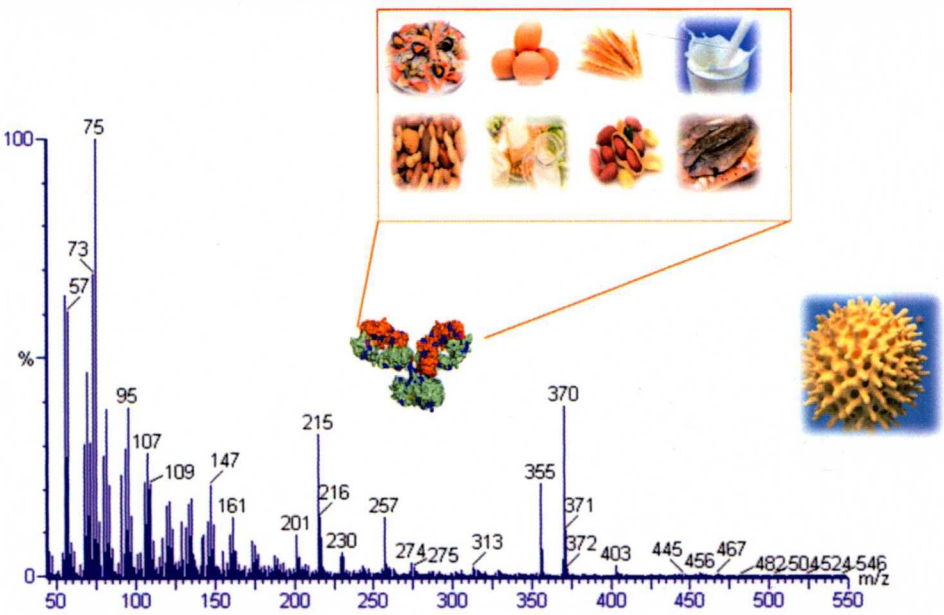
Food Allergy

Methods of Detection and Clinical Studies



Editor

Anas M. Abdel Rahman

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FOOD ALLERGY
Methods of Detection and Clinical Studies

Editor

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FOOD ALLERGY

Methods of Detection and Clinical Studies

Preface

Bridging the gap between the clinicians and basic science researchers in food allergy was the idea of writing this book. A few dozen of authors from around the world were invited to share their bedside and bench top research experience in the field of food allergy. We tried to cover all the clinical updates in the first seven chapters starting from nomenclature to immunotherapy. The other half of the book includes state of the art technology role in enhancing the molecular knowledge in food allergy research and the updated experience of the authors' laboratories. The authors of these chapters introduced their expertise in the novel technologies such as mass spectrometry and biosensors, bioinformatics and databases, and the food labeling regulations. This book will be a useful reading material for the young and expert scientists in food allergy with the theme of introductory to the basic knowledge and literature updates, respectively.

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CHAPTER 1

Food Allergy Nomenclature

Sten Dreborg

Introduction

Nomenclature is the basis for appropriate communication between scientists and clinicians. Studies should be performed using defined methods, grouping populations of patients with given characteristics, using words which describe patients clearly enough to be understood by others. Results can be applied to similar patients using the same methodology and patient characteristics using established nomenclature. This makes nomenclature crucial to both investigators as well as to clinicians to convey the message from research to the clinic. Allergists as well as other scientists interested in allergy, and not least lay persons and lay organizations must have a common language when communicating.

The nomenclature of allergy and allergic diseases has varied from time to time. However, within some areas confusing terms have been used such as "non-atopic atopic dermatitis", i.e., a dermatitis, clinically resembling that of so called "atopic dermatitis" (with allergen specific IgE antibodies also called eczema (Johansson *et al.*, 2004)), but without allergen specific IgE antibodies. That was, and still is, confusing. Accordingly, Gunnar O. Johansson formed a task force within the European Academy of Allergy and Clinical Immunology, EAACI, to write a position paper expressing the meaning of the Academy of allergy nomenclature (Johansson *et al.*, 2001). To make the message general he later formed a group within the World Allergy Organization, WAO to discuss the EAACI position paper (Johansson *et al.*, 2001), adding views from other continents and to agree on a common nomenclature for the worldwide allergy community (Johansson *et al.*, 2004). One of the main achievements was to start using "eczema" instead of "atopic dermatitis". However, as often happens,

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conservatives maintained atopic dermatitis as a parallel option to eczema, why "non-atopic atopic dermatitis" could not be eradicated. Since then, many people have tried to implement the new nomenclature. However, allergy and thereby allergy nomenclature, concerns not only allergists, but even specialists within adult and pediatric gastroenterology, dermatology, Ear, Nose and Throat (ENT), and respiratory medicine, who therefore have an interest in allergy nomenclature. All these related specialists and even lay persons and lay organizations must be involved to implement the allergy nomenclature to achieve global mutual understanding.

Recently, a Nomenclature Review Committee was set up by the WAO Board of Directors (Rosenwasser *et al.*, in prep.) for the purpose of updating the present nomenclature (Johansson *et al.*, 2004).

This chapter presents the existent nomenclature (Johansson *et al.*, 2004) discussing possible changes of the Food Allergy Nomenclature (Johansson *et al.*, 2001; Johansson *et al.*, 2004).

General considerations

Hypersensitivity is the global term describing not tolerating an environmental factor tolerated by the majority. Hypersensitivity can be mediated either by an immunological mechanism, i.e., allergy, or by non-immunological mechanisms. It does not include infection, autoimmunity or toxic reactions (Johansson *et al.*, 2004).

The WAO nomenclature 2004

The WAO nomenclature describes hypersensitivity as "objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons".

Hypersensitivity is either mediated by an immunological mechanism or not, dividing hypersensitivity into immunologically mediated hypersensitivity or allergy and non-immunologically mediated hypersensitivity, Fig. 1.1.

Immunologically mediated food hypersensitivity or allergy

Originally, allergy was defined by Clemens von Pirquet in 1906 as "changed reactivity", based on the old Greek words "allos" (different or changed) and "ergos" (work or effect) (von Pirquet, 1906). The WAO nomenclature defines allergy as "an immunologically mediated specific hypersensitivity" and this definition is still accepted by the allergy community (Fig. 1.1) (Johansson *et al.*, 2004).

Immunologically mediated symptoms and diseases are named allergic. The WAO definition is: "Allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms" (Johansson *et al.*, 2004). Allergy includes many mechanisms caused by environmental influences. "Allergy can be

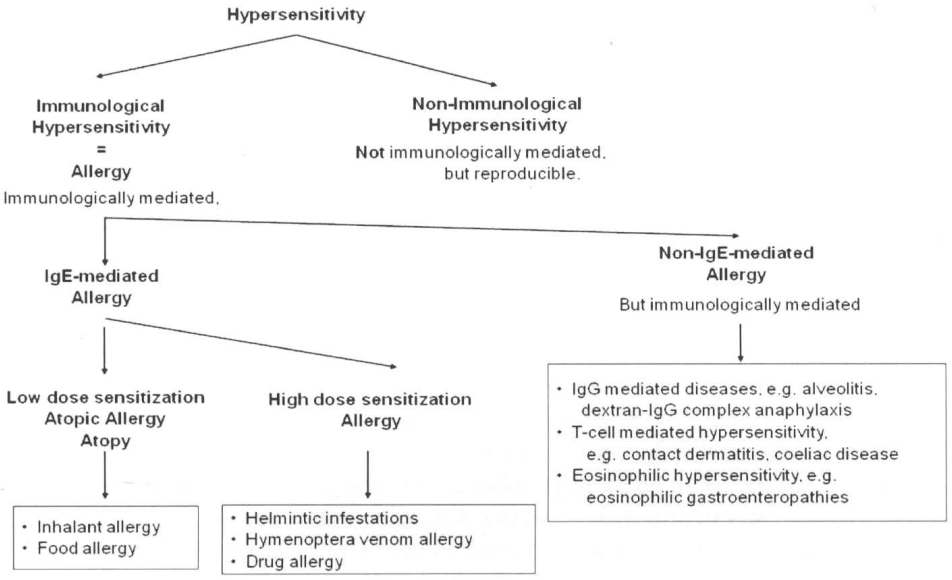

Fig. 1.1: Principles of Allergy nomenclature. Modified after (Johansson *et al.*, 2001; Johansson *et al.*, 2004).

antibody-mediated or cell-mediated. In most patients with allergic symptoms from mucosal membranes in the airways and gastrointestinal tract, the antibody belongs to the IgE isotype, and these patients may be said to have an IgE-mediated allergy or atopic allergy" (Johansson *et al.*, 2004). Even diseases/symptoms with obvious inflammatory components but without known mechanism should be classified as allergic.

The WAO position paper classifies allergies mediated by IgE antibodies as IgE-mediated allergy (previous paragraph). Atopic allergy is caused by low dose of allergen exposure to mucosal membranes in genetically predisposed individuals causing long standing sensitization. IgE-mediated allergy consists of atopic allergy and high dose dependent IgE-mediated allergies. Doses are discussed later.

Atopic allergy

Atopic allergy is due to an immunological response induced by very low doses of seemingly harmless proteins (mainly) in the environment, stimulating the immune system to respond with a humoral response of Th2 type with production by B-cells of allergen specific IgE antibodies.

High antigen dose IgE-mediated allergy

To this category belong, e.g., IgE mediated reactions to Hymenoptera venoms and IgE reactions against helminths (Fig. 1.1).

Comments

According to the WAO nomenclature (Johansson *et al.*, 2001; Johansson *et al.*, 2004), there are two types of IgE-mediated allergy, low dose sensitization (atopic) and reactivity and high dose sensitization and reactivity.

Low doses of allergen sensitizing via the mucous membranes is typical for atopic sensitization. **Atopy** was introduced by Cooke and Coca in 1923 (Coca and Cooke, 1923). Individuals with a predisposition to develop diseases like asthma, rhino-conjunctivitis, eczema and urticaria, combined with a hereditary predisposition to be sensitized to proteins that they were exposed to, were classified as atopic. In 1975, Pepys defined atopy as a tendency to develop IgE antibodies when exposed to low concentrations of environmental, normally harmless, proteins called allergens (Pepys, 1975). The diseases caused by sensitization were called atopic diseases. The WAO position paper (Johansson *et al.*, 2004) states: "The term atopy should be reserved to describe the genetic predisposition to become IgE-sensitized to allergens commonly occurring in the environment and to which everyone is exposed but to which the majority do not produce a prolonged IgE antibody response. Thus, atopy is a clinical definition of an IgE-antibody high-responder. The term atopy cannot be used until an IgE sensitization has been documented by IgE antibodies in serum or by a positive skin prick test". And, "Allergic symptoms in a person of the atopic constitution may be referred to as atopic, as in atopic rhinitis. A positive skin test or the presence of IgE antibody to a less common allergen, especially if the exposure is not low dose or does not occur via mucosal membranes, is not a diagnostic criterion for atopy. Typical examples are Hymenoptera sting allergy and most drug allergies. Such patients should be referred to as skin test positive and IgE-sensitized, respectively" (Johansson *et al.*, 2004). This is confusing, since not all cases of atopic diseases are caused by IgE sensitization and reactions involving allergens, allergen specific IgE and mast cells. In fact, patients with long standing atopic eczema (atopic dermatitis) or asthma show a neutrophil inflammation (Johansson *et al.*, 2004). The use of the "atopic diseases" concept has led to the term "atopic dermatitis" for infantile eczema, even present in adults. However, since many patients with that disease do not show any IgE-sensitization, i.e., are not atopic, the term "non-atopic atopic dermatitis" was coined that is causing confusion. As mentioned, this was one of the reasons for starting the nomenclature discussions that led to development of the present WAO nomenclature (Johansson *et al.*, 2001; Johansson *et al.*, 2004).

Comments on doses

Inhalant allergies belong to the low allergen exposure group, reactions to parasites to the high exposure group of IgE-mediated diseases. Insect venom allergy and penicillin allergy and the like were considered to be high dose allergy (Johansson *et al.*, 2001). However, the oral dose of penicillin is at the

milligram to gram level, a little higher than that of ordinary food allergens (Eller *et al.*, 2012). The injected dose of Hymenoptera venom is 100 mg of venom, corresponding to 6–10 mg of major allergen.

This should be compared to the doses of food allergen that food allergic patients are exposed to and are reacting to in double blind placebo controlled food challenges, i.e., for hen's egg, hazelnut and peanut with a 95% confidence interval between 42 and 190 mg of fresh, solid food, for cow's milk 1.5–5.4 ml corresponding to 30–200 mg protein. It can also be compared with the amount of inhalant allergen eliciting a reaction in the skin, conjunctiva or bronchi that ranges from 0.001 to 1 mg of major allergen (Dreborg *et al.*, 1987; Dreborg and Einarsson, 1992).

The concentrations of inhalation allergens causing sensitization are difficult to establish. However there are some data from the MAS study (Wahn *et al.*, 1997). During the first 3 years of life, children sensitized to mite or cat were exposed to significantly higher house dust mite (median, 868 ng/gm vs. 210 ng/mg; $p = 0.001$) and cat (median, 150 ng/gm vs. 64 ng/gm; $p = 0.011$) allergen concentrations in domestic carpet dust compared with the group without sensitization. Thus, lower concentrations in the environment of children can be expected to sensitize than those causing asthma attacks, i.e., between 2 and 8 μg/g of carpet dust. However, the doses of airborne inhalant allergens causing increase in bronchial hyperreactivity are much lower, less than 1 ng/day (Dreborg and Einarsson, 1992; Ihre and Zetterstrom, 1993).

In conclusion, there is a floating dose level causing sensitization and reactivity, between allergens and administration forms. The concentrations causing sensitization are more difficult to define.

Non-IgE-mediated allergic diseases

Non-IgE-mediated allergic diseases are caused by other mechanisms than allergen-IgE-mast cell interaction. Most non-IgE-mediated allergic diseases are due to induction of allergen specific T-cells. Another mechanism is by IgG-antibodies complement binding to dextran (Richter and Hedin, 1982), etc., Fig. 1.1.

Comment

Since 2004 (Johansson *et al.*, 2004), several diagnostic entities have been recognized, Figs. 1.2 and 1.3.

Non-immunologically mediated mechanisms

The non-immunologically mediated diseases and symptoms were not given any short name, are easy to understand and use.

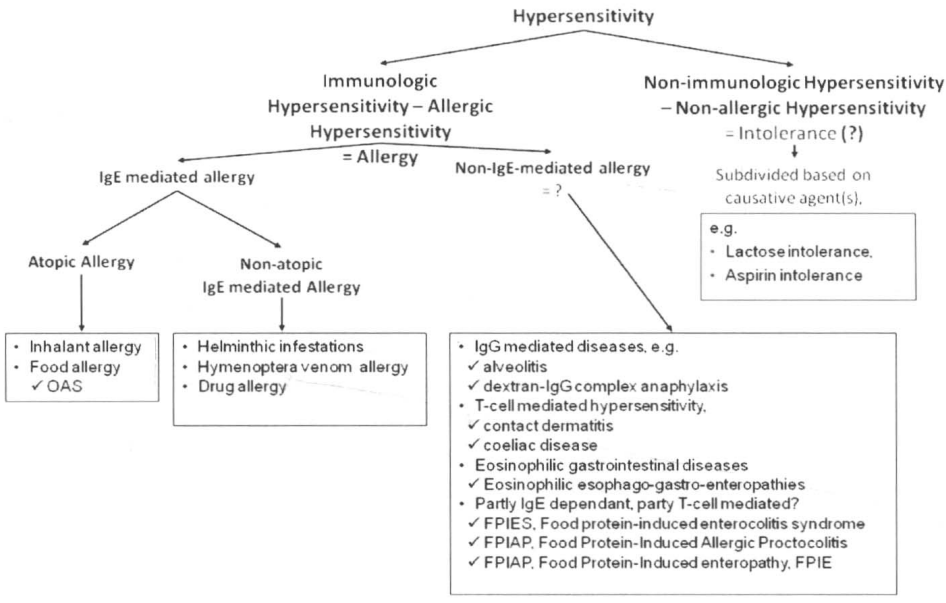

Fig. 1.2: The WAO nomenclature modified including recently defined diagnostic entities.

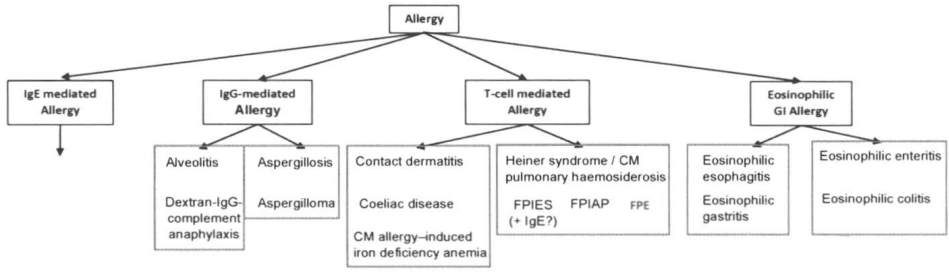

Fig. 1.3: Proposed preliminary grouping of non-IgE-mediated allergies. The T-cell mediated diseases can be partly further differentiated according to T-cell mechanism.

Comments

Recently, it has been proposed to use the word "Intolerance" to describe non-immunological/non-allergic hypersensitivity conditions (Dreborg, 2015). Intolerance has been used to describe the two most important groups of diseases under this heading, i.e., not tolerating di-saccharides (lactose, sucrose, fructose) (Durand, 1960; Holzel *et al.*, 1962) due to enzyme deficiency in the intestine and sometimes intolerance is used describing not tolerating aspirin, e.g., aspirin induced asthma (Samter and Beers, 1967).

Auto-immune diseases

Auto-immune diseases are not included within allergy, since the causative agents are not environmental but internal/of human origin. However, the limit

between autoimmunity and allergy is floating, since, e.g., with time, asthma and atopic eczema shift from an eosinophilic inflammation to an inflammation dominated by neutrophils with not fully understood mechanisms.

Food allergy nomenclature modification

The general principles applied to food allergy are those of the general allergy nomenclature, Fig. 1.1.

IgE-mediated food allergy

The contact with food allergens is mainly after oral intake, sometimes via the skin.

Comments

After oral intake, symptoms can be induced in every organ system, mostly gastrointestinal and skin symptoms, but even respiratory symptoms.

IgE-mediated food allergic symptoms appear within 2 hours of intake but can appear immediately after intake of minute amounts of allergenic food. Mostly, symptoms do not appear after intake of pg., ng or μg of allergenic protein as is the case for inhaled allergens, even inhaled food proteins, but rather after intake of mg to grams of whole food material (Eller *et al.*, 2012). Whether the difference in amount inducing a reaction is due to difference in route of administration including digestion, difference in timing or difference in mechanism, is not clear. See also above doses of food, injected, ingested or inhaled allergen needed for induction of reactions.

Very seldom, allergic symptoms appear after inhalation of food protein. It has been described in very sensitive food allergic patients and when handling crops (Mason *et al.*, 2015).

Contact via the skin of cold-buffet managers has caused a form of IgE-mediated contact dermatitis, "IgE-associated allergic protein contact dermatitis" (Cronin, 1987) that is a serious occupational allergy in cold-buffet managers in restaurants.

A special form of food allergy is the local reaction in the oral mucosa, sometimes spreading to the nose, eyes and larynx after ingestion of foods containing allergens mostly cross-reacting with allergens in pollens (Juhlin-Dannfelt, 1948), "para-allergies", nowadays named Oral Allergy Syndrome, OAS (Ortolani *et al.*, 1988), Fig. 1.2. With the exception of laryngeal involvement (Pastorello *et al.*, 1999), these reactions are not life-threatening. The laryngeal mucosa is as much part of the local oro-facial mucosa as the conjunctiva, lips and the salpinges. If OAS symptoms escalate within minutes, involving organs at distance, there is a high risk of severe anaphylaxis (Cox *et al.*, 2010; Dreborg, 2013).

Non-IgE-mediated or non-atopic food allergy

Non-IgE-mediated food allergy is not discussed in detail in the WAO nomenclature document (Johansson *et al.*, 2004), stating: "If IgE is involved in the reaction, the term IgE-mediated food allergy is appropriate. All other reactions should be referred to as non-allergic food hypersensitivity", thus not mentioning, e.g., the non-IgE-mediated mechanisms involved in some, probably T-cell mediated food induced gastrointestinal diseases. On this point, the newly instituted "WAO Nomenclature Review Committee" will update the present nomenclature.

Opposite to IgE-mediated allergic reactions, most reactions caused by non-IgE-mediated mechanisms do not start until 2 hours after ingestion of the food.

Comments

Since non-IgE-mediated diseases were not clearly pointed at in the WAO document (Johansson *et al.*, 2004) this must be updated.

In addition to the diseases mentioned in the WAO and EAACI nomenclature documents (Johansson *et al.*, 2001; Johansson *et al.*, 2004) a number of diseases have been identified that are immunologically mediated without obvious IgE involvement, although the mechanisms involved are not fully understood (Nowak-Wegrzyn *et al.*, 2015), Fig. 1.3. Furthermore, eosinophilic oesophagitis (Furuta and Katzka, 2015), enterocolitis (Nowak-Wegrzyn *et al.*, 2015) and proctocolitis (Lake, 2000) can be IgE-mediated but even other mechanisms have been proposed.

To this group also belongs Heiner syndrome, also known as pulmonary haemosiderosis (Heiner *et al.*, 1962).

Although not IgE-mediated, the mechanism causing gluten allergy (formerly gluten intolerance or coeliac disease) is immunological. Therefore, it should be considered allergic, i.e., belonging to the non-IgE-mediated, mostly T-cell mediated, allergic diseases. It should not be confused with IgE mediated wheat and gluten allergy. Furthermore, contact dermatitis belongs to this group.

Non-immunologically mediated food hypersensitivity

The main alimentary disease among diseases/symptoms that are not caused by an immunological hypersensitivity/allergy is lactose intolerance, i.e., primary or secondary enteric lactase deficiency (Durand, 1960; Sicherer and Sampson, 2014), leading to bacterial fermentation of lactose in the gut. Lactose in dairy products not digested in the intestine are fermented in the gut leading to acid loose stools. Similarly, inherited lack of enzyme for digestion of sucrose (Weijers *et al.*, 1961) and fructose (Cox, 1990) leads to similar symptoms. The other major cause of non-allergic food hypersensitivity is aspirin intolerance (Samter and Beers, 1967).

Comments

It is proposed to use the term intolerance to describe the non-immunologically mediated hypersensitivities.

Non-acceptable entities and terms

Among laypersons, gastrointestinal symptoms of different kinds are named allergy or intolerance.

The basis for classification should be according to mechanism, i.e., according to the WAO nomenclature. As mentioned non-atopic atopic dermatitis is still used by some dermatologists, but should, in my opinion, be avoided.

Some gastroenterologists are using terms that cannot be accepted from an allergological point of view such as cow's milk protein allergy/intolerance, CMPA/I and "cow's milk related symptoms".

Comments

For some years, Yves Vandenplas and colleagues used the term cow's milk protein allergy/intolerance, CMPA/I (Vandenplas *et al.*, 2011; Vandenplas *et al.*, 2013). The same group of mainly pediatric gastoenterologists (Vandenplas *et al.*, 2015; Vandenplas *et al.*, 2016a) launched a series of non-proven stepwise hypotheses, supporting the use of the non-defined diagnosis "cow's milk related symptoms". The 10 steps are:

1. Double Blind Placebo Controlled Food Challenges, DBPCFC, are the gold standard for diagnosis of food allergy. However, this is expensive and not possible to perform in primary care. Therefore, elimination and reintroduction should be the standard diagnostic procedure when diagnosing CMPA in primary care.
2. The next step is claiming simple gastrointestinal symptoms like infantile colic, regurgitation and constipation may be due to CMPA (Vandenplas, 2015; Vandenplas *et al.*, 2011; Vandenplas *et al.*, 2016a), based on the fact infantile colic, regurgitation and constipation sometimes are present in infants with CMPA.
3. Since these symptoms sometimes are seen in children with CMPA, children with such symptoms may have CMPA.
4. Thus, CMPA should be diagnosed in these children. Primarily they proposed an elimination diet, followed by reintroduction at home in those improving after some months.
5. To "easily" diagnose CMPA in infants, they worked out a non-validated scoring system mainly based on the common symptoms, infantile colic, regurgitation and obstipation (Vandenplas *et al.*, 2015).

6. Those improving on an elimination diet and not relapsing when normal formula is re-introduced are said to have "cow's milk related symptoms" (Vandenplas *et al.*, 2016a).
7. The treatment recommended is an elimination diet, in this age group a hypoallergenic formula.
8. Since, in infants, the common symptoms mentioned are self-limited, the therapeutic success will be marked.
9. The parents will be stigmatized and the "diagnosis" of "CMPA/I" (or CMPA) will follow the child.
10. Furthermore, parents without economic resources will suffer from economic loss to the benefit of formula companies.

The terms CMPA/I and "cow's milk related symptoms" may not be used, especially since the concept is not evidence based and has been developed in cooperation with formula industry (Vandenplas *et al.*, 2014). It should be regarded a marketing concept.

The GI Committee of the European Society on Paediatric Gastroenterology, Hepatology and Nutrition, ESPGHAN, does not mention CMPA/I or "cow's milk related symptoms" in their practical guidelines on the management of CMPA in infants and children (Koletzko *et al.*, 2012). Recently, a committee within ESPGHAN has banned the widespread use of partially hydrolyzed formulas among non-diseased children (Vandenplas *et al.*, 2016b).

Future Perspectives

I reviewed (Dreborg, 2016) the paper by the group of gastroenterologists led by Yves Vandenplas (Vandenplas *et al.*, 2015). At the same time, I wrote the con paper on "Intolerance does not exist" (Dreborg, 2016) for the WAO Journal. Simultaneously Vandenplas wrote the "pro intolerance" paper (Vandenplas, 2016) in a series of pro-con debates in the WAO J. I found the reasoning of the gastroenterologists to be threatening the present nomenclature. Therefore, I asked the World Allergy Organization, WAO Board of Directors to initiate an update of the old nomenclature document (Johansson *et al.*, 2004) that resulted in the formation of a "WAO Nomenclature Review Committee" that has started its work. It can be foreseen that the new version of the allergy nomenclature will mainly follow the design of the old nomenclature document and this summary, but if possible be more detailed (Rosenwasser *et al.*).

Furthermore, reactivity is not limited to the organ that gets sensitized. Patients react to the sensitizing allergen in other organs than that causing most symptoms, e.g., a majority of patients with asthma also report rhinitis (conjunctivitis) (Passalacqua *et al.*, 2006). Furthermore, in asthmatics, the skin, conjunctiva and bronchi (Dreborg *et al.*, 1986) react, in rhinitis patients the nose or conjunctiva and skin (Dreborg *et al.*, 2016; Østerballe, 1982) and in food allergic patients the skin, gut and conjunctiva (Kvenshagen *et al.*, 2010).