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JMS Journal of Medical Science

Modern diagnostics in IgE-mediated cow's milk allergy

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DOI: https://doi.org/10.20883/medical.e690

Keywords: component-resolved diagnostics, cow's milk allergy, milk proteins

Published: 2022-03-31

How to Cite: Matysiak J. Modern diagnostics in IgE-mediated cow's milk allergy. Journal of Medical Science. 2022;91(2);e690. doi:10.20883/medical.e690

ABSTRACT

Cow's milk allergy (CMA) is the most common food allergy in infants and young children. Allergic reactions may vary from mild to severe, such as an anaphylactic shock. In the case of a suspected CMA diagnosis, skin prick tests (SPT), immunoassays of specific IgE (sIgE) in blood serum (in vitro tests) and oral food challenge (OFC) tests can be performed. SPT wheal diameter and the level of serum specific IgE to milk do not correlate with the severity of clinical symptoms, and the OFC procedure is frequently difficult or even impossible in practice. Therefore, component-resolved diagnostic (CRD) tests are a new diagnostic tool, which allows a better correlation of laboratory test results with the observed clinical symptoms as well as identification of the triggering allergens.

Introduction

Cow's milk allergy (CMA) is the most common food allergy in infants and young children [1]. According to various sources, the incidence reaches up to 7.5% [2–4]. In Poland, CMA affects between 0.5 to 4.8% of infants, although this food allergy occurs also in even 1% of adult patients [5]. Moreover, milk allergy is one of the major causes of anaphylaxis not only in the pediatric population, but also in adults [6]. It should be noted that epidemiological data regarding CMA prevalence highly depends on age, geographical region and the methodology of the diagnosis. The results of a pan-European Euro-Prevall birth cohort study constitute an example of these relations. The study has shown that diagnostics based on the gold standard – i.e. the food challenge, confirms the presence of CMA in less than 1% of children up to 2 years of age, and the occurrence of this allergy differs in European countries – the highest in the Netherlands and the United Kingdom (about 1%), and the lowest in Lithuania, Germany and Greece (less than about 0.3%) [7]. The symptoms of CMA may be associated with the skin, the gastrointestinal tract, the respiratory system, the cardiovascular system and the nervous system. Allergic reactions can vary from mild to severe, such as an anaphylactic shock [8].

Diagnostics tools in CMA

The first step in the allergy management is always a detailed interview and a clinical examination. In case of CMA suspicion, skin prick tests (SPT), immunoassays of specific IgE (sIgE) in

blood serum (in vitro tests) and oral food challenge (OFC) tests can be performed.

Skin prick tests (SPT) and sIgE determination in the blood comprise the first-line tests. Both methods demonstrate good sensitivity in the IgE-mediated CMA, but low specificity. Similarly to SPT, the determination of milk sIgE in the blood serum is associated with a high rate of false-positive results. Nevertheless, both of these methods constitute poor predictors of the severity of allergic reactions [9]. According to the data, the SPT wheal diameter and the level of serum specific IgE to milk do not correlate with the severity of clinical symptoms [2].

The key element in the diagnosis of food allergy is an attempt to eliminate a given food product, with a subsequent gradual introduction of it into the patient's diet. The diagnostic elimination diet should last for 2–6 weeks (usually 4–6), so that the patient does not present with any symptoms related to the food allergy [10]. After a few weeks, a gradual introduction of the food associated with the suspected allergy into the diet in increasing quantities occurs. This diagnostic procedure is commonly known as the oral food challenge test (OFC). OFC can be performed openly – the patient and the physician know what product is introduced into the diet, or as a blinded method. In the blinded challenges, either the patient (single-blind), or both the patient and the medical professionals (double blind) do not know whether the "real" test food, or the placebo is consumed. The double-blind, placebo-controlled food challenge (DBPCFC) is still a gold standard in food allergy diagnosis [11], although it is rarely performed in the clinical practice – usually only in research studies. OFC is very efficient in cases when the medical history and allergy tests results (skin and serological), are inconclusive. It verifies the actual allergic reactions to a given food allergen, and it is possible to differentiate between immediate and delayed reactions. Moreover, it is the only diagnostic method of non IgE-mediated allergy. Nevertheless, performing the OFC procedure in practice is frequently difficult due to the need to cooperate with the patient (or his parents) and the fact that it is time-consuming (an elimination diet must continue for several weeks before the food challenge). Additionally, in the case of severe allergy symptoms in the medical history, it must be performed at a hospital, which also limits the availability of this diagnostic method [12]. Moreover, severe anaphylaxis due to a suspected food allergen, is a significant contraindication to OFC, in view of the high risk of life-threatening reactions [10, 13].

Component-resolved diagnostics

Currently, the significance of the component-resolved diagnostics (CRD) in allergology is continuously increasing, particularly in terms of food allergy [14, 15]. SPT and the determination of sIgE in the blood serum allows the detection of the specific IgE against the whole extract, and in turn, each extract comprises a mixture of many allergens. However, the evaluation of patients' reactivity to the whole food extract is currently insufficient. Therefore, diagnosis based on allergenic components should be the basis for the diagnosis of IgE-mediated allergy [16, 17]. The allergen component is a protein constituting a fragment of the allergen extract with allergenic properties. The allergen component includes epitopes with either a linear, or conformational structure, and sIgE levels for individual allergenic molecules, or epitopes of allergens, can be detected by using CRD [18, 19].

CRD tests use a single, natural allergen isolated directly from the source, or an artificial recombinant allergen [20].

The European CRD molecular allergology user's guide indicates when to perform the component-based diagnostics [21]:

- inconsistency between the interview and the results of SPT and sIgE tests,
- inconclusive history, as well as clinical symptoms and tests results,
- allergy to one or more food allergens,
- coexistence of allergy to food and inhaled allergens,
- idiopathic anaphylaxis.

CRD technology improves the quality of life, since these methods allow for differentiating the cross-reactions from the real source sensitization and for the identification of the triggering allergens [22]. Additionally, it contributes to the optimization of the elimination diet and to enhanced identification of the patients requiring adrenaline [23].

CMA is one of the main food allergies where tests based on allergenic components should be performed in the clinical practice.

Cow's milk proteins

Milk is a mixture of many proteins. The latest data indicate that milk is a source of over 3100 different proteins [24]. The most important of which are the following allergens:

Casein (Bos d8) constitutes 80% of milk proteins, it consists of several fractions: α, β, γ and κ-casein (the most thermostable fraction). Sensitization to α fractions is the most frequent one, to κ fractions is the rarest. Casein is resistant to high temperatures and digestive enzymes, therefore, it is one of the most common triggering factors of anaphylaxis. Moreover, its resistance to high temperatures renders it a major cheese allergen. Beta-casein is present in A1 and A2 types. During A2 type digestion, peptide beta-casomorphin-7 occurs and is associated with gastrointestinal symptoms similar to lactose intolerance [25]. Casein is an important marker of persistent allergy to cow's milk proteins. Studies have demonstrated that basal levels of sIgE for both milk and casein may contribute to identifying the patients who may develop tolerance to milk [26].

Whey proteins – beta – lactoglobulin – **BLG** (Bos d 5), alpha- lactoalbumin – **ALA** (Bos d4), bovine serum albumin – **BSA** (Bos d 6), bovine immunoglobulins and bovine lactoferrin – constitute 20% of milk proteins and they are thermolabile at the temperature of 120°C (120°C for 20 minutes inactivates all whey proteins). Only bovine serum albumin is inactivated during cooking (already at 70–80°C). It should be emphasized that β-lactoglobulin sensitizes up to 80% of patients with whey proteins allergy, and it is not present in the human milk.

Casein, BLG and ALA comprise the major milk allergens and co-sensitization to these components is common [27]. Nevertheless, some patients are sensitized only to minor allergens – e.g. allergy to BSA is independent of sensitization to the other milk proteins. According to the recent studies, over 90% of children with CMA demonstrate sensitivity to caseins, between 35 and 61% to whey proteins [28].

Three CMA phenotypes can be distinguished, depending on the tolerance of baked and non-baked milk: reactive to baked milk, non-reactive to baked milk and non-reactive to non-baked milk [6, 29]. In fact, baked-milk intolerance phenotype is associated with casein allergy. The studies found that patients with this phenotype produce sIgE targeting against sequential milk proteins epitopes (mainly casein). This type of CMA is associated with severe clinical reactions to milk. In contrast, patients with detected sIgE against conformational epitopes showed tolerance to the extensively heated milk. Therefore, the inability to tolerate baked-milk products is a marker of the persistent CMA phenotype [28]. Patients who are non-reactive to non-baked milk are a phenotype with outgrew milk allergy.

Conclusion

Currently, it is possible to determine sIgE antibodies against casein, beta-lactoglobulin, alpha-lactalbumin, bovine serum albumin and bovine lactoferrin, which allows for a better correlation of laboratory test results with the observed clinical symptoms, as compared to sIgE against the whole milk extract. In many cases it is possible to observe that, despite the negative sIgE result to the whole milk, increased levels of sIgE against milk components are found. Conversely, a negative result for the allergen components allows to exclude with a high probability an IgE-dependent allergy. However, many studies indicate that CRD tests are still not a perfect diagnostic tool in food allergy, and have not replaced OFC yet [17]. The data demonstrate that CRD have a high specificity but low sensitivity in the diagnosis of food allergy [14].

Concluding, CRD diagnostics provides the opportunity for a better diagnosis of patients with Ige-mediated CMA, although it does not replace other diagnostic methods, particularly OFC.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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