White paper

Diagnosis of Cow's Milk Allergy: Are low levels of specific IgE significant?

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Diagnosis of Cow's Milk Allergy: Are low levels of specific IgE significant?

Reported here are the results of a clinical study conducted on infants referred to our clinic at the Sant Joan de Déu Hospital for suspicion of cow's milk allergy.

Management of food-allergic children

In Spain, allergy to cow's milk proteins is the third most frequent cause of food allergy occurring in infancy, after allergy to eggs and fish. Diagnosis of cow's milk allergy (CMA) is based on clinical case history, determination of IgE sensitization using a skin prick test (SPT) along with measurement of total IgE (tIgE) and allergen-specific IgE (sIgE), and oral food challenge (OFC).

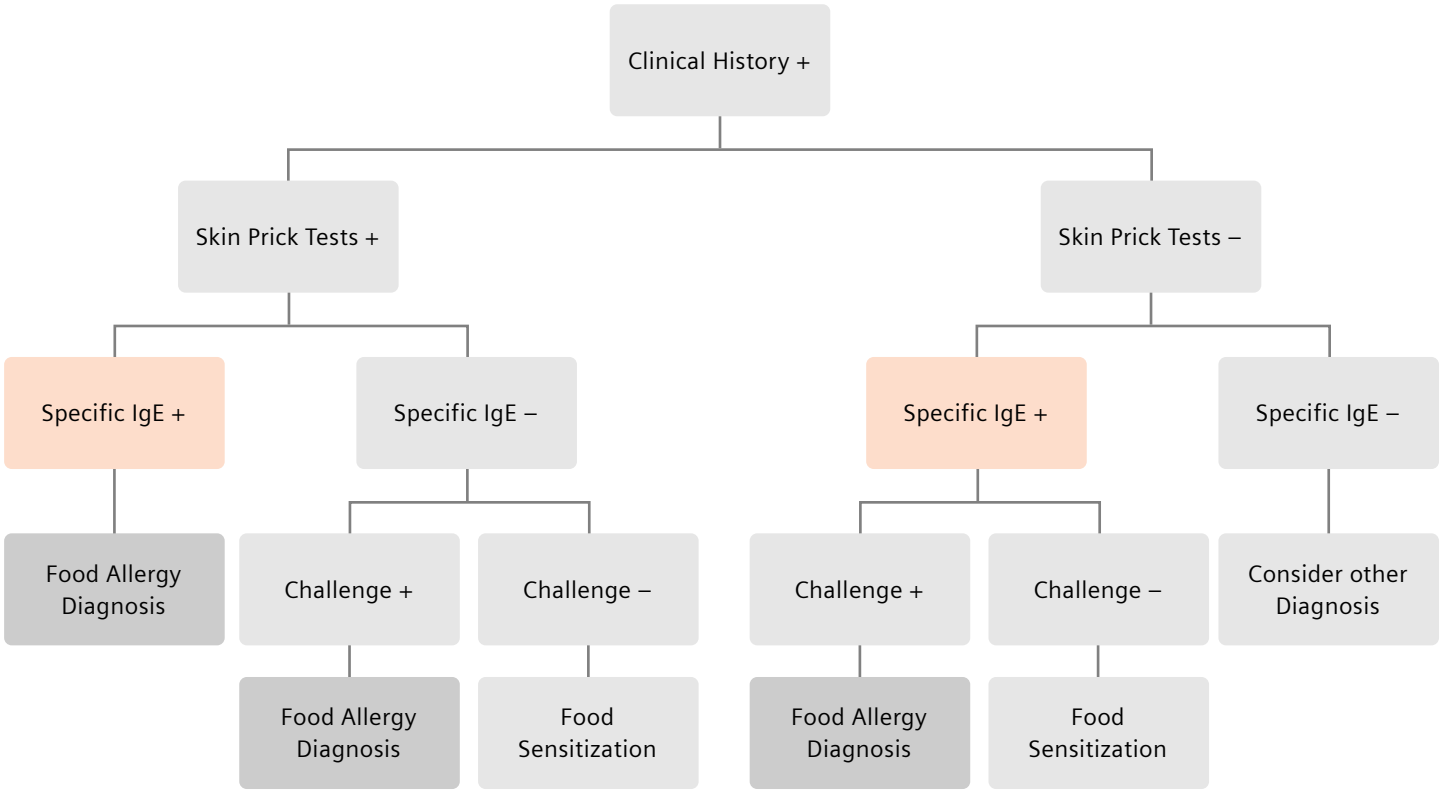
Figure 1 displays the algorithm for diagnosis of food allergy in infants at Sant Joan de Déu Hospital. A positive clinical history of allergy is followed by a skin prick test. A positive reaction to skin prick test and a negative result for sIgE requires resolution by an oral challenge. The same rule is applied with a negative skin prick test and a positive result for sIgE. When oral challenges are negative, a food sensitization is diagnosed. When the oral challenge is positive,a food allergy is diagnosed.

Measurements of sIgE against single cow's milk protein components (α-lactalbumin, β-lactoglobulin, casein) are preferred to measurement of sIgE against cow's milk extract. Single components provide additional information; for example, a correlation between elevated levels of casein sIgE levels and the persistence of clinical symptoms has been reported.[1]

Study objectives

In allergology, OFC is considered the "gold standard" method since it is the only test that can establish a causal relationship between the offending allergen and clinical symptoms. However, OFC can also induce severe patient reactions and side effects, and is a time-consuming practice. Therefore, the objective of this study was to evaluate the diagnostic efficiency of two in vitro sIgE methods for identifying allergic patients, and to improve selection criteria of patients who should undergo OFC. Measurements of sIgE down to 0.1 kU/L were also assessed to determine if low-level detection improves identification of allergic patients.

Figure 1. **Algorithm for diagnosis of food allergy in infants at Sant Joan de Déu Hospital, Barcelona.**



Population

Sixty consecutive infants (27 females and 33 males) who visited the Allergy Service of the Sant Joan de Déu Hospital for suspicion of cow's milk allergy were studied. Parents were asked to sign an informed consent for their children. The age of clinical symptom onset was 3.5 months (range: 0.5 –12), whereas the age at diagnosis was 9 months (range: 0.8 –14). A family history of atopy was reported in 16 infants, and the clinical symptoms listed in Table 1 were observed. Some infants had more than one symptom.

Skin Prick Tests

SPTs were performed on the patients' forearms (data not shown) using a positive and negative control. Extracts (LETI®) for total milk (5 mg/mL), α-lactalbumin (5 mg/mL), β-lactoglobulin (5 mg/mL), and casein (10 mg/mL) were used. A wheal diameter larger than 3 mm was considered positive.

Specific IgE Measurements

Two different methods for measurement of sIgE were used: the ImmunoCAP® system FEIA, with a positive cutoff of 0.35 kU/L; and the IMMULITE® 2000 3gAllergy™, with an analytical sensitivity and positive cutoff of 0.1 kU/L and 0.2 kU/L, respectively. Cow's milk, α-lactalbumin, β-lactoglobulin, and casein allergens were tested by both methods.

Table 1. Clinical symptoms of infants referred to Sant Joan de Déu Hospital on suspicion of cow's milk allergy.

Symptoms	N
Skin Symptoms	**44**
Erythema	14
Urticaria	28
Angioedema	5
Atopic Dermatitis	10
Gastrointestinal Symptoms	**27**
Vomiting	22
Diarrhea	8
Rejection	9
Anaphylaxis	**4**

Oral Food Challenge

The children who underwent the OFC received, on the first day, increasing doses of 2, 5, and 10 mL of milk at 90-minute intervals. On the second day, the doses were 25 and 50 mL; and on the third day, 150 and 200 mL. An OFC was considered positive if any clinical symptom appeared.

Statistics

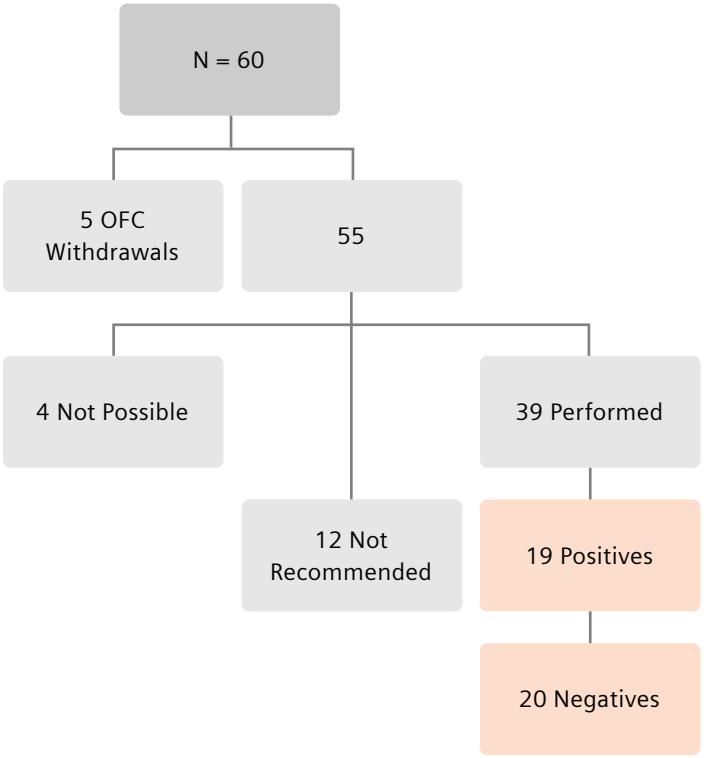
SPTs were performed on the patients' forearms (data not shown) using a positive and negative control. Extracts (LETI®) for total milk (5 mg/mL), α-lactalbumin (5 mg/mL), β-lactoglobulin (5 mg/mL), and casein (10 mg/mL) were used. A wheal diameter larger than 3 mm was considered positive.

Results

Oral Food Challenge (Primary Variable)

Four children who were at high risk of anaphylaxis and 12 children with sIgE levels against milk or milk components higher than 3 kU/L[2] did not undergo OFC testing. In addition, five patients' parents did not give their authorization for the challenge. In total, 21 patients were excluded from the challenge. Among 39 children who underwent the OFC, 19 had a positive response to OFC and 20 were negative, as shown in Figure 2.

Figure 2. Outcome of OFC.



Skin Prick Tests

Comparison of SPT results to OFC showed a specificity of > 85% for all allergens tested, whereas sensitivity varied from 38% (casein) to 53% (α-lactalbumin). When results for all milk allergen components were combined, the sensitivity and specificity were 63% and 85%, respectively (Table 2).

Table 2. Results of skin prick tests (Fischer's exact test study).

	Sensitivity	Specificity
Cow's Milk	47%	90%
α-Lactalbumin	53%	90%
β-Lactoglobulin	41%	90%
Casein	38%	100%
All Proteins Combined	63%	85%

Specific IgE Measurements

Agreement between OFC and the two in vitro methods at their respective positive cutoffs was 80% for 3gAllergy and 72% for ImmunoCAP.

Table 3. Results of sIgE for 3gAllergy assay.

3gAllergy	Positive Oral Food Challenge*	Negative Oral Food Challenge	Agreement
IMMULITE 2000 ≥ 0.2 kU/L	29	5	
IMMULITE 2000 < 0.2 kU/L	6	15	
Total	35	20	80%

Table 4. Results of sIgE for ImmunoCAP assay.

ImmunoCAP	Positive Oral Food Challenge*	Negative Oral Food Challenge	Agreement
ImmunoCAP ≥ 0.35 kU/L	25	5	
ImmunoCAP < 0.35 kU/L	10	15	
Total	35	20	72%

The ROC analysis is summarized in Table 5 and Table 6. In all cases, 3gAllergy assay sensitivities were higher than those for the ImmunoCAP assay, maintaining specificities of ≥ 85%. The area under the curve was closer to the optimal point of 1 for the 3gAllergy assay.

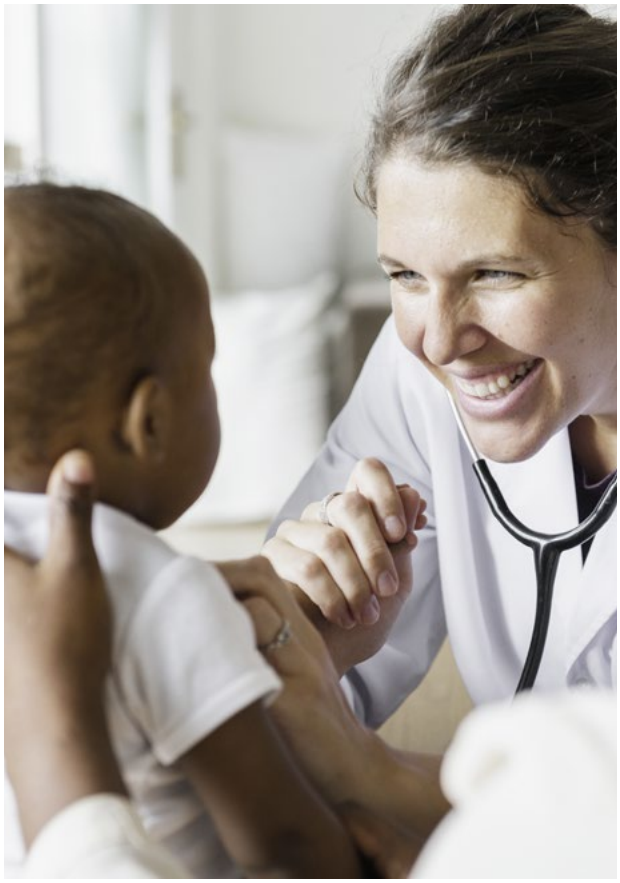
Table 5. ROC analysis for 3gAllergy assay.

3gAllergy	Cutoff	Sensitivity	Specificity	AUC
Cow's Milk	0.24	79.4%	85%	0.879
α-Lactalbumin	0.42	61.8%	95%	0.785
β-Lactoglobulin	0.46	67.6%	90%	0.831
Casein	0.13	79.4%	90%	0.846

Table 6. ROC analysis for ImmunoCAP assay.

3gAllergy	Cutoff	Sensitivity	Specificity	AUC
Cow's Milk	0.87	70.6%	100%	0.827
α-Lactalbumin	0.40	55.9%	100%	0.768
β-Lactoglobulin	0.47	55.9%	95%	0.751
Casein	0.35	58.8%	95%	0.778

**The 12 children with IgE levels above 3 kU/L and the 4 who had experienced anaphylaxis, although excluded from OFC in this study, were considered OFC positive and counted accordingly.*



Conclusions

In our study, 64% of infants were diagnosed as allergic to cow's milk by OFC, which remains the gold standard to diagnose food allergy. SPT had a low sensitivity (63%) to diagnose cow's milk allergy, and the use of in vitro diagnostic tools alone could not entirely prevent unnecessary oral food challenge (agreement of only 80%). Diagnostic performances of the in vitro 3gAllergy and ImmunoCAP methods at a 0.35 kU/L decision point were comparable (statistically significant). Finally, a suggestive clinical history and low levels of IgE (<0.35 kU/L) for milk and casein allergen should be considered of clinical importance.

References

1. Chatchatee P, et al. J Allergy Clin Immunol. 2001;107:379-83.
2. García-Ara MC, et al. J Allergy Clin Immunol. 2001;107:185-90.

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