro de 2014 a março de 2016.

Resultados

Entre 1,5% e 21,0% dos entrevistados indicaram produtos inadequados para o tratamento da alergia às proteínas do leite de vaca, incluindo leite de cabra, bebidas ou sucos à base de extrato de soja, fórmula de leite sem lactose e fórmula parcialmente hidrolisada. A recomendação diária de cálcio para crianças entre zero e 36 meses de idade foi corretamente indicada por 27,0% de pediatras e 46,0% de nutricionistas (p=0,001). Além disso, 96,1% dos pediatras e 82,7% dos nutricionistas (p<0,001) forneceram orientação sobre os rótulos dos produtos industrializados.

Conclusão

Pediatras e nutricionistas apresentam lacunas no conhecimento sobre o tratamento da alergia às proteínas do leite de vaca em lactentes. Estratégias educacionais que aumentam o conhecimento dos profissionais são importantes para o gerenciamento da alergia às proteínas do leite de vaca.

Palavras-chave: *Alergia ao leite de vaca. Crianças. Conhecimento, atitudes e prática. Nutricionistas. Pediatras.*

INTRODUCTION

Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly following exposure to a given food [1]. The main cause of food allergies in children under three years old is Cow's Milk Protein (CMP) [2].

The estimated prevalence of Cow's Milk Protein Allergy (CMPA) is 2% to 3% in the first year of life [2]. In Brazil an observational study conducted in pediatricians' offices revealed a gastroenterologist-diagnosed prevalence of 5% in the group of patients [3].

The immune mechanisms involved in CMPA may be immunoglobulin (Ig)E mediated (with production of IgE-specific antibodies), which presents immediate symptoms such as urticaria and angioedema, or the non IgE-mediated (T-cell mediated), which manifests through later reactions, such as vomiting, diarrhea, colic and intestinal constipation. Mixed reactions (immediate and late) can also occur, such as eosinophilic esophagitis, eosinophilic

gastroenteropathy, atopic dermatitis and asthma [1,4-6].

The diagnosis and treatment of CMPA is based on the exclusion of CMP from the diet. Cow's milk elimination without adequate replacement may impair the normal growth and development of the child [1,4-7].

During the period of exclusion of CMP, a nutritional status assessment should be performed by the health professional to establish the adequacy of food consumption for the child's nutritional needs [1,4,5,8] and family members must be oriented to perform a thorough reading of the labels of industrialized foods offered to their children [1,5,7,9]. Despite the existence of several guidelines [1,4-7,10-13] for the diagnosis and treatment of CMPA, some surveys [6,7,14-22] have shown that the practices and knowledge of health professionals are not fully in line with these recommendations. Few studies have investigated the knowledge and practices of pediatricians and nutritionists about CMPA treatment. Studies [15,16,19] conducted in Brazil have shown gaps in knowledge and have confirmed that not all behaviors are consistent with the recommendations.

Thus, this study aimed to evaluate the knowledge and practice of pediatricians and dietitians about CMPA in infants, with an emphasis on issues related to the exclusion diet and nutritional status.

METHODS

Study design

This study had a cross-sectional descriptive design involving a convenience sample of 406 professionals. Data collection was conducted from November 2014 to March 2016.

The invitation to professionals to participate in the study was issued randomly at five scientific events held in the city of *São Paulo*: 10th Update Course on Pediatrics, Nutrition Mega Event, 9th Conference on Pediatric Nutrition, 6th Brazilian Conference on Integrated Nutrition (Ganepão) and 14th *São Paulo* State Conference on Pediatrics.

The study was approved by the Ethics Committee in Research of the *Universidade Federal de São Paulo* (UNIFESP, Federal University of *São Paulo*) under No.842.114. Free and informed consent was obtained in writing from all participants.

Structured form

Data collection was performed through a structured and self-administered form that was previously described by Cortez *et al*. [15]. This form was reevaluated and adapted based on updates for the treatment of CMPA. The form was composed of an initial section to characterize the professional (*i.e.*, gender, time since college graduation, graduate course and location of professional action). The second section consisted of questions about knowledge of and practices for the treatment of infants with CMPA.

The following statements were presented to enable the interviewees to express agreement, disagreement or lack of knowledge and multiple choice questions.

Knowledge about breastfeeding and bottle feeding

1) Casein is the only milk protein involved in triggering CMPA; 2) The early introduction of cow's milk increases the risk of CMPA development; 3) Exclusively breastfed infants can develop CMPA; 4) A child with CMPA may present a cross reaction to soybean proteins; 5) Goat's milk or milk from any other mammal (*e.g.*, sheep, mare, or donkey) can be used as a substitute for cow's milk for children with CMPA; 6) Patients with lactose intolerance should exclude all foods containing CMP from the diet.

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One question evaluated whether the interviewees knew the products that could be used to replace CMP in the diets of infants over six months of age with suspected non-IgE-mediated or IgE-mediated CMPA. The alternatives were presented with the definition of the type of formula (with the respective brand name) as follows: (1) extensively hydrolyzed formula; (2) soy protein-based formula; (3) Goat's milk; (4) soy extract-based beverage/juice; (5) lactose-free milk formula; (6) amino acid-based formula; and (7) partially hydrolyzed formula. More than one option could be chosen for these questions. Some care practice scenarios were also presented.

We asked what the initial prescription for special formula would be for an infant less than six months of age (using infant formula) with suspected gastroesophageal reflux disease secondary to CMPA associated with a weight deficit. The following alternatives (with their brand names) were presented: (1) extensively hydrolyzed formula; (2) soy protein-based formula; (3) Goat's milk; (4) soy extract-based beverage/juice; (5) lactose-free milk formula; (6) amino acid-based formula; and (7) partially hydrolyzed formula.

Other food allergens

For children with CMPA, other allergenic foods, such as soy, eggs, fish and peanuts, should also be eliminated from the diet as a preventive measure to avoid other reactions.

Daily calcium requirements (clinical scenario)

A question was based on a clinical scenario involving a 15-month-old patient fed 450mL of extensively hydrolyzed formula with complementary feeding and whether this patient would require calcium supplementation. Three alternatives were offered as a response (yes, no and I do not know). Another issue addressed the recommendation for the daily calcium intake according to age group. The following question was asked: what total dose of calcium do you recommend as a daily intake (mg/day) for the following age groups? The response options were as follows: 0-6 months: 200, 260 or 400; 7-12 months: 260, 400 or 600; 13-36 months: 400, 700 or 900; another dose; and I do not know. Another question explored the need for calcium supplementation (considering the consumption of different substitution formulas) for patients with a CMPA. The following alternatives were presented: (1) for patients aged 0-6 months; (2) for patients aged 7-12 months; (3) for patients aged 13-36 months; and (4) other.

Reading of labels and identification of terms related to cow's milk and dairy products in industrialized products

The answers were based on yes and no alternatives. If the answer was yes, the interviewee chose which of the following ingredients should be recognized by the parents/guardians and excluded from the diet: maltodextrin; calcium; lactalbumin; casein; caseinate; hydrogenated vegetable fat; milk compound; calcium stearoyl lactyl lactate; lactic acid; serum proteins; lactic yeast; cocoa butter; and hydrolyzed or partially hydrolyzed milk protein.

Statistical Methods

Statistical calculations were performed using the Epi-Info software version 3.4.3 (Atlanta, Georgia, United States) by setting the level for rejection of the null hypothesis at 5%. The Chi-square test was used for the comparison of proportions. When necessary, the exact Fisher test was used.

RESULTS

A total of 406 professionals were interviewed (204 pediatricians and 202

nutritionists). Regarding gender, women predominated, corresponding to 88.7% (360/406) of the sample. The percentage of female respondents was higher (p<0.001) among the nutritionists (97.0%; 196/202) than in the pediatric group (80.4%; 164/204).

All of the pediatricians worked in a clinic, outpatient clinic, basic health unit, inpatient/intensive care unit, pediatric emergency and/or family health program. Of the nutritionists, 23/202 (11.4%) did not work in nutritional assistance services for patients.

Table 1 presents the results related to the knowledge and practices of the interviewees about CMPA and its treatment. Generally, the frequency of correct answers was greater among the pediatricians. The nutritionists had less knowledge about the ineffectiveness of milk from other mammals as a substitute for cow's milk and the exclusion of other allergenic foods to prevent other reactions. Notably, the highest frequency of incorrect responses for both the pediatricians and dietitians was found for the possibility of a cross-reaction between CMP and soy proteins.

Figure 1 shows the products considered suitable by pediatricians and dietitians to replace CMP for infants with non-IgE-mediated CMPA (0-24 months) or IgE-mediated CMPA (older than six months). The infant formulas most frequently advocated were extensively hydrolyzed and amino acids. One result that should be highlighted is the use of soy protein-

Table 1. Number and percentage of correct answers provided by pediatricians and nutritionists for the following statements about cow's milk protein allergy. *São Paulo* (SP), Brazil, 2016.

Statements	Correct answer	Number (%) of hits				p[1]
		Pediatricians (n=204)		Nutritionists (n=202)		
		n	%	n	%	
Early introduction of cow's milk increases the risk of developing a cow's milk protein allergy	Agree	193	94.6	181	89.6	0.091
Casein is the only milk protein that is involved in the triggering of a cow's milk protein allergy	Disagree	187	91.6	149	73.7	<0.001
Exclusively breastfed infants can develop cow's milk protein allergy	Agree	183	89.7	130	64.4	<0.001
A child allergic to cow's milk protein may cross-react with soy proteins	Disagree	6	2.9	30	14.8	<0.001
Goat's milk or any other animal milk (*i.e.*, sheep, mare, or donkey) can be used as a cow's milk substitute for children with a cow's milk protein allergy	Disagree	180	88.2	112	55.4	<0.001
Patients with lactose intolerance should exclude all foods containing cow's milk protein from their diet	Disagree	170	83.3	148	73.3	0.192
For children with cow's milk allergy, other allergenic foods, such as soy, eggs, fish, and peanuts, should also be eliminated from the diet as a preventive measure to avoid other reactions	Disagree	131	64.2	104	51.5	0.125

Note: [1]Standard of Chi-square.

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Figure 1A. Non-IgE mediated reactions (0-24 months of age).

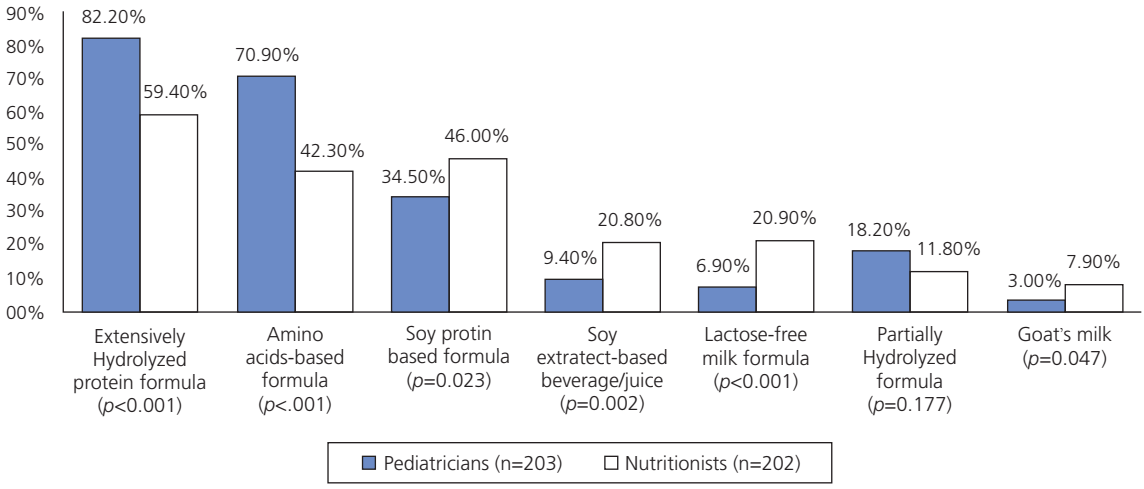

Figure 1B. IgE-mediated reactions (6-24 months of age).

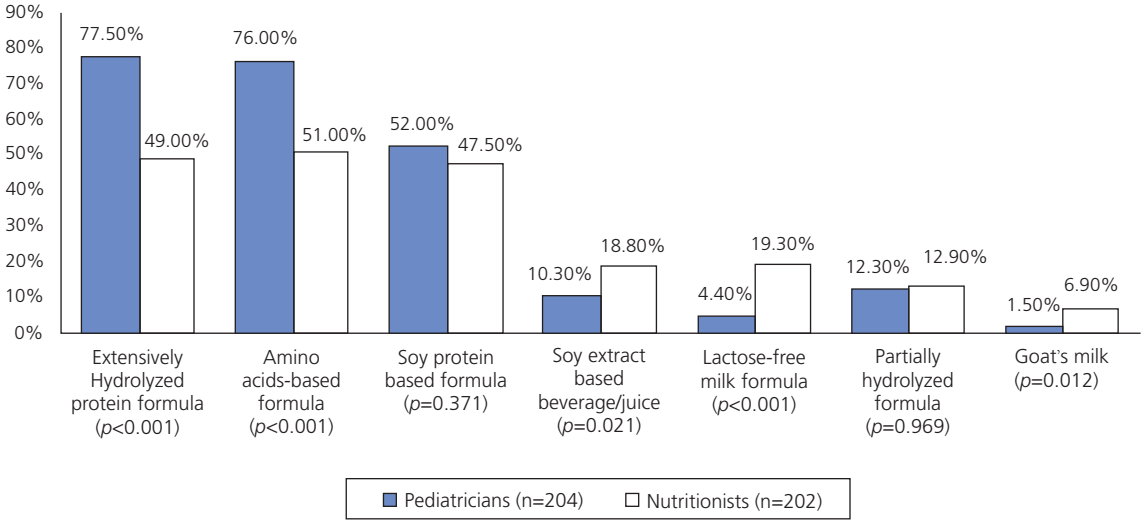

Figure 1. Options considered suitable by pediatricians and c for the elimination diet of infants with a suspected or diagnosed allergy to cow's milk protein. *São Paulo* (SP), Nrazil, 2016.

based formulas, which was considered by pediatricians in 34.5% of the non-IgE mediated reactions and 52.5% of the immediate reactions after six months of age and by nutritionists in 46.0% and 47.5% of the reactions, respectively.

Between 1.5% and 21.0% of the interviewees would use non-acceptable alternatives for the treatment of CMPA, including goat's milk, a beverage or juice based on soy extract, lactose-free milk formula and partially hydrolyzed formula. Some significant differences were found according to the professional category.

Regarding the orientation on reading industrialized product labels, 96.1% (196/204) of the pediatricians and 82.7% (167/202) of the dietitians ($p<0.001$) reported that they provided guidance to parents and/or guardians of children for the identification of all ingredients that might indicate the presence of CMP in industrialized products.

Table 2 presents a series of terms/ingredients that should/should not be used in the elimination diet of infants with CMPA. The frequency of correct answers generally was

Table 2. Exclusion recommendation by pediatricians and nutritionists of terms/ingredients observed on labels of industrialized products offered to infants with a suspected or diagnosed allergy to cow's milk protein. *São Paulo* (SP), Brazil, 2016.

Terms/ingredients	Pediatricians (n=204)		Nutritionists (n=202)		p[1]
	n	%	n	%	
Correct exclusion recommendation					
Lactalbumin	151	74.0	94	46.5	<0.001
Casein	166	81.4	127	62.9	<0.001
Caseinate	127	62.3	101	50.0	0.169
Milk compound	163	79.9	99	49.0	<0.001
Whey protein	145	71.1	127	62.9	0.098
Lactic yeast	120	58.8	71	35.1	<0.001
Unnecessary exclusion recommendation					
Maltodextrin	18	8.8	5	2.5	0.010
Calcium	3	1.5	3	1.5	1.000[2]
Hydrogenated vegetable fat	7	3.4	8	4.0	0.984
Calcium stearoyl lactyl lactate	31	15.2	26	12.9	0.595
Lactic acid	29	14.2	31	15.4	0.856
Cocoa butter	29	14.2	18	8.9	0.129

Note: [1]Chi-square test; [2]Fischer's exact test.

greater among the pediatricians in relation to the ingredients that should or should not be excluded from the diets of patients with CMPA than among the nutritionists.

Table 3 presents the frequency of correct answers about the calcium recommendation by the pediatricians and nutritionists. Approximately half of the respondents did not respond or indicated that they did not know the answer.

Regarding the first elimination formula that would be recommended for an infant with gastroesophageal reflux disease and a weight deficit, only one alternative was chosen by 366 (91.0%) of the 402 professionals interviewed, of whom 189 were pediatricians and 177 nutritionists. Regarding pediatricians, 58.2% (110/189) would prescribe an extensively hydrolyzed formula, 23.8% (45/189) would prescribe an amino acid-based formula, 5.8% (11/189) would prescribe a formula based on soy protein and 12.2% (23/189) would prescribe other formulas. For the nutritionists, 39.6% (70/177) would prescribe an extensively hydrolyzed formula, 24.3% (43/177) would prescribe an amino acid-based formula, 10.7% (19/177) would prescribe a formula based on soy protein and 25.4% (45/177) would prescribe other formulas.

The need for calcium supplementation was questioned in a clinical scenario involving a 15-month-old patient receiving 450mL of extensively hydrolyzed formula in addition to complementary feeding. Of the 202 pediatricians, 42.5% answered that they would supplement calcium. Accordingly, 62 (31.2%) of the 199 nutritionists would also provide this supplementation. We questioned in which age group calcium supplementation is generally necessary and found that 42.9% (85/198) of the pediatricians and 49.5% (100/202) of the nutritionists required supplementation between 13 and 36 months of age (p=0.223).

DISCUSSION

Our results showed that the interviewees' knowledge was adequate for most of the contents investigated. However, a non-negligible portion of the professionals interviewed would

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Table 3. Knowledge of pediatricians and nutritionists about the Adequate Intake (AI) and Recommended Dietary Allowance (RDA) of calcium from the Dietary Reference Intakes (DRI) by age group. *São Paulo* (SP), Brazil, 2016.

Variables	Pediatricians (n=204)		Nutritionists (n=202)		p^1
	n	%	n	%	
0-6 months					
200*	31	15.2	35	17.3	0.670
260	4	2.0	9	4.5	
400	31	15.2	31	15.3	
Another dose	5	2.4	4	2.0	
Do not know	83	40.7	60	29.7	
Did not answer	50	24.5	63	31.2	
7-12 months					
260*	11	5.4	30	14.9	0.002
400	41	20.1	32	15.8	
600	17	8.3	24	11.9	
Another dose	4	2.0	5	2.5	
Do not know	80	39.2	51	25.2	
Did not answer	51	25.0	60	29.7	
13-36 months					
400	48	23.5	24	11.9	
700**	13	6.4	28	13.9	0.020
900	19	9.3	32	15.8	
Another dose	6	3.0	11	5.4	
Do not know	89	43.6	72	35.7	
Did not answer	29	14.2	35	17.3	

Note: *Values considered correct according to the AI; **Value considered correct according to the RDA; [1]Chi-square test.

prescribe inadequate cow's milk substitutes for an infant with suspected or diagnosed CMPA. The results also showed that knowledge and practical guidelines should be improved about the reading of labels of industrialized products and the prescription of calcium supplements. This study meets the demands of pediatricians and nutritionists regarding the clinical practice of treating allergy to cow's milk proteins in infants. Based on this premise, it is important to highlight that these professionals present gaps in the knowledge of the treatment of this clinical entity, which may negatively impact the growth and development of these infants. Thus, our study makes an important diagnosis of the actual situation of the knowledge of these pediatricians and nutritionists about the theme.

Regarding Table 1, most a greater number of nutritionists compared to pediatricians did not believe that a child under an exclusive breastfeeding period could develop CMPA. The same result was found regarding the possibility that milk from other animals could be used as a substitute for cow's milk. Previous study [15] also reported that most dietitians did not agree that infants could develop CMPA when exclusively breastfed. However, food ingested by the mother can be transferred to her child through breast milk [1,4,11]. For example, 49.0% of published cases of eosinophilic colitis occurred during exclusive breastfeeding [23].

In total, 44.6% of nutritionists and 11.8% of pediatricians agreed that milk from other animals could be used as a substitute for cow's milk for children with CMPA. Previous Research [15] showed that 15.2% of pediatricians and 13.7% of nutritionists agreed that milk from other mammals could be used as a suitable substitute for cow's milk. The inadequacy of the use of the milk from other animals is due to the similarity of the proteins from these mammals with the proteins in cow's milk (*i.e.*, there is a high possibility of the occurrence of a cross-allergic reaction) [4,24]. Conversely, the reaction is not crossed with soy formula. Instead, children with CMPA who develop gastrointestinal tract involvement when soy formula is initiated as a substitute exhibit sensitization [1,5-7,25].

Although soy formulas are not recommended for infants with non-IgE-mediated CMPA, the use of this therapeutic option is accepted in infants over six months of age with an IgE-mediated allergy because sensitization to soy formula occurs less often in the immediate reaction [1,4-7,10,12,25]. Our results showed that almost all pediatricians and nutritionists wrongly considered a cross-reaction between cow's milk and soybeans a possibility, when in fact there is the possibility of developing sensitization and a reaction after exposure to this type of protein.

Approximately 35.0 to 46.0% of the interviewees (Figure 1) considered soy protein as an option for children with non-IgE mediated reactions. Conversely, approximately half of the interviewees did not consider soy formula as an option for cow's milk substitution for children with IgE-mediated reactions over six months of age, although this approach is suggested by several guidelines [1,5,7,10-12,25]. Virtually all of the guidelines recommend that extensively hydrolyzed formulas be used as the first alternative for children with suspected or diagnosed CMPA, whereas amino acid formulas are recommended for use in severe cases and for patients with persistent symptoms using an extensively hydrolyzed formula [4,5,7,11,12].

In our study, approximately 80% of pediatricians recognized the extensively hydrolyzed formulas as an option for CMPA treatment, and approximately 70.0 and 76% of these professionals knew that they could indicate amino acid formulas for cases with non-IgE-mediated and IgE-mediated reactions, respectively. Approximately half of the nutritionists respondents recognized extensively hydrolyzed and amino acid formulas as substitutes for cow's milk. This question sought to explore all possible options for the replacement of cow's milk in infants with CMPA. Cortez *et al*. [15] found that 66% of pediatricians and 48% of nutritionists would indicate at least one product considered inappropriate for the treatment of CMPA.

The choice of substitute formula was evaluated in the question about the first option that would be recommended for a child less than 6 months of age with a weight deficit using infant formula with suspected gastroesophageal reflux secondary to CMPA. For this case, 58.2% of pediatricians would prescribe an extensively hydrolyzed formula obeying the guidelines [2,4,5,7,11,12]. However, 24.0% of the respondents would prescribe an amino acid formula. In this context, we should note that the guidelines contain no clear definition of serious cases. Thus, the decision to prescribe an amino acid formula was probably motivated by considering the presented case as a serious form of CMPA by least some of these interviewees, since the case presented a weight deficit. Another explanation is that some suggestions from the literature consider the possibility of using amino acid formulas to diagnose CMPA more quickly [26].

During the adoption of the exclusion of CMP diet for children with CMPA, relatives and/or guardians should be guided on reading the labels of industrialized products. Our results were similar to those found in a previous studies [9,15,27] which showed that the majority of

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respondents had difficulty recognizing the terms/ingredients that indicated the presence of cow's milk allergens. In this context, since July 2015, food and beverage labels have been required by the promulgation of the Resolution of the Collegiate Board of Directors - RDC No.26 of the *Agência Nacional de Vigilância Sanitária* (ANVISA, National Sanitary Surveillance Agency) [28], to contain a description of 18 allergy-causing food ingredients/products, including milk. This regulation is expected to provide conditions for a better understanding of labels by patients and caregivers, thereby solving problems in the identification of allergens demonstrated in Brazil [9,27] and other countries [29,30].

Regarding the recommendation for the daily calcium intake for the different age groups, our findings showed a low level of satisfaction among the professionals interviewed. A previous study [15] showed that only 22% of pediatricians and 61% of nutritionists knew the calcium recommendations for all age groups. Some of this knowledge gap is possibly due to the recent changes in the Dietary Reference Intakes (DRI) [31] following the release of new values in 2011 [*i.e.*, 200mg/day (0-6 months), 260 mg/day (7-12 months) and 700mg/day (13-36 months)]. There is no need for calcium supplementation in infants less than one year of age who are receiving more than 500mL/day of infant formulas for specific dietary needs, since the formulas meet the nutritional needs of the patients [32]. For patients older than one year, the nutritional composition of the diet and the volume of food ingested should be considered, because calcium supplementation may be necessary [2,32]. Another important nutrient is vitamin D, which aids in the intestinal absorption of calcium and bone metabolism [32].

For the clinical scenario involving the 15-month-old patient receiving 450mL of an extensively hydrolyzed formula in addition to a complementary diet, the percentage of professionals who would not indicate calcium supplementation was higher among the pediatricians than among the nutritionists. The extensively hydrolyzed formulas available in the Brazilian market contain approximately 50mg of calcium per 100mL of product. A 15-month-old patient who ingests 450mL of the formula daily will receive approximately 225mg of calcium. Considering that the other foods present in the patient's diet contain 100mg of calcium, 375mg of calcium should be supplemented.

One of the limitations of our work was that the data collection was performed only at scientific events in the city of *São Paulo*. In addition to the regional character, professionals who participate in scientific events can be assumed to be more concerned with their scientific knowledge and therefore do not accurately represent the universe of professionals. However, our results are generally similar to the results from other studies [17-25] that evaluated the knowledge and practices of health professionals. These studies [17-25] used procedures for recruiting interviewees that were similar or different to the procedure used herein.

CONCLUSION

We conclude that gaps still exist in the knowledge and practices of pediatricians and nutritionists about CMPA treatment. Therefore, educational strategies should be proposed and performed to enable these professionals to act in an adequate manner in the establishment of the diagnosis and treatment of CMPA in infants. Thus, it is possible for these professionals to review their therapeutic behaviors for guarantee of the quality of life of the infant, that is, the faster reversal of clinical manifestations and nutritional recovery, avoiding the use of dietary elimination based on inadequate behaviors and that can lead to nutritional deficits, besides rationalizing the use of resources in the treatment of patients with CMPA.

CONTRIBUTORS

DPB FARIA analyzed data, performed statistical analyses and wrote the paper. APB CORTEZ and PGL

SPERIDIÃO contributed to writing the manuscript. MB MORAIS reviewed it critically for important intellectual content, analyzed data, and wrote the paper. All authors participated in the conception and design of the study and gave final approval of the submitted version.

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