

Oral Provocation Test on the Diagnosis of Cow's Milk Protein Allergy in Children: Integrative Review

REVIEW

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Abstract

Introduction: The cow's milk protein allergy (CMPA) is considered the most prevalent food allergy in children, developing, usually, during the first three years of life and can cause gastrointestinal, respiratory and skin changes. Among the diagnostic methods used, there is the oral food challenge test. However, little used in clinical practice.

Objective: Identifying the importance of Oral Provocation Test (OPT) in the diagnostic confirmation of CMPA in children.

Method: An integrative review of studies of the last ten years, with six relevant articles related to the theme and used and described the OPT in children with suspected CMPA.

Results: The OPT is important to confirm the diagnosis, avoiding prolonged exclusion diets, nutritional risks and unnecessary expenses. The oral test with milk can be adopted as the gold standard and used as a basis for comparative studies that aims to advance the molecular diagnosis, determining the specificities and sensitivities of such tests. It can also be used with other foods. In innovative studies to determine the tolerance of dairy foods, allowing include them in the feeding of these patients during the elimination diet.

Conclusion: It is important that the OPT is performed early in the onset of symptoms suggestive of CMPA, in order to avoid prolonged exclusion diets, nutritional risks and unnecessary expenses.

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Keywords

Allergy; Food hypersensitivity; Cow's milk; Child; Diagnosis.

Introduction

Food allergies are hypersensitivity reactions initiated by an immune mechanism, in the presence of a food antigen, and can be triggered by a single protein. The most food related to food allergies in North America are cow's milk, eggs, peanuts, shellfish, wheat and soy, respectively [1].

The early introduction of cow's milk in the diet, in inadequate replacement for breast milk, contributes substantially to the cow's milk protein allergy (CMPA) that is considered the most prevalent food allergy in children, developing, usually during the first three years of life [2-3].

The allergy to milk protein also affects older children; however, the higher the age, the lower the incidence and the greater the chance of resolution. About 50% of children have resolution of CMPA at one year old and at the fifth year of age, this percentage ranges from 80-90% [4].

Although symptoms suggesting CMPA be found in 5-15% of children, five European studies show that the prevalence in childhood ranged from 1,9% in a Finnish study to 4,9% in a survey in Norway [5-6]. In Brazil, there is little information on the prevalence of CMPA, but on an analysis of new cases, we obtained an approximate prevalence of 5.4% [7].

It is estimated that the reporting of relatives is four times larger than the actual diagnosis. This fact increases the importance of giving accurate diagnosis and guide the family properly, as improper exclusion diet can lead to nutritional and developmental damage in children [4].

A variety of epidemiological data can be explained by the observation of various gastrointestinal, respiratory and skin symptoms common to other food allergies, and the non standardization of diagnostic methods, generating false positives [6].

The oral sensitivity test, currently, the gold standard is considered by several authors [8], but due to the risk of anaphylaxis, other methods such as skin testing, dosage of IgE antibodies and the do-

sage of protein degrading enzymes milk, gained ground in the diagnosis of CMPA [9].

The choice of subject was defined by the authors as they consider the relevant issue and realize difficulties on the part of health professionals, as the handling diagnosis of an allergy suspected framework cow's milk protein. Another existing problem are situations in which parents subject their children to extreme diets without proper professional guidance and without performing Oral Provocation Test (OPT), by supposing that they have said allergy.

It is therefore an integrative review of articles published in the last ten years on the diagnostic management of CMPA in children seeking understanding to the question: what is the importance of the OPT to confirm the diagnosis of CMPA in children?

Because of the scarcity of Brazilian studies about the subject and stressed the epidemiological need, this study aims to evaluating the importance of the main recommended diagnostic method for CMPA, the Oral Provocation Test (OPT).

Method

It is an integrative literature review, carried out in different stages [10]:

Step 1: Issue identification and selection of the research question

When considering the diagnosis of cow's milk protein allergy formulated the following question: How important is the Oral Provocation Test in confirming the diagnosis of CMPA?

Step 2: Criteria for sample selection

On 28th October, 2014, the survey was initiated by the database found in the Virtual Health Library (BVS): LILACS (Latin American and Caribbean Health Sciences) and the International PubMed database (Medical Plubished - serve of the US National Library of Medicine). The descriptors used were: *Journal of*

Human Growth and Development. allergy, to cow's milk, immunology, child, food hypersensitivity, allergic reaction, child nutrition, and milk protein.

The criteria used for inclusion of the articles were: articles published between 2005 and 2014 October, with abstracts and free-fulltext available in the used bases, which they referred to the diagnosis of CMPA or the diagnosis was included in its methodology, with methods that selected, clinical studies, randomized controlled trials, systematic reviews and meta-analyses.

In LILACS, after use as descriptors in Advanced Search child AND food hypersensitivity were found 68 articles, and selected two of these. Besides these were used child AND allergy and immunology, with 45 articles; Child AND allergic reaction, yielding 165 results; DNA cow's milk allergy, articles 45; AND food hypersensitivity milk proteins, lying 59 articles. None of these articles were selected and in the latter there were two articles that had already been selected, there were also used child AND nutrition in children not getting results. Through the words AND allergy cow's milk, 21 articles were found, and of these, three were selected. In other searches we used child AND allergy and immunology, resulting in two articles; not getting results related to the topic. With the descriptors child AND food hypersensitivity, child AND nutrition in children have not obtained results.

In the international basis PubMed there were used two searches. In the first are 506 articles after the descriptors: *cow's, milk, allergy, diagnoses and children*. Applying filters as a free-fulltext, text published in the last 10 years, humans, clinical studies, randomized clinical trial, systematic reviews and meta-analysis, remaining 7 articles, of which 3 were selected. In the second search the words used were *children and milk protein allergy*, and found 21 articles, but only two were selected.

Step 3: Identification of pre-selected and selected studies

After the initial selection, which evaluated the titles and resumes of the articles found, there were ob-

tained seven articles in LILACS and five in PubMed. Detailed were read such articles, analyzing whether they would fit in profiling to work. Therefore, only six articles were selected, three of these in PubMed and three in LILACS.

Step 4: Categorization of studies

Step similar to data collection performed in traditional researches. Therefore, we used an instrument validated by Ursi [11], to collect important information about the articles selected for this integrative review, containing the following items: identification of the original article, methodological characteristics of the study, assessment of methodological rigor, the measured and the results found interventions.

An array of synthesis with articles and most relevant points contained therein guided the thorough analysis of the contents of the articles and synthesis of these, taking into account their levels of evidence and its relevance to give reference to the conclusions reached.

Step 5: Analysis and interpretation of results

A critical analysis of selected articles from the inclusion criteria was carried out; the various conflicting results as to obtain the response to the inquiry based study. Information was gathered and synthesized to expose consistent information of the work and confront the discordant or unrelated to each other.

Step 6: Presentation of synthesis of knowledge

The findings were based on the evidences obtained and on the critical analysis of results found.

Results

Specifics about the articles analyzed

Frame 1 made from synthetic matrix lists the articles selected as titles, objectives, authors, publication year and the level of evidence.

As for the date of publication, an article was published in 2012, three in 2013 and two in 2014.

Frame 1. Specifics about the articles analyzed, as for the title, purpose, search type and level of evidence.

Authors	Title, language and periodic	Objective	Type of the study	Level of evidence
Sommanus e col., 2013 [17]	Cow's milk protein allergy: immunological response in children with cow's milk protein tolerance. Inglês/Asian Pac J Allergy Immunol	To study changes in immunological responses in patients with CMPA during symptomatic and asymptomatic episodes of cow's milk protein tolerance status.	Non-randomized clinical study	IV
Dambacher e col., 2013 [5]	Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses Inglês /Nutr J	To evaluate if excluding CMA by a DBPCFC that includes assessment of late reactions prevents unnecessary elimination diets in the long term.	Randomized double blind study	III
Alessandri e col., 2012 [18]	Tolerability of a Fully Maturated Cheese in Cow's Milk Allergic Children: Biochemical, Immunochemical, and Clinical Aspects Inglês/PlosOne	To biochemically and immunologically characterize PR samples at different maturation stage and to verify PR tolerability in CM allergic children. Seventy patients.	Randomized double blind study	III
Correa e col., 2010 [15]	Open challenge for the diagnosis of cow's milk protein allergy Português/J. Pediatr. (Rio J.)	To report the results of an open challenge protocol performed in two Brazilian pediatric gastroenterology services in children fed with cow's milk-free diet.	Cross-sectional study	V
Lins e col., 2010 [16]	Oral food challenge test in the diagnostic confirmation of allergy to cow's milk protein Portuguese/J Pediatr (Rio J)	To determine the prevalence of cow's milk protein allergy in children with symptoms attributed to cow's milk intake.	Non-randomized clinical study	IV
Epifanio e col., 2013 [19]	Cow's milk allergy: color Doppler ultrasound findings in infants with hematochezia Portuguese and English/J Pediatr (Rio J)	To describe grayscale and color Doppler ultrasound findings in infants with hematochezia due to allergic proctocolitis.	Case report	VI

Source: Prepared by the authors. PubMed; LILACS, 2005-2014 oct.

Regarding the languages found three articles are written in English, two in Portuguese and is available in both languages mentioned.

The articles were published in the following journals: Journal of Allergy and Immunology (1 article), Nutrition Journal (1 article), PLoS ONE (1 article), Journal de Pediatria (Rio J.) (3 articles). These cover areas such as general pediatrics, allergology, immunology and nutrition.

The number of patients studied in the surveys ranged from 13 to 121, aged zero to 16, with prevalence below 24 months.

The method used in the six articles was the randomized clinical trial with <1000 patients (level III), non-randomized clinical study (level IV), cross-sectional observational study (level V) and case reports (level VI). Thus, most, has good evidence, considering the clinical question addressed [12-14].

Evidence about the use of OPT in the studies evaluated

To guide the review of the evidence found in the articles selected, **Frame 2** reports the importance of completing the OPT in the studies.

Frame 2. F Importance of Oral Provocation Test (OPT).

Authors	Diagnostic criterion	Identification criterion of cure	Definition of the threshold of tolerability
Sommanus e col., 2013 [17]	The OPT was the method used to diagnose children with suspected CMPA, subjected to immunological studies, with dosage of specific IgE in symptomatic and asymptomatic periods. The positivity of the method was pre-selected patients inclusion criteria, in order to avoid the dosage of immunoglobulins in Qatar, for causes not related to CMPA.	The OPT was held six months or a year old, after the diagnosis, to subdivide patients into two distinct groups, those who have achieved the cure and those who remained allergic, and thus, their dose immunoglobulins and correlate with the status of the patient's tolerance.	-
Dambacher e col., 2013 [5]	Performed the oral food challenge test double-blind placebo-controlled to prevent patients make unnecessary use of exclusion diet cow's milk proteins. In addition, the test still aimed to estimate a minimum tolerated by each patient in order to avoid a strict exclusion diet, for those patients diagnosed with CMPA, which tolerate trace amounts of cow's milk.	-	Determine the minimum quantities of cow's milk tolerable by CMPA patients, to prevent severe reactions to ingestion of foods that may contain traces of milk, and stringent exclusion diets.
Alessandri e col., 2012 [18]	The test confirmed the diagnosis of patients with suspected CMPA and was adopted as the gold standard diagnosis to determine the sensitivity and specificity of other tests that assist in the diagnosis.	-	The OPT was performed with the cheese matured in order to highlight this milk product tolerance in patients with CMPA.
Correa e col., 2010 [15]	The test was negative at 76.86% of children who were on a diet of exclusion of cow's milk and derivatives allowing the suspension of this conduct. In addition, it allowed catch different symptoms of the initially reported on 12 of 28 patients with positive test.	-	-
Lins e col., 2010 [16]	It was important to give the definitive diagnosis and determined the prevalence of CMPA in 65 patients, to diagnose CMPA, after 15 days on a diet of exclusion with observation period of up to 4 weeks after the test.	-	-
Epifanio e col., 2013 [19]	Confirm the diagnosis of proctocolite secondary to CMPA in 13 newborns with presence of hematochezia. The test was used after 4 weeks on a diet of exclusion, to assess the tolerability or the persistence of CMPA.	-	-

Source: Prepared by the authors. PubMed; LILACS, 2005-2014 Oct.

The purpose of the use of OPT in the methodology of the articles was set the diagnosis or evaluating the diagnosis and tolerability of patients after exclusion diets. However, two studies, [15-16] mainly aimed minimally evaluate the results after the imple-

mentation of the oral food challenge test, including the prevalence of CMPA.

A study was conducted where the OPT, dosage immunoglobulin antibodies (IgE) and specific *skin prick test* (SPT) in 37 children with suspected CMPA,

between zero and five years old to dose levels of immunoglobulins and interleukins, the symptomatic period and asymptomatic patients with CMPA. But regardless of IgE and SPT values, six children (16%) of the 37 selected were excluded from the study for not presenting positive reaction to OPT. In carrying out the retest, six months after diagnosis or one year old, while 11 children had high IgE positive and 20 children SPT positive, 13 (42%) of the patients had tolerance to cow's milk protein. The average age of diagnosis of CMPA was eight months; however, the first symptoms appeared at three months [17].

The OPT demonstrates that the dosage of specific IgE and SPT cannot be relied upon to give the diagnosis or confirm it. This is because, despite the high levels of IgE or SPT positivity, children can be tolerant and do not need more of an exclusion diet [17].

Another study evaluated children treated in a regional hospital in the Netherlands, with signs and symptoms suggesting CMPA, with protein diet free of cow's milk for at least four weeks during the period from October 2005 to June 2009 there were included 116 children who have achieved the OPT [5].

In this research the OPT was conducted as double-blind food challenge placebo-controlled trial, considered placebo infant formula of the child hydrolyzed, with which she had no symptoms. On the other hand, the test food containing a concentration of cow's milk protein 1.8g/100mL [5].

Of the children evaluated, 76 (66%) did not confirm the diagnosis of CMPA, after the OPT. Allergic reactions observed in 38 (33%) children with a positive OPT, 12 were acute (32%), 15 were late (39%) and 11 (29%) had acute and delayed reactions. Another important fact observed in the study was that infants under one year old. Of higher doses showed triggering reactions than other children, suggesting that children require larger amounts of cow's milk protein to have allergic reactions when compared to older children [5].

Likewise, the study of Correa [15] and collaborators demonstrated the importance of OPT to confirm the

CMPA, decreasing the number of patients exposed to unnecessary diets and that can generate changes in the neuro-psychomotor development of children.

A randomized clinical study to define the tolerance of patients with CMPA to a particular kind of matured cheese and trace their biochemical profile and the immune response to cheese. For this, the researchers conducted a double blind placebo controlled food test (DBPCFC), cow's milk and an open oral test, with cheese specified [18].

In the sample, 54 (77.1%) of 70 patients responded to milk, the diagnosis was excluded in 16 patients (29.6%); 4 children of the sample tracking lost kids 29 (58%) of the 50 allergic patients tolerated the cheese. Only they were considered symptoms caught soon after test [18], a fact considered a failure since delayed reactions can happen. The guests were considered tolerant to continue consuming the cheese later according to the family habits, but the follow-up of these patients did not occur rigorously.

In work of Correa [15] and collaborators there was a data collection of the results of realization of the open OPT in 121 children followed at two different clinics of Pediatric Gastroenterology. The elimination diet, before performing the test, was less than 12 weeks in 31 patients (21.6%); between 12 and 23 weeks in 28 patients (23.1%); between 24 and 47 weeks in 42 children (34.7%) and over 48 weeks in 20 children (16.5%). That's over half of the patients, 51.2% performed the test over six months of exclusion diet. The test was positive only in 28 patients (23.1%), 12 of these had different manifestations of the initial; 14 reactions were within 4 hours, 7 hours and 24 and 3 in over 24 hours. Different reactions and symptoms reported with onset after 24 hours were observed. The positivity of the test only 23.1% and was greater in children use of substitute formulas, may have given a result of the prolonged elimination diet, in most patients, may have favored the appearance of tolerance before the actual diagnosis [15].

A study corroborates this conclusion, that in six months after diagnosis, nearly half of patients who

had positive OPT developed tolerance, indicating early remission of the disease [17].

Another study determined the prevalence and diagnosis of 65 patients with suspected CMPA, sent to pediatric gastroenterology reference services at the Hospital das Clinicas in São Paulo and the Federal University of Pernambuco in Recife. In 46.8% of patients the CMPA was not confirmed. Outpatient follow-up four weeks was extremely important, because 77% of diagnosed patients had only delayed reactions [16].

Studies conducted in the Netherlands [5] and another in Brazil [16] showed that the realization of the OPT is necessary to avoid diagnoses based on complaints, and that the follow-up is necessary, not to underestimate them.

The OPT conducted research in the Netherlands [5] quantified the symptoms of diagnosed patients. Of the 35 patients who were positive, 24 had a symptom and 11, two symptoms. The result confronts the many symptoms reported in previous visits to the OPT.

Findings on ultrasound (US), Color Doppler Ultrasound (USDC), colonoscopy and biopsy suggestive of CMPA, with OPT. There were evaluated 13 neonates, with ages ranging from one to six months of age who had hematochezia. Of these, 92.3% (12 patients) had abnormalities at US and USDC. Only one child showed no change in the thickness pattern of the intestinal wall or circulatory loop submucosa that was suggestive of allergic colitis [19].

Thus, the authors [19] showed that the ultrasound and the USDC helped establish the diagnosis of colitis and complemented the CMPA. However, it was not required for the diagnosis of CMPA, as changes can be found in infectious colitis. As the above tests, colonoscopy with biopsy, which was performed in some patients, it does not bring a pathognomonic finding of CMPA, but suggests the presence of allergic colitis.

The OPT was performed after four weeks of elimination diet (patients used extensively hydrolyzed

formula, amino acid formula and exclusive breastfeeding with exclusion diet made by the mother). The authors [19] explain that the negative result to the US may have been caused by a delay in the examination, which took place four days after the elimination diet, allowing the patient had improved intestinal inflammatory condition.

Discussions

Although some studies attempting to demonstrate that the diagnosis could be given by CMPA molecular diagnostics and skin prick test (SPT), respectively, [8-9], the way of giving more reliable diagnosis is by OPT or challenge test [21].

Some studies have demonstrated the need for adequate quantities of rotulações on cow's milk protein in food products. This would be important to assess the level of tolerability with older children, allowing parents to observe the amount of protein tolerated by children, and thus lowering dietary restriction [22-23].

The findings of the research of Dambacher [5] and collaborators held in the Netherlands demonstrated the determination of lower doses of cow's milk proteins that cause reactions in the patients studied, drawing attention to products that may contain traces of milk in the composition and generate reactions. This fact was also noted and evaluated in another study [20], by showing children respond to soybean milk products due to the use of common output lines to cow's milk. In addition, authors [5] says that older children have a response threshold to lower allergen that children under 12 months, provided also by other scholars factor [20], which claim that most children with CMPA presents tolerance only after the seven years old; emphasizing the care that we also have with children older than one year.

Most studies do not provide specifications for all stages or of its preparations, hindering compared studies published on the subject. However, research carried out in Italy [8] differs from other analyzed

to specify, in detail, how the test is performed and the preparation containing proteins. Adopting the gold standard for the DBPCFC milk and OPT with cheese, the authors could determine the sensitivity and specificity of other tests that aid in the diagnosis, as SPT and dosage of specific IgE.

In a study conducted in New York [24], confirmed the tolerance of some patients with CMPA to cooked milk and cheese baked under certain temperatures. However, authors [18] shows that there can be tolerance to milk products are not subjected to high temperatures. The authors [18, 24] corroborate that OPT can be used with cow's milk, to make diagnosis and perform it with other foods supposed tolerated by patients, to include such foods in the diet, either so strict, the supposedly allergic children.

Failure to achieve OPT leads to an increase of the time of elimination diet, exposure of these children to unnecessary nutritional risks and increased costs diets which include protein hydrolysates or amino acids formulas.

In addition to the nutritional changes that occur due to the fact that milk is the main source of fat and protein in early childhood, the exclusion diet of cow's milk is a problem due to the high number of foods that use of this ingredient in its composition [20, 25].

One of the largest studies in Brazil to map the nutritional status of patients on elimination diets, which had not made the OPT, showed nutritional deficits arising or inadequate substitutes or insufficient duration of treatment [7].

Before the study work, one can see one common information to all: the discrepancy between the numbers reported symptoms related to CMPA and the actual diagnosis of these after the OPT. In Brazilian studies related to the confirmation of the diagnosis with the OPT, the prevalence of diagnosis in patients with symptoms suggesting CMPA ranged from 23% [15-16].

In food allergies in general, when diagnosis is performed using the described symptoms by the parents, the rates ranging up to 35% and, when

double-blind placebo-controlled study used approximately 1% [7].

Similar results were observed in the surveys [5, 17, 20], pointing out that the exaggeration by the relatives to report symptoms allegedly presented, may lead patients to unnecessary exclusion diets.

It was evident between studies analyzed a disparity between the ages of patients without diagnostic signed, and there was no adoption of methodological forms equal to the realization of the OPT. These observations demonstrate the need to hold the OPT, the remission of symptoms, and adoption of similar methodologies in its realization, to enable a comparison of results between studies.

Conclusions

The OPT is important to confirm the diagnosis of CMPA, for studies that seek the affirmation of new diagnostic tests and to determine the tolerance of dairy foods that undergo high temperatures or maturation processes.

However, the elimination diet followed by the OPT remains the gold standard in the diagnosis of CMPA, despite the risk of obtaining false positives and false negatives results. It can be seen that current studies have not yet managed to develop specific laboratory tests or identify clinical changes pathognomonic of CMPA.

Studies examined here showed high rates negative for oral provocation test, ranging from 16% to 66%. Reaffirming the importance that it be held earlier the onset of symptoms suggestive of this condition in order to avoid prolonged exclusion diets, nutritional risks and unnecessary expenses, based only on clinical complaints. In addition, the quantity and the variety of reactions to milk proteins, reported by relatives, may differ markedly from those observed after application of OPT.

While the evidence of the studies analyzed have varied, the level of evidence III to VI, the results were discordant with each other. Differences in prevalence of CMPA after performing the OPT, in studies,

occurred due to methodological differences of the analyzed works.

Studies examined here showed high rates negative for oral provocation test, ranging from 16% to 66%. Reaffirming the importance that it be held earlier the onset of symptoms suggestive of this condition in order to avoid prolonged exclusion diets, nutritional risks and unnecessary expenses, based only on clinical complaints. In addition, the quantity and the variety of reactions to milk proteins, reported by relatives, may differ markedly from those observed after application of OPT.

Furthermore, there is, in most cases, a prolonged time interval between the first symptoms exhibited by children and to confirm the diagnosis, both in the studies reviewed, as in the available literature, devaluing the importance and relevance of OPT.

Finally, the test with milk can also serve as a basis for comparative studies that aims to advance the molecular diagnosis and innovative studies to determine the tolerance of dairy foods in order to include them in the feeding of these patients during the elimination diet.

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