Original article

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Cow's milk allergy: Can oral food challenges be avoided? A probabilistic analysis based on clinical data

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ABSTRACT

Introduction. The oral food challenge (OFC) for the diagnosis of cow's milk protein allergy (CMPA) poses risks and requires resources. Our objective was to assess conditions and complementary tests used to identify a high probability of CMPA.

Population and methods. Secondary analysis of a study of patients seen at a unit of allergy between 2015 and 2018. Pre-testing probabilities associated with symptoms and their combinations and post-testing probabilities after skin prick testing and serum immunoglobulin E (IgE) levels were determined.

Results. The data from 239 patients were assessed. A probability greater than 95% was observed for angioedema and a combination of urticaria and vomiting. Based on the cut-off points proposed by Calvani et al., the combination of vomiting with rhinitis, without angioedema, also exceeded 95%.

Conclusion. A methodology is provided to identify patients in whom CMPA may be diagnosed without an OFC.

Keywords: *milk allergy; clinical diagnosis; predictive value of tests.*

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INTRODUCTION

Food allergies have increased worldwide;[1,2] cow's milk protein allergy (CMPA) is the most frequent allergy during childhood. CMPA diagnosis requires a systematic process, but the oral food challenge (OFC) is the gold standard.[3,4] However, its implementation requires a considerable amount of resources and is not without risks, including anaphylaxis.[5]

In order to avoid the inherent risks of OFC in some patients, it is suggested that both the specific conditions and skin prick test (SPT)/ specific serum IgE (sIgE) results could help to identify patients with an increased probability of CMPA, avoiding the performance of further tests.

Several authors have proposed the use,[5,6] during the decision-making process, of a 95% probability threshold. However, although several attempts to elucidate this point have been made, the methodology for estimating the pre-OFC probability has not been clearly established.[5]

Recently, we performed a utility analysis of diagnostic tests to diagnose CMPA in the population attending our unit between 2015 and 2018, with patients who received a final diagnosis after doing an OFC.[7] From the same data set, we obtained information on conditions present at the time of the visit that help to determine the pre-test probability of developing CMPA due to any of them. This information could be used in combination with SPTs and sIgE results to estimate the probability of CMPA before performing an OFC.

POPULATION AND METHODS

Data source

This is a secondary analysis based on data from the same group of patients reported in our previously published study titled: "Usefulness of analytic tests for the diagnosis of cow's milk protein allergy,"[7] a cross-sectional, retrospective analysis of 239 medical records of patients who had performed an OFC. The methodology used in our unit is based on that suggested in the DRACMA guidelines,[8] with some changes already described in our previous publication (*Figure 1*).[7]

VARIABLES

The variables of analysis included symptoms, signs, and conditions present at the time of consultation (diarrhea, vomiting, intestinal bleeding, colic, urticaria, angioedema, growth retardation, excessive crying, or anaphylaxis) and the patient's age. Some patients arrived at our hospital referred by other health care teams with conditions that had been diagnosed in advance (atopic dermatitis, gastroesophageal reflux, or rhinitis). These conditions were included as variables in the analysis because they were present at the time of the consultation.

Statistics

We used a Bayesian approach throughout the analysis. According to it, any combination of conditions at the time of consultation allows us to establish an initial probability of CMPA (referred to as "pre-test probability") that will then increase or decrease based on the results of the tests performed, which will yield a new probability (referred to as "post-test probability"). The likelihood ratios (LR) obtained in the previous study were used here to make a conversion between both values.[7]

The pre-test probability was established using a logistic regression, which allowed us to obtain the estimated probability in each patient in the data set.

To separate patients into groups according to their probability, conditions, and age, we used a decision tree whose leaves included estimated probabilities. We used these estimated probabilities to apply positive likelihood ratios (LR+) and negative likelihood ratios (LR-) and thus obtain post-test probabilities. We also used different cut-off points (milk SPT: 8 mm, alpha SPT: 4.9 mm, beta SPT: 5.6 mm, casein SPT: 4.3 mm), based on Calvani et al.,[5] to assess changes in post-test probabilities. We relied on a probability value of 95% as a decision threshold to avoid the performance of an OFC.

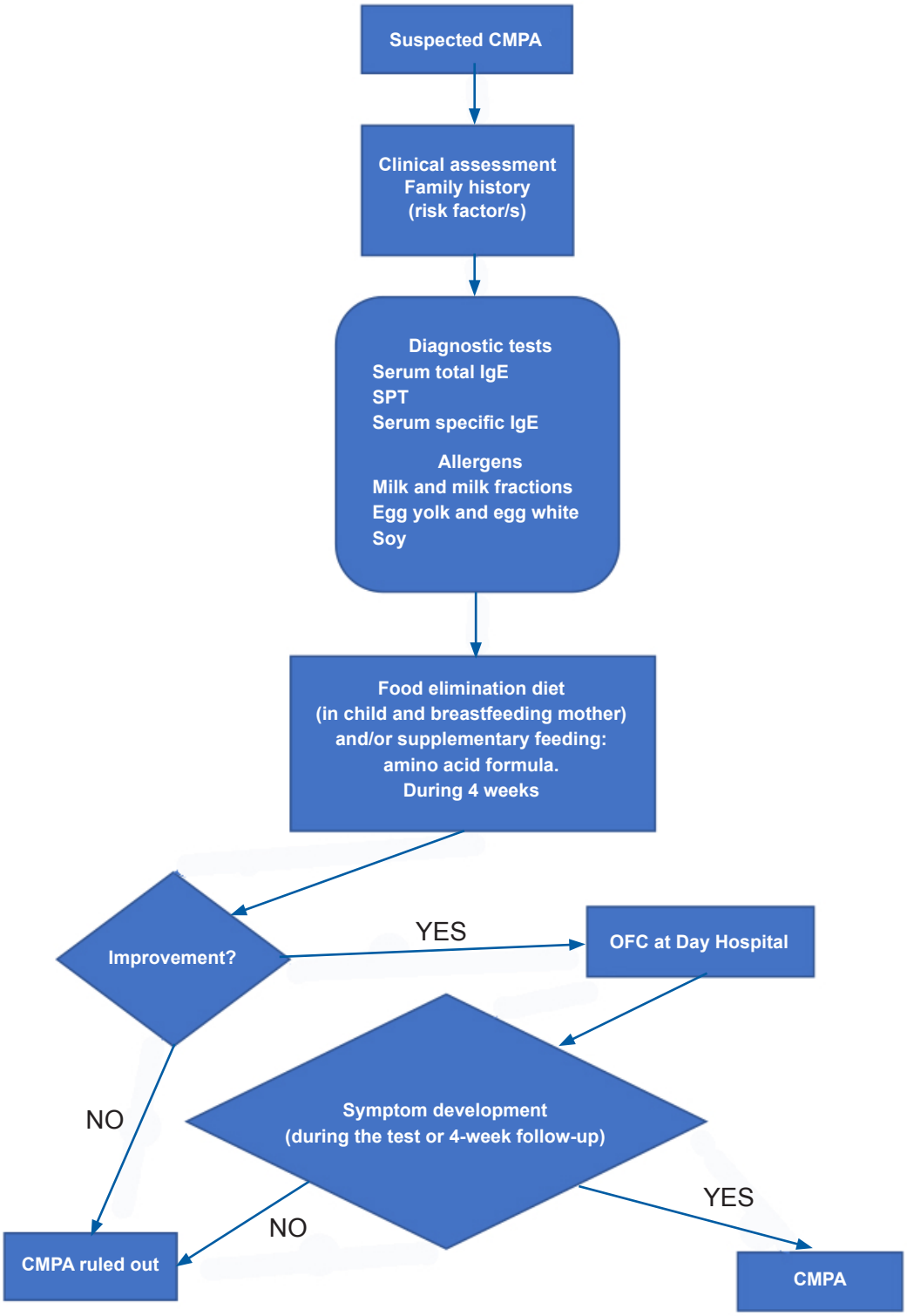
RESULTS

We identified the presence of urticaria, angioedema, rhinitis, and vomiting as significant independent predictors (*Table 1*).

The visualization of the decision tree allowed us to easily obtain the probabilities in any disease pathway (*Figure 2*).

Using that condition-associated probability, we applied the maximum LR+ and minimum LR- obtained during the previous study (4.46 for casein SPT and 0.69 for SPT and sIgE combined, respectively) and estimated the post-SPT and post-sIgE probability for the maximum probability associated to those conditions (angioedema was associated with a CMPA probability of 88% and the combination of urticaria and vomiting, with a CMPA probability of 80%). Combined symptoms

Figure 1. Diagnostic algorithm for the assessment of patients with suspected cow's milk protein allergy used in the Unit of Allergy of Hospital Elizalde (according to the DRACMA guidelines)



IgE: immunoglobulin E. SPT: skin prick test. OFC: oral food challenge. CMPA: cow's milk protein allergy.

Table 1. Multivariate logistic regression coefficients for conditions associated with cow's milk protein allergy

Variable	Estimation	Standard error	z value	Pr(> |z|)
(Intercept)	-0.75	0.37	-2.05	*0.04085
Vomiting	0.98	0.33	2.30	**0.00274
Angioedema	1.98	0.71	2.78	**0.00549
Rhinitis	1.06	0.47	2.25	*0.02438
Urticaria	0.73	0.34	2.15	*0.03199
Age	-0.0007	0.0004	-1.73	0.08377
Excessive crying	1.003	0.98	1.02	0.30700
Anaphylaxis	1.26	1.27	0.99	0.32217
Growth retardation	0.31	0.38	0.80	0.42127
Colic	0.18	0.49	0.37	0.71124
Diarrhea	0.23	0.32	0.72	0.47151
Intestinal bleeding	-0.24	0.34	-0.71	0.48102
Atopic dermatitis	-0.19	0.39	-0.50	0.61873
Gastroesophageal reflux	0.10	0.38	0.26	0.79195

Pr(> |z|): probability of obtaining a value higher than the absolute z value.
** p < 0.05.*
*** p < 0.01.*

showed a post-test probability of 97% and 95%, respectively (*Table 2*).

After applying modifications to the cut-off points, as suggested by Calvani et al,[5] we obtained better positive predictive values (PPV), specificities, and LR+. The best LR+ was 6.8, which was obtained for the milk SPT, with a LR- of 0.94.

Again, using the condition-associated maximum probability (angioedema: CMPA probability of 88%, combined urticaria and vomiting: CMPA probability of 80%, and combined vomiting and rhinitis in the absence of angioedema or urticaria: CMPA probability of 76%), the post-test probability obtained was 97.8%, 96.2%, and 95%, respectively (*Table 2*).

DISCUSSION

In this study, we used the patient's conditions present at the time of consultation to determine their pre-test probability of CMPA. We applied the previously determined LR+ and estimated the post-test probability of CMPA to establish whether the proposed probability threshold of 95% could be reached. In this way, we were able to observe that patients with a history of angioedema or urticaria plus vomiting, in the context of cow's milk exposure, had a post-test probability at or above such clinical decision threshold.

In our study, the overall prevalence at the time of the initial consultation was 52.7%. Therefore, these results may be useful at departments with a similar CMPA frequency. Many studies have described prevalence values closer to our prevalence.[6,9–15]

The pre-test probability, which is based on symptoms, may be difficult to establish.[5] Using a methodology such as the one described here, other authors could also make an estimation.

In addition, we explored different cut-off points, as suggested in other studies.[5] With the different cut-off points, we obtained better post-test probabilities, which allowed us to include more patients above the proposed decision threshold.

A limitation of our study was the presence of cases diagnosed at home, before performing the OFC at the hospital. However, we believe that this study reflects the reality of daily practice in our region, so our results may be useful even in the aforementioned scenario. We also believe that using amino acid formulas from the beginning allowed us to rule out the diagnosis of CMPA with greater reliability.

These analytical tools could be used by other health care teams to add useful information in their clinical decision-making processes in relation to patients with CMPA. ■

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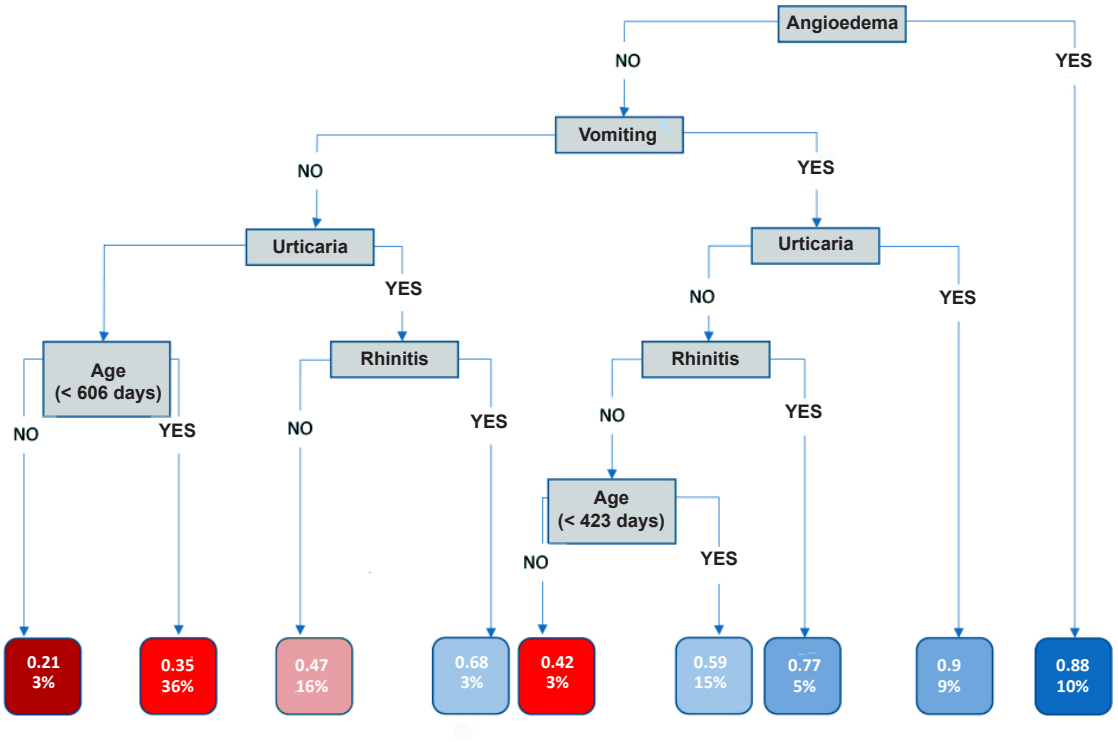
Figure 2. Prediction tree to determine the probability of being diagnosed with cow's milk protein allergy associated with age, presenting conditions, and/or combinations



** The age cut-off points arise, in the decision tree process, from the division of a parent node into two child nodes; we sought to maximize the difference for the probability of being diagnosed with cow's milk protein allergy between these child nodes. The most intense blue color means the highest probability of being diagnosed with CMPA. The intense red color means the lowest probability. The lighter colors indicate intermediate values. The cut-off point for a change in color is 0.5.*

Table 2. Pre- and post-test probability values for different combinations of initial conditions and after applying the positive likelihood ratios corresponding to the tests, according to the original and the modified cut-off points proposed by Calvani

Cut-off points	Test	LR+	Conditions	Pre-test probability	Post-test probability
Original	Casein SPT	4.46	Angioedema	88.0%	97.0%
			Urticaria and vomiting	80.0%	95.0%
Calvani	Milk SPT	6.80	Angioedema	88.0%	97.8%
			Urticaria and vomiting	80.0%	96.2%
			Vomiting and rhinitis, no angioedema	77.0%	95.0%

LR+: positive likelihood ratio.
SPT: skin prick test.

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