EDITORIAL

Perspectives in allergy

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Over the last decades, the prevalence of allergic diseases is rising. Numerous studies have demonstrated an increase in rhinitis, asthma, atopic dermatitis, food allergy and anaphylaxis. The availability of better diagnostics and increased awareness is not the main cause of this rise. Western lifestyle and particularly a decrease in microbial burden in early childhood appears to skew the immune system to a T-helper 2 cell domination resulting in an increase in the production of IgE antibodies. Particularly, helminth infections and infections from microbes such as *Helicobacter pylori* may be protective in the development of allergic diseases. As the increase in allergic diseases does no fully coincide with the hygienic measures taken in the early 20th century, factors such as obesity, less physical activity, less outdoor activities with increased exposure to indoor allergens as a result and the progressive use of antibiotics have been put forward as lifestyle factors contributing to the rise of allergic diseases.[1] Whereas the Western world is reaching a level of saturation, the prevalence of allergic diseases is still increasing in developing countries. It has been estimated that allergic rhinitis affects approximately 400 million people around the world, whereas asthma affects 300 million subjects. A dramatic increase in allergy to peanuts has been observed from 1990 to the present in the USA and the UK. Factors such as differences in peanut preparation, delayed oral consumption of peanut products, changes in skin due to daily bathing thereby facilitating penetration of allergens through the skin, with subsequent sensitisation, have been put forward.[1]

The high prevalence of allergic diseases has a major socioeconomic impact. Rhinitis and asthma interfere with school, work and leisure. Allergic rhinitis affects school performance and the results of examinations. Whereas asthma results in absence from work, rhinitis may substantially decrease work productivity. In addition, many studies point to impaired quality of life in patients with food allergy. Instruments have been developed to estimate this burden of disease.[2] The high prevalence of allergic disease is also mirrored by the substantial level of health care costs and indirect costs. A review[3] reported that annual costs for rhinitis and asthma may increase to more than € 1000 and € 2000, respectively, per patient, depending on the country. The extra costs for households with members with self-reported food allergy have been estimated at € 3933 per year in the Netherlands, whereas the total costs of cow milk allergy in the Netherlands for new cow milk allergy sufferers up to the age of 1 year were estimated to be € 11.28 million. In addition, a French study estimated the costs for food- or drug-associated anaphylaxis at € 1895 per case.

In recent years, the diagnosis of allergic diseases has been improved. Major developments have been made, particularly in the field of food allergy. The key role of IgE antibodies in type I allergic reactions is well established. The diagnosis of food allergy has traditionally been based on clinical history and food specific IgE testing, including skin prick testing. These tests are characterised by a high sensitivity but the specificity is limited: positive test results to foods that are tolerated are common.

The golden standard in the diagnosis of food allergy is the double blind placebo controlled food challenge (DBPCFC).[4] This test is time consuming, expensive and not without side effects. Therefore, additional diagnostic tests are needed to make the correct diagnosis. During the last two decades significant progress in biochemistry and molecular biology enabled the detection and quantification of specific IgE antibodies to allergen protein components and epitope-emulating peptides, also called molecular allergy diagnosis or component resolved diagnosis.

This new methodology in clinical food allergy diagnosis is improving the ability to identify specific clinical phenotypes. Component resolved diagnosis measures specific IgE against individual allergens, utilising native or recombinant allergens. Native allergens are purified from allergen extracts and recombinant allergens are biotechnologically produced by bacteria or yeasts.

Component resolved diagnosis can, for instance, distinguish between genuine sensitisation and that based on cross-sensitisation of food allergens mutually

or food allergens and inhalation allergens (pollen-food syndrome) and consequently gives insight into the sensitisation pattern and the risk of a mild or more severe allergic reaction. There are relatively harmless, unstable allergens, such as profilins, and potentially dangerous allergens that are extremely resistant to proteolysis, heat denaturation and pH changes, such as the allergens of the Prolamin superfamily including lipid transfer proteins and 2S albumins. Pathogen-related proteins, such as PR-10 proteins, play an important role in the pollen-food syndrome and usually cause mild to moderate symptoms such as 'oral allergy'. Furthermore, diagnostic cut-off values have been difficult to determine for allergens where component testing has been demonstrated to be beneficial. Consequently, there is a growing number of studies measuring predictive values of specific allergen components for food allergy.[5] The recently published European Academy of Allergy and Clinical Immunology Molecular Allergology User's Guide provides comprehensive information on important allergens and describes the diagnostic options using component resolved diagnosis. The User's Guide documents the rapid progression of molecular allergology from basic research to its integration into clinical practice, a quantum leap in the management of allergic patients.[6] However, we should take into account that, for example, age and geographic differences affect the results of component resolved diagnosis and it should always be utilised in the context of clinical history. Therefore, component resolved diagnosis is not ready to replace the DBPCFC and evaluations of component testing for a number of major food allergens are lacking. So, in conclusion, DBPCFCs are as yet indispensable, and well-described guidelines on the performance and interpretation of the DBPCFC are much needed.

Recently, a Dutch national multidisciplinary guideline was published under the auspices of the Dutch Society of Allergology, which aims to standardise the indications and performance of the food challenge in the Netherlands. The merit of this guideline is that allergists, paediatricians, dieticians and dermatologists reached consensus. Patient organisations were involved in a survey to identify the barriers and bottlenecks in food allergy. This guideline advises not to replace food challenges by sensitisation tests or component resolved diagnosis to establish the diagnosis of food allergy, in patients who have never eaten the tested food, who did not react with convincing symptoms, who reacted more than one year before presentation, or who did not react to a clearly identifiable allergenic food.[7]

The growing demand of allergic patients on health care services asks for measures to prevent disease. However, large and long-lasting studies with a focus on allergen avoidance in early childhood have failed to prevent the development of allergic diseases. In recent years the paradigm of early allergen avoidance was challenged by observations that introduction of peanut in the first months of life protects against the development of peanut allergy.[8] Other preventive studies try to address the effectiveness of early introduction of egg. It remains, however, a matter of debate how to translate the findings of these studies to general measures at a population level.

Dietary restriction of food allergens is, however, still the hallmark of treatment for those individuals with well-established allergy to specific foods. As food avoidance may be a burden interfering with social life and accidental exposure resulting in anaphylactic reactions may occur, attempts have been made to induce tolerance by different forms of immunotherapy. Most studies focus on oral immunotherapy. Until now, 12 studies with peanut, five with egg and ten with milk have been published.[9] In general, oral immunotherapy induces desensitisation during treatment. Patients are able to tolerate food challenges with the culprit allergen at the end of the trial. However, sustained tolerance to food after the end of treatment has only been evaluated in a few studies. Egg and milk allergy recurred in 70% of the children after discontinuation of treatment leading to the question whether oral immunotherapy should be given life-long.[9] Finally, oral immunotherapy is being hampered by common adverse events and drop-outs, which makes it difficult to position this treatment in daily practice.

In contrast, for more than a century sustained efficacy has been achieved with inhalant allergen immunotherapy. Subcutaneous immunotherapy is being considered a treatment modality that can change the natural course of allergic disease. Attempts to find more patient-friendly and safe ways to administer allergens led to the introduction of sublingual immunotherapy. Ineffective sublingual immunotherapy products hindered the acceptance of this treatment, but currently the efficacy of grass pollen and house dust mite tablets is well established in large randomised trials. The long-term treatment, problems with adherence and safety aspects of immunotherapy have been the starting point for a search for effective, safe and less demanding forms of immune-modulation. These new developments can be divided into different routes of administration (intralymphatic or epicutaneous), use of allergens in combination with anti-IgE, allergen fusion with immune response modifiers, use of allergens coupled with adjuvants, use of recombinant allergens or modified allergens or the administration of allergen peptides.[10] Finally, the availability of biologicals such as anti-IgE (omalizumab) for severe asthma and spontaneous urticaria, anti-IL5 (mepoluzimab) for severe eosinophilic asthma and new biologicals in the pipeline will broaden the therapeutic arsenal for the allergic patient.

In conclusion, allergy is an evolving field in science and patient care. Improvement and standardisation of diagnostic procedures, as illustrated by the paper by Van Maaren et al.,[7] and the availability of new therapeutic possibilities will clearly benefit the allergic patient.

REFERENCES

1. Platts-Mills TA. The allergy epidemics: 1870-2010. J Allergy Clin Immunol. 2015;136:3-13.
2. Muraro A, Dubois AE, DunnGalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. Allergy. 2014;69:845-53.
3. Jutel M, Angier L, Palkonen S, et al. Improving allergy management in the primary care network--a holistic approach. Allergy. 2013;68:1362-9.
4. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130:1260-74.
5. Van der Valk JP, Gerth van Wijk R, Vergouwe Y, et al. IgE Ana o 1, 2 and 3 accurately distinguish tolerant from allergic children sensitized to cashew nuts. Clin Exp Allergy. 2016:doi: 10.1111/cea.12794. [Epub ahead of print].
6. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. Pediatr Allergy Immunol. 2016;27 Suppl 23:1-250.
7. Van Maaren MS, Dubois AE. Dutch guideline on food allergy. Neth J Med. 2016;74:375-81.
8. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803-13.
9. Peters RL, Dang TD, Allen KJ. Specific oral tolerance induction in childhood. Pediatr Allergy Immunol. 2016.
10. Van der Valk JP, de Jong NW, Gerth van Wijk R. Review on immunotherapy in airway allergen sensitised patients. Neth J Med. 2015;73:263-9.