



Non-IgE-mediated food allergies

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Thirteen years ago, this journal published a review specifically dedicated to IgE versus non-IgE mediated food allergy [1]. In that article, the knowledge gaps were underlined. The immunopathogenesis of non-IgE-mediated food allergy involves the activation of lymphocytes, the recruitment of eosinophils and mast cells, and the development of inflammatory cells, but there is no common mechanism for determining these diseases. Their unifying factor is the reaction time: non-IgE-mediated conditions appear a few hours – a few days after the ingestion of the allergen. The diagnosis is mainly based on elimination-reintroduction at General Practitioner level, often without involvement of the allergy specialist. For therapeutic decisions, the identification of allergenic foods is particularly difficult. Their slow mechanism of action makes skin-prick tests and specific food-specific IgE determinations useless. These disorders often arise from multiple food allergens.

Despite these differences, non-IgE-mediated food allergy displays often clinical overlap with the IgE-mediated manifestations. This can create discrepancies in the diagnostic and therapeutic interpretation between allergists and organ specialists who deal with the cutaneous or gastrointestinal manifestations of non-IgE-mediated allergy [1]. Thus, gastroenterologists and dermatologists are privileged interlocutors of the allergist in the attempt to unify the diagnostic and therapeutic languages for all forms of food allergy. This issue of the journal offers a revision of non-IgE-mediated food allergy in terms of pathogenesis [2,3], skin manifestations [4], eosinophilic gastrointestinal manifestations [5], and Food Protein-Induced Enterocolitis Syndrome (FPIES) [6]. Current Opinion already presented an update on eosinophilic esophagitis [7]. We also will present the last data on the role of the microbiota in food allergy development – an aspect that thirteen years ago was hardly suspected [8].

This overview seems to us particularly useful to us on the eve of the launch of the new Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA) guidelines [9]. They represent the first attempt to reconcile diagnostic and therapeutic processes in food allergy under the umbrella of

evidence-based medicine, with particular regard to allergy cow's milk allergy (CMA). The DRACMA guidelines are unique in that they are the only specific guidelines focused on a type of allergen: the World Allergy Organization identified CMA as a delicate field because it involves a vulnerable age, in which rapid and informed decision-making processes are needed [10]. Governments are also interested in CMA because the cost of replacement therapies is high and the opportunity to pay them back is a political decision. For this reason, many scientific societies have produced guidelines on CMA tailored to specific countries or regions, often adapting the global guidelines to the local situation [11–13].

The main limitation of the original DRACMA document is its exclusive destination to the IgE-mediated forms. Many cases of CMA in the young child are not identifiable with an IgE-specific mechanism, but non-IgE-mediated cases are difficult to catch in epidemiological studies and may have been underestimated [14]. Including these forms in the new DRACMA guideline is a major challenge that the World Allergy Organization (WAO) is affording by a metaanalysis of the whole literature on CMA and a panel of extensive gastrointestinal expertise.

They are attempting to rationalize the diagnostic process for CMA. Open or blinded milk oral food challenge (OFC) may be difficult to apply in most clinical situations. Mounting a challenge test is not easy, may not always be accepted by patients [15], and has never been completely accepted by the scientific community for non-IgE-mediated allergies [16,17]. OFCs are also difficult to carry in small infants and in patients who presented life-threatening anaphylaxis upon exposure to cow's milk. For this reason, a series of alternative diagnostic processes have been developed.

A strict use of medical history may be able to capture the diagnosis of food allergy in most cases

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[18]. On the basis of clinical history alone, systems for the diagnostic evaluation of CMA have been developed, which are certainly useful for its follow-up [19], but whose diagnostic effectiveness is under scrutiny [20,21]. Their validity will be an object of evaluation in the new DRACMA guidelines. This is particularly urgent as, despite the uncertainty of the diagnostic performances of such processes, some research are now open to the inclusion of CMA not confirmed with the gold standard challenge test [22]. In the United Kingdom, the guidelines allow to pose the diagnosis on a sequence of improvement on a strict cow's milk protein-free elimination diet for at least two weeks, followed by clinical relapse on subsequent cow's milk open challenge [16]. This may lead to an overestimation of CMA and to a use of hypoallergenic formulas in a percentage of children much greater than that confirmed as allergic to milk proteins in epidemiological studies [23,24].

In this situation, the diagnosis of food allergy fluctuates between underestimation and large overestimation. It has also been insinuated that an over-inclusive diagnostic behavior is functional to the large-scale use of therapeutic products in situations where it may not be necessary [25,26]. The problem is complicated by the fact that, like other food allergies, non-IgE-mediated milk allergy is not a single entity from a clinical and pathogenetic point of view. It may be associated with high fecal calprotectin, low levels of β -lactoglobulin and α -casein-IgG4 and IgA [27], but none of these features identify the condition. This is particularly evident in dramatic forms of non-IgE-mediated food allergy as milk-induced FPIES [28].

Owing to the complexity of the issues they face, the DRACMA guidelines require a conscientious elaboration by the panel and the authors of the metaanalyses produced. These guidelines will include non-IgE-mediated forms of CMA that are still lacking global evidence-based protocols. They represent a test bench on which the possibility of a wider collaboration for the diagnosis and consequent therapeutic interpretation of all food allergies will be verified. The hope is that, as always, WAO can best serve its mission in the scientific, clinical, patient, industry, and government settings to identify, prevent, and treat allergic patients.

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