The multifactorial nature of food allergy

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CHAPTER 1

GENERAL INTRODUCTION
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“Food allergy is the invisible gun pointed at our son’s head and we have no way of taking out the culprit” - Suzi Catchpole, mother of five-year old boy with peanut allergy.

Food allergy is a prevalent disorder with a large impact on patients and with substantial health costs.1,2 It significantly reduces health related quality of life (H-RQOL) of patients due to limitations in social activities and the fear for an accidental exposure, which can elicit a potentially lethal anaphylactic reaction.3 Food allergy is characterized by an adverse reaction to foods, often accompanied by the presence of specific IgE (sIgE) antibodies against harmless proteins in food. The latter is called sensitization and common allergenic foods are milk, egg and (pea)nuts.

In 2007-2010, the prevalence of self-reported food allergy among 20 686 US participants was approximately 7% in children and 10% in adults4. Among 3864 Dutch adults studied in 2006-2009, 25% reported adverse reactions to any food including 10.8% who reported adverse reactions to 24 foods previously associated with food allergy5. Self-reported food allergy is shown to over-estimate the prevalence of food allergy as confirmed by food challenges, the gold standard6. Two studies from 2010 and 2011 estimated that approximately 2-3% of children has peanut allergy, as confirmed by food challenges and approximately 9-10% is sensitized to peanut7,8. Multiple studies and reviews concluded that the prevalence of self-reported food allergy and food allergy diagnoses among children increased over the past 20 years9–14.

The rise in prevalence indicates that food allergy will become a larger problem in the nearby future. Familial aggregation of atopic diseases including food allergy is common. However, the increase in prevalence over the past decade cannot be explained by changes in genetic variants alone. The pathogenesis of food allergy is likely to involve both genetic and environmental factors.

AETIOLOGY OF FOOD ALLERGY

In 1996, one study reported a 5-fold increase in the risk of peanut allergy for a child with a peanut allergic sibling or parent.15 A subsequent twin study showed a likelihood of 64% to have peanut allergy for a child with a peanut allergic monozygotic twin, compared to 6.8% for dizygotic twins.16 Both studies indicate that peanut allergy is at least partly heritable. The literature regarding the genetics of allergic disorders, especially food allergy, is extensively discussed in the next chapter of this thesis, together with a review of the immunological pathway leading to allergy.

Several environmental factors have been identified which influence the risk of atopic diseases. The hygiene hypothesis states that exposure to diverse microbial stimuli early in life is associated with a decreased risk of allergic disease since these stimuli induce a type 1 T-helper cell (Th1) response which inhibits a type 2 T-helper cell (Th2) response.17 In addition, subsequent altered dendritic cell and regulatory T cell functioning may add to this pathway.17 Multiple epidemiological studies have shown that there exists an inverse relation between...
proxy markers of early life infection (such as sib ship size, maternal animal contact or growing up at a farm) and allergic diseases such as atopic dermatitis and asthma. Another study supported this hypothesis by showing that a greater diversity of bacteria in the gut early in life might prevent allergy development. Caesarean delivery may also alter the gut microbiota and therefore increase the risk of allergy, especially to cow’s milk.

A review from 2010 concluded that there is evidence suggesting an association between a reduced intake of antioxidants and an increased risk of asthma, eczema and allergic rhinitis. Unfortunately, no such data is available for food allergy. Other hypotheses focused on the association between food allergy and vitamin D deficiency, nutritional supplements, season of birth, obesity and timing of introduction of foods during infancy. Especially the latter is interesting since avoiding early life exposure to foods was long thought to reduce the risk of developing food allergy. However, new data shows the opposite since early exposure to allergenic foods such as peanut was associated with a lower risk of food allergy. In addition, a healthier diet of home-prepared meals, fruits and vegetables in the first year of life was associated with a lower risk of challenge-proven food allergy at the age of two year.

In contrast to other atopic diseases, a preventive effect of breastfeeding on the development food allergy has been suggested although the evidence is weak and inconclusive. A review from 2004 concluded that being fed human milk for at least 4 months is associated with a lower incidence of cow’s milk allergy in high-risk children. Two more recent reviews could not draw robust conclusions because of inconclusive evidence and a meta-analysis showed no association between breastfeeding and food allergy, potentially due to great heterogeneity of available studies. The use of medication can also influence the risk of developing food allergy since the use of acid suppressing medications is associated with increased prevalence of food allergy, possibly due to the reduced breakdown of immunogenic peptides from food.

**Symptoms and Anaphylaxis**

When ingesting the allergenic food, the majority of food allergic patients develop symptoms within the first hour. Generally, severe reactions develop more quickly after the ingestion of the allergenic food and symptoms of the oral cavity and throat such as a metallic taste and a tingling sensation are experienced first. These are followed by gastrointestinal symptoms such as nausea, abdominal pain and vomiting. Later in the reaction skin and respiratory symptoms are observed.

A study in Sweden showed that the incidence of all-cause anaphylaxis was 32 per 100,000 person years and food was causative in 92% of cases. The most common elicitors of anaphylaxis are nuts, peanuts, fish and shellfish. Young children also commonly react to egg and milk.

Airway obstruction in combination with cardiovascular symptoms such as syncope, loss of consciousness or palpitations is concerning. A study of 6 fatal food induced anaphylactic
reactions showed lower respiratory symptoms in all cases, gastrointestinal symptoms in 5 cases and only 1 patient showed skin symptoms.\textsuperscript{41}

\textbf{DIAGNOSTIC PROCEDURES}

The Double-blind Placebo-controlled Food Challenge (DBPCFC) is the gold standard to diagnose food allergy.\textsuperscript{42} With this test one is able to distinguish between patients only sensitized and patients being clinically reactive to food. The food challenge is performed in two days with two weeks in between. On both days the patient is given either food containing the allergenic food masked in a matrix or a matched placebo. The order of administration is randomized, and everyone with patient contact is blinded. The subjects receive the food in six to eight carefully graded steps and are monitored closely. After both test days the code is broken and reactions are interpreted. Remarkably, our experience with these food challenges shows that only approximately half of children highly suspected to be food allergic had a positive test result and were diagnosed to be clinically reactive to the suspected food.\textsuperscript{42} A systematic review revealed that the prevalence of self-reported food allergy was approximately six times higher than the point prevalence of challenge-proven food allergy, confirming that in the majority of subjects with self-reported food allergy, this cannot be confirmed in an oral food challenge.\textsuperscript{43} The DBPCFC is a time-consuming but highly reliable test. Practitioners must be experienced in the use of this food challenge because of the small risk of anaphylaxis. The DBPCFC is not available in primary care. Interestingly, children suspected to be food allergic who underwent a DBPCFC showed an improvement in H-RQOL.\textsuperscript{44} This shows that children benefit from a DBPCFC and as expected, the increase in H-RQOL is greater for a negative outcome, i.e. allergy refuted.\textsuperscript{44}

Skin prick testing (SPT) is a rapid and easy way to test for sensitisation to foods.\textsuperscript{45} A food allergen is applied intracutaneously together with positive (histamine) and negative (saline) controls. Severe atopic dermatitis may preclude a SPT, because false positive reactions easily occur. The estimated sensitivity and specificity of the SPT for the diagnosis of food allergy as confirmed by food challenges ranges between 30-90\% and 20-60\%, respectively.\textsuperscript{46} This means that a negative test result can be valuable in ruling food allergy out, but a positive result is less specific. Measurement of specific Immunoglobulin E (sIgE) in serum, for example with the CAP-FEIA technology (Phadia, Uppsala, Sweden) is available for patients with atopic dermatitis. A strong limitation of this test is the discordance of cut-off values among centres worldwide, per allergens and in age groups.\textsuperscript{47} Studies indicated a positive correlation between outcome of oral food challenges and both SPT and IgE levels although no conclusions can be drawn for individual patients, a phenomenon which is frequently misunderstood by primary care physicians.\textsuperscript{47,48} Next to the level of specific IgE values, component specific IgE antibodies can be valuable in the diagnosis of food allergy. Several studies showed an association between sensitization to the major allergens Ara h1, Ara h2, and or Ara h3 and (severity of) peanut allergy.\textsuperscript{49,50}
TREATMENT
Currently, there is no treatment for food allergy other than avoidance and treatment of a potentially lethal anaphylactic shock. The patient should be carefully instructed by caregivers and dieticians on how to avoid the suspected food, reading labels on packaged foods, informing restaurants about their diet and carrying an epinephrine auto injector. In addition, it is important to ensure that their diet still contains all essential nutrients.

When despite of all effort, the allergenic food is ingested, an anaphylactic shock can occur. The treatment of anaphylaxis induced by food is similar to the treatment of anaphylaxis due to other causes37 and patients at high risk of food allergy should be prescribed an epinephrine auto injector (EAI). These auto injectors can be used for intramuscular injection by the patient themselves, family members or bystanders such as teachers. Careful instruction is important, since early treatment can reduce the severity of the reaction. In Groningen and many other centres, prompt (self) administration of epinephrine is advised at the first reasonably clear signs of anaphylaxis following possible ingestion of the allergenic food. Subsequently, immediate assessment by a clinician is indicated. Sometimes repetitive administration of epinephrine is indicated to reduce the symptoms.

New methods to treat food allergy and thereby prevent anaphylaxis are epicutaneous, oral and sublingual immunotherapy. These methods include a repetitive and increasing administration of the allergen which should induce tolerance and as recently reviewed, results of oral and sublingual immunotherapy are promising51. However, oral immunotherapy is associated with adverse effects in 10-20% of the patients and these represent a barrier to implement the therapies in clinical practice52.

AIMS AND OUTLINE OF THE THESIS
The prevalence of food allergy is thought to have increased over the last decades11 although the prevalence of food allergy is highly dependent on the definition of food allergy and the method of case finding33,53. A variety of risk factors were robustly associated with sensitization to foods but limited literature is available regarding their role in food allergy. In clinical settings, familial aggregation of atopic diseases such as eczema and food allergy is common, and previous studies indicate that food allergy is strongly heritable16,54. We hypothesize that environmental factors and the genetic makeup of a child influences the risk of sensitization, and especially, the risk of food allergy as diagnosed by the DBPCFC (in those already sensitized).

Previous studies on food allergy mostly investigated associations with sensitization or open food challenges, which are characterized by high frequencies of false positive assignments compared to the DBPCFCs55,56, the gold standard. In Groningen, we have an internationally unique database of children tested by the DBPCFC, a test which is time-consuming and not available in primary care. Using this definition of food allergy gives the most reliable results, so more robust conclusions can be made on the mechanisms leading to food allergy. Especially when focussing on the pathway which drives the difference between asymptomatic sensitisation and clinical reactivity. In addition, the lifelines cohort including adults from the
northern Netherlands is well-powered to study risk factors associated with questionnaire-defined food allergy.

In summary, we aimed to:
1) establish more insight regarding the prevalence of food allergy and the burden for food allergic patients in the Netherlands, as discussed in chapter 3 and 4.
2) identify environmental factors associated with food allergy, as discussed in chapter 3-6. Specifically, we investigated the association between food allergy and atopic comorbidities, rural living environment during childhood, breastfeeding and birth order.
3) identify gene variants associated with food allergy, as discussed in chapter 7-11. To this aim, we performed two candidate gene studies regarding the role the Filaggrin and STAT6 gene in food allergy. In addition, we replicated associations of a Canadian genome-wide association study on peanut allergy and performed a hypothesis free genome-wide association study in Dutch adults with questionnaire-defined food and peanut allergy.

This thesis mostly aims to improve knowledge regarding the pathway leading to food allergy. More insight into the pathophysiology can identify new therapeutic targets for the treatment of food allergy. Selecting genetically supported targets for the development of new drugs is generally associated with a doubled success rate in clinical development\(^{57}\). Furthermore, identified genetic markers can be helpful in increasing our scientific insights in food allergy and developing new diagnostic or screening models. These latter may reduce the prevalence of perceived food allergy and give opportunities for prevention.
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