

A pilot study on the application of a symptom-based score for the diagnosis of cow's milk protein allergy

SAGE Open Medicine
2: 2050312114523423
© The Author(s) 2014
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/2050312114523423
smo.sagepub.com


Yvan Vandenplas¹, Althera Study Group, Philippe Steenhout² and Dominik Grathwohl³

Abstract

Objective: A challenge is the recommended test to diagnose cow's milk protein allergy. However, many parents and physicians prefer to not challenge because the procedure may cause (severe) symptoms. In clinical routine, diagnostic testing is only available for IgE-mediated allergy. The aim of this study was to test the diagnostic accuracy of a symptom-based score to select infants at risk of having cow's milk protein allergy.

Methods: A symptom-based score was developed and consensus was reached that a score of ≥ 12 would select infants at risk of cow's milk protein allergy. Diagnosis of cow's milk protein allergy was demonstrated with a positive challenge after 1-month elimination diet.

Results: An open challenge was performed in 85/116 (73%) infants suspected of cow's milk protein allergy based on a symptom-based score ≥ 12 and was positive in 59/85 (69%). Although "a challenge test" was planned in the protocol, 27% of the parents refused the challenge. The mean decrease after 1 month of elimination diet with an extensive hydrolysate was -8.07 (95% confidence interval = $-8.74, -7.40$). If the symptom-based score during the elimination diet decreased to 6 or lower, 80% of the infants had a positive challenge test. If the symptom-based score remained >7 , the challenge test was positive in only 48% ($p < 0.001$).

Conclusion: In daily practice, a symptom-based score of ≥ 12 is a useful tool to select infants at risk of cow's milk protein allergy. If an elimination diet reduces the symptom-based score to ≤ 6 , the challenge test is positive in 80%.

Keywords

Cow's milk protein allergy, hydrolysate, symptom-based score

Date received: 13 October 2013; accepted: 20 January 2014

Introduction

Food allergy in general and cow's milk protein allergy (CMPA) specifically are defined as an adverse health effect arising from a specific immune response that occurs reproducibly to exposure to a cow milk allergen.¹ Cow's milk protein (CMP) is the leading cause of food allergy in infants.²⁻⁴ Most symptoms of CMPA involve the skin (such as atopic dermatitis), the gastrointestinal tract (vomiting, diarrhea, constipation), and the airways (wheezing, sneezing), or they are more general (colic).⁵ However, none of these symptoms are specific or pathognomonic.⁵ Allergy is an immune reaction that may be IgE or non-IgE mediated, or mixed. But only IgE testing (total and specific IgE, skin prick test (SPT)) is available in clinical routine. A challenge test is recommended to diagnose CMPA,^{2,5} but does not demonstrate involvement of the immune system. As a consequence, the

diagnosis of CMPA remains a topic of debate and controversies: none of the symptoms are specific, and involvement of the immune system cannot be demonstrated in many patients. Without a correct diagnostic work-up, including food challenge procedures, the risk is high for both over- and underdiagnosis.^{3,6} A correct diagnosis allows the appropriate diet to

¹Department of Pediatrics, Universitair Kinderziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

²Nestlé Nutrition, Vevey, Switzerland

³Nestlé Research Center, Lausanne, Switzerland

Corresponding author:

Yvan Vandenplas, Department of Pediatrics, Universitair Kinderziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.

Email: yvan.vandenplas@uzbrussel.be

Table 1. Most frequent symptoms of mild to moderate CMPA.^a

Therapeutic area	Symptoms
Gastrointestinal	<ul style="list-style-type: none"> • Frequent regurgitation • Vomiting • Diarrhea • Constipation • Blood in stool without failure to thrive
Dermatological	<ul style="list-style-type: none"> • Atopic dermatitis • Swelling of lips or eye lids • Urticaria unrelated to acute infections, drug intake, or other causes
Respiratory	<ul style="list-style-type: none"> • Runny nose • Recurrent otitis media • Chronic cough • Broncho-constriction unrelated to infection
General	<ul style="list-style-type: none"> • Persistent distress • Colic (≥ 3 h/day wailing/irritable) over a period of >3 weeks

CMPA: cow's milk protein allergy.

^aInfants with CMPA in general show one or more of the listed symptoms.

be given to affected infants and thus supports their normal growth and development.² On the other hand, diets that are not medically indicated or kept unnecessarily long should be avoided since they impair the quality of life of affected children and their families, and incur unnecessary costs.² Therefore, we developed a symptom-based score (SBS), considering the most frequent presentations of mild to moderate CMPA (see methods), and tested whether this score would help select infants with a “likely” diagnosis of CMPA, using a positive challenge as standard diagnostic test.

Methods

Formula-fed infants (singleton birth; gestational age = 37–42 weeks; birth weight = 2500–4500 g; age between 2 weeks and 6 months) of both sexes and of any ethnicity who presented symptoms suggesting a “mild to moderate CMPA” were eligible for inclusion in this trial. Mild to moderate symptoms have been described before (Table 1).^{2,5} Suspicion of a mild to moderate CMPA was based on the presence of a combination of the following symptoms: general discomfort and gastrointestinal, respiratory, and dermatological manifestations.

The exclusion criteria were exclusive breastfeeding, already on an extensive hydrolyzed formula (eHF), disease impairing a normal gut transit, known intolerance to lactose, antibiotics at enrollment, severe or chronic diarrhea, failure to thrive, neurologic disease, surgical intervention, any medical treatment which could interfere with the protocol, parents or caregivers who cannot be expected to comply with treatment, and having participated or participating in other clinical trials.

An SBS was developed by consensus following a round-table discussion by all participating pediatricians (Table 2). Suspicion of mild to moderate CMPA was based on the presence of a combination of the following symptoms: general discomfort (persistent distress or colic (≥ 3 h/day wailing/irritable, at least 3 days/week over a period of >3 weeks), gastrointestinal (frequent regurgitation, vomiting, diarrhea, constipation (with/without perianal rash), blood in stool), respiratory (runny nose (otitis media), chronic cough, wheezing (unrelated to infection), and dermatological (atopic dermatitis, angio-edema, urticaria unrelated to acute infections, drug intake, etc.) manifestations. Due to the fact that the SBS needed to be purely based on clinical manifestations, the estimation of the degree of severity of the respiratory symptoms is very subjective. It was postulated that this score would contribute to the selection of infants at risk for CMPA. The range of the score varies from 0 to 33. After intense face-to-face discussions between all participants, a cut-off value of ≥ 12 was arbitrarily decided to be “a good cut-off value to diagnose CMPA.” A score of 12 necessitates the presence of at least two symptoms, if they are severe. A score > 12 necessitates the presence of at least three symptoms and two organ systems involved. It was hypothesized that a decrease of the score with ≥ 3 points ($>25\%$) was clinically meaningful; power calculation was based on the latter.

Patients with a score of ≥ 12 were fed exclusively during 1 month with an extensive whey (Althera[®], Nestlé) or casein (Nutramigen[®], Mead Johnson) hydrolysate. Each of the hydrolysates was given exclusively and at libitum during 1 month. After 1 month, an open challenge was performed under medical supervision in the hospital with regular starter formula (Nan Pro1[®], Nestlé). The challenge test was performed in accordance with previous published methodology.⁵ The challenge starts with a small quantity that is increased every 30 min if no reaction occurs. If at the end of the challenge the child is asymptomatic, the child should drink at home at least 250 mL of Nan Pro1 each day for the next week.⁵ A daily telephone contact was organized during the first week following the “in-hospital challenge.” Whenever the parents mentioned that a reaction occurred, the child was seen again by the physician, and the final decision for a “positive versus negative” challenge was made by the physician. If the challenge was positive, the infant was fed the same test formula as before up to the age of 1 year.

The aim was to assess the predictive value of the SBS regarding the diagnosis of CMPA, which was a positive challenge test. IgE (total, cow milk, alfa-lactalbumin, beta-lactoglobulin, casein) and SPTs were performed at baseline.

The study was approved by the Ethical Committee of the UZ Brussel as leading center and from each participating center. Informed consent was obtained from both parents or one parent in single-parent families.

Table 2. Symptom-based score.

Symptom	Score			
Crying ^a	0–6	0: 1 h/day 1: 1–1.5 h/day 2: 1.5–2 h/day 3: 2–3 h/day 4: 3–4 h/day 5: 4–5 h/day 6: >5 h/day		
Regurgitation	0–6	0: 0–2 episodes/day 1: ≥3 to ≤5 of small volume 2: >5 episodes of >1 coffee spoon 3: >5 episodes of ±half of the feedings in <half of the feedings 4: continuous regurgitations of small volumes > 30 min after each feeding 5: regurgitation of half to complete volume of a feeding in at least half of the feedings 6: regurgitation of the complete volume after each feeding		
Stools (according to Bristol scale)	0–6	4: type 1 and 2 (hard stools) 0: type 3 and 4 (normal stools) 2: type 5 (soft stool) 4: type 6 (liquid stool, if unrelated to infection) 6: type 7 (watery stools)		
Dermatological symptoms	0–6	Atopic eczema	Head–neck–trunk	Arms–hands–legs–feet
		Absent	0	0
		Mild	1	1
		Moderate	2	2
		Severe	3	3
	0–6	Urticaria (no: 0/yes: 6)		
Respiratory symptoms	0–3	0: no respiratory symptoms 1: slight symptom 2: mild symptoms 3: severe symptoms		

^aCrying was only considered if the child was crying for 1 week or more, assessed by the parents, without any other obvious cause.

Results

A total of 116 infants with clinical symptoms suggesting CMPA with an SBS of ≥12 were included. Patient characteristics are listed in Table 3. The mean score at inclusion was 13.65 (±1.75; range = 12–21). (There was a protocol violation for one patient, as one patient with a score of 5 was included.) Overall, there was a statistical and clinical significant decrease of the SBS during the first month of elimination diet: -8.07 (95% confidence interval (CI) = -8.74 , -7.40 , $p < 0.001$). The score increased in 1% with <3 points and decreased with ≤3 points in 5% of the patients. According to the working hypothesis, a clinically meaningful decrease of the clinical score with ≥3 points was observed in 94% of the children.

At baseline, the number of infants with total IgE > 2 kU/L (43%) was significantly higher than those with IgE > 0.35 kU/L for cow milk (7%), alpha-lactalbumin (5%), beta-lactoglobulin (5%), and casein (5%). The level of total IgE at baseline did not predict the outcome of the challenge. The number of infants with a total IgE < or ≥ 2 kU/L did not

Table 3. Patient characteristics.

	Median or %	Lower/upper Q
Male/female	56/44%	
Birth weight (kg)	3.31	3.04–3.58
Length, birth (cm)	50.0	48.5–52.0
Gestational age (weeks)	39	38–40
Delivery vaginal/C sect	86/14%	
Family history atopy 0–1/2–3/≥4 ^a	46/47/7%	
Age diagnosis (days)	72	53–122
IgE cow milk > 0.35 kU/L	8%	
IgE α-lactalbumin > 0.35 kU/L	4%	
IgE β-lactoglobulin > 0.35 kU/L	4%	
IgE casein > 0.35 kU/L	4%	
IgE tot > 2 kU/L	45%	
IgE tot (kU/L)	2.45	2.00–4.04
SPT positive wheal	10%	

Q: quartile; C sect: cesarean section; SPT: skin prick test (positive if the wheal diameter is ≥3 mm greater than negative control).

^aNumber of family members with atopy.

Table 4. Challenge test result in relation to the symptom-based score (SBS) during the elimination diet.

	Challenge		Total
	Positive	Negative	
SBS < 6	45 (80%)	11 (20%)	56
SBS > 7	14 (48%)	15 (52%)	29
Total	59	26	85

differ according to the height of the SBS. Out of 33 infants with a total IgE > 2 kU/L, 29 had a positive challenge (positive predictive value 88%). Total IgE was ≤ 2 kU/L in 43/76 (57%) of the infants; 25 of these had a positive challenge (negative predictive value 42%; sensitivity 54%; specificity 82%). We confirm a high specificity and positive predictive value of a specific IgE > 0.35 kU/L.

SPTs were as well performed at baseline. An SPT is defined as positive if a wheal 3 mm greater in diameter than the negative control reaction develops, accompanied by surrounding flare (erythema). The information obtained by the SPT is in line with the results of IgE. The positive predictive value of the SPTs was 78%, sensitivity and negative predictive values were 13% and 32%, respectively.

After 1-month elimination diet, an open challenge was performed in 84 (73%) infants, and was positive in 58/84 (69%). Although the challenge test was part of the protocol end mentioned in the “informed consent,” many parents refused to perform the challenge test; therefore, we had 27% missing challenge tests. The majority of infants did have a positive challenge, but a higher SBS was not associated with a higher incidence of a positive challenge: we found in infants with score values of 12, 13, 14, and ≥ 15 , 73% (19/26), 62% (15/24), 59% (10/17), and 82% (14/17) of positive challenges, respectively. There was no difference in SBS at baseline according to a (later) negative or positive challenge (mean (standard deviation (SD)); min–max): 13.35 (1.26); 12–17 versus 13.59 (1.68); 12–19, respectively. However, after 1 month of dietary treatment, the score was higher in the group which did have a negative challenge than in the group in which the challenge was positive (6.81 (3.01); 1–13 versus 5.12 (3.39); 0–18, respectively) ($p = 0.039$). If the SBS decreased to ≤ 6 after 1-month elimination diet, the challenge test was positive in 80% (45/56) versus only 48% positive challenge tests if the SBS was still ≥ 7 after 1 month of elimination diet ($p < 0.001$) (Table 4). In all, 25 (43%) of all the positive challenges that occurred were reactions occurring more than 6 h after the start of the challenge.

Discussion

The contribution of a newly developed SBS to diagnose CMPA was validated with an open challenge test after 1 month of an elimination diet with an eHF. In order to assess the accuracy of the SBS, the SBS should be calculated in all

infants undergoing a cow’s milk (CM) challenge, and construct a receiver operating characteristic (ROC) curve to define the existence of a cut-off score and then verify this “best score” in a larger population to confirm the findings. A challenge test is considered to be the golden standard to diagnose CMPA.^{2,5} Since no symptom of CMPA is specific, a suspected diagnosis based on presenting symptoms often results in a negative challenge. It was hypothesized that an SBS based on a combination of symptoms would possibly improve diagnostic accuracy. In daily clinical situations, many parents refuse a challenge because symptoms disappeared and they will not take the risk to make their child sick again. As a consequence, many children are unnecessary on elimination diets.²

The SBS decreased with more than 3 points within 1 month of elimination diet in 94% of all children and with more than 6 points (a 50% decrease of the minimal baseline score) in 77%. However, we are aware that a considerable part of this decrease could also be due to regression to the mean.⁷ The challenge was positive in 69% of all the infants. The decrease of the SBS after 1 month of elimination diet was significantly larger in the group with a positive challenge than in the group with a negative challenge. A decrease of an initial SBS ≥ 12 with >50% after 1 month of elimination diet strongly correlated with a positive challenge. The stronger the decrease of the SBS, the more effective the elimination diet was and the more the challenge test was positive.

Some of the published recommendations or guidelines give mainly recommendations for suspected IgE-mediated CMPA.⁸ However, it is often difficult to distinguish between IgE- and non-IgE-mediated CMPA on presenting symptoms and physical examination. Several studies in unselected patients have shown that a high proportion of infants with CMPA proven by double-blind, placebo-controlled food challenge have negative test results for CMP-specific IgE.^{1,9} In daily routine, only IgE testing and SPTs are available (but SPT is also an IgE-mediated reaction). In many clinical situations, IgE-mediated allergy is relatively easy to suspect because of its rapid onset. The more rapid the reaction, the easier it is to relate ingestion of certain foods to the appearance of symptoms. In the population studied, SPT and specific IgE positivity are very low, resulting in a low sensitivity but a high specificity. All infants with a positive SPT and positive cow milk-specific IgE levels at baseline had a positive challenge. As a consequence, it could be questioned if a challenge test needs to be performed to confirm the diagnosis of CMPA if one of these tests is positive. However, on the other side, the sensitivity of these parameters is very low, questioning their utility to be performed at baseline.

It is generally accepted that many allergic reactions are non-IgE mediated.^{2,5} Especially for non-IgE-mediated allergy, it would be of great additional value to have an SBS. Non-IgE-mediated allergy is frequently of the delayed type. We developed an SBS in the hope that this may help

diagnose CMPA, which would be of interest especially in the non-IgE-mediated group. Since SPT and specific IgE cannot be performed or measured everywhere in the world, we decided to not include such a “diagnostic test” in the SBS. Within 4 weeks of treatment, the SBS decreased from a mean of 13.65 to 5.57; the score did not decrease with ≥ 3 points in only 6 infants. Since there was no placebo group, a placebo effect cannot be excluded. The open challenge was positive in 69% of the patients. The debate remains open if for a subgroup of infants the elimination diet was effective to treat functional complaints or non-IgE-mediated allergy.¹⁰ There is some pathophysiologic overlap between both entities: an allergic reaction causes inflammation and secretion of substances such as histamine and serotonin. The gastrointestinal tract reacts to the inflammation by altering motility. As a result, the question raises if there is “coincidence” or if “one is the logic consequence of the other.”⁵ The overlap in increased level of light chain immunoglobulins between allergic and nonallergic infants makes this parameter not useful to discriminate allergic from nonallergic patients on an individual basis.¹¹ It was a physician’s task to decide whether a challenge was positive or negative. A decrease of SBS of ≥ 12 at baseline with $>50\%$ is the best predictive factor for a positive challenge test.

In conclusion, the SBS is a helpful parameter in the selection of patients suspected of CMPA. A sharp decrease to an SBS ≤ 6 has a high predictive value for the challenge to be positive.

Acknowledgements

Statement of the authorship: Althera study group included the patients; P.S. and Y.V. developed the study design; D.G. did the statistics; D.G. and Y.V. wrote the article.

Althera Study Group: J. Christens, C. Halut, B. Hauser, T. Devreker, S. Mullier, P. Mariën, G. Veereman, K. Kamoen, S. Peeters, F. Smets, F. Bury, M. Verghote, P. Bollen, O. Beauraind, P. Lenoir, S. Colinet, and M. Van Winckel.

Declaration of conflicting interests

D.G. and P.S. are employed by Nestlé Nutrition; Y.V. is consultant for Biocodex and United Pharmaceuticals.

Funding

The study was performed with the support of Nestlé Nutrition.

References

1. 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 (Suppl. 6): S1–S58.
2. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow’s milk protein allergy in infants and children: a practical guideline of the GI-committee of ESPGHAN. *J Pediatr Gastroenterol Nutr* 2012; 55: 221–229.
3. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007; 120: 638–646.
4. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol* 2011; 127: 594–602.
5. Vandenplas Y, Koletzko S, Isolauri E, et al. Guidelines for the diagnosis and management of cow’s milk protein allergy in infants. *Arch Dis Child* 2007; 92: 902–908.
6. Eggesbo M, Botten G, Halvorsen R, et al. The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy* 2001; 56: 393–402.
7. Barnett AG, Van der Pols JC and Dobson AJ. Regression to the mean: what it is and how to deal with it. *Int J Epidemiol* 2005; 34: 215–220.
8. Fiocchi A, Brozek J, Schunemann H, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA) Guidelines. *Pediatr Allergy Immunol* 2010; 21 (Suppl. 21): S1–S125.
9. Klemola T, Vanto T, Juntunen-Backman K, et al. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow’s milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr* 2002; 140: 219–224.
10. Vandenplas Y, Gottrand F, Veereman-Wauters G, et al. Gastro-intestinal manifestations of cow’s milk protein allergy and gastro-intestinal motility. *Acta Paediatr* 2012; 101: 1105–1109.
11. Schouten B, Van Esch BCAM, Kormelink TG, et al. Non-digestible oligosaccharides reduce immunoglobulin free light-chain concentrations in infants at risk for allergy. *Pediatr Allergy Immunol* 2011; 22: 537–542.