Exploring immunological mechanisms in cow’s milk allergy
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Chapter I describes a general introduction about the definition, prevalence and pathogenesis of food allergy followed by a review of the natural history, prognosis, clinical presentation, diagnosis, therapy and the CMP-specific B-and T-cell mediated immune response of CMA. Furthermore, the aims of the studies are described. The overall goal of this thesis is to attain more insight in the immunological mechanism which underlies clinical allergic hypersensitivity reactions to CMP in infancy and the development of tolerance or persistency of CMA later in childhood. In addition, diagnostic methods based on the variety of presenting clinical symptoms of CMA are presented which could help clinicians to decide whether to refer an infant suspect for CMA to a specialized centre to perform a DBPCFC or to initially perform an open food challenge.

In Chapter II a detailed description of the study population which has been included in the studies of this thesis is provided. Infants aged equal or less than 12 months with symptoms suspected of CMA were referred from Baby Health Clinics in the region of Amsterdam to the Emma Children’s Hospital Academic Medical Center, Amsterdam, The Netherlands. All infants performed a diagnostic procedure, including a DBPCFC with CMP. CMA was diagnosed by a positive DBPCFC. Infants with a negative DBPCFC were included as non-allergic controls. To study the development of tolerance, all children diagnosed with CMA in infancy performed a DBPCFC to CMP yearly until tolerance to CMP was established. Seventy (42 boys, 28 girls) children were included in the study. In 73% (n=51) of the children the symptoms suspected of CMA improved during the elimination phase. Twenty-six children where diagnosed with CMA, in 25 children the diagnosis CMA was rejected after completing the diagnostic procedure. Baseline characteristics of the study population are provided in this chapter.

In Chapter III we present a study in which we investigated whether CMP-specific T- and B-cell responses and clinical reactions to CMP in CMA infants are associated with the induction of tolerance to CMP or persistent CMA beyond the first year of life. Furthermore, we used a HLA-DR1-binding matrix based computer algorithm designed to identify pan-DR binding T cell epitopes to identify CMP-specific T cell epitopes on the major CMPs. In this study we found that the CMP-specific T cell response of children with persistent CMA is characterized by a combination of enhanced CMP-specific CD4+ T cell proliferation, IL-10 production and a Th2 skewed cytokine pattern in infancy. Furthermore, we found that CMA infants with elevated serum CMP-specific IgE levels or immediate type allergic clinical reactions to CMP are likely more prone to persistent CMA than CMA infants with no detectable CMP-specific IgE levels or delayed type allergic reactions in infancy. In addition, we identified 8 potential CMP-specific T cell epitopes. No difference in epitope recognition was detected between infants with and without CMA. We conclude that enhanced CMP-specific CD4+ T cell proliferation with a Th2 cytokine pattern and IL-10, elevated serum CMP-specific IgE levels and immediate type allergic clinical reactions to CMP are associated
with persistent CMA and thus may be useful prognostic markers to identify the infant at risk for persistent CMA and possibly the allergic march.

In **Chapter IV** a study is presented which aimed at the development of a clinical triage model based on clinical parameters which could help physicians in deciding to refer a patient suspected of cow's milk allergy to a specialized centre for a double-blind placebo-controlled food challenge or to initially perform an open food challenge and thereby possibly circumvent the need for a double-blind placebo-controlled food challenge. Our results show that a diagnostic model containing as predictors the clinical symptoms *abdominal cramps* and *inconsolable crying*, and an atopic dermatitis severity score system the objective *SCORAD-index* discriminated moderately well between infants with and without a positive DBPCFC. We conclude that a clinical diagnostic model based on easy obtainable parameters may help primary care physicians in deciding to refer a patient suspected of CMA to a specialized centre for a DBPCFC or to initially perform an open food challenge.

**Chapter V** describes a study in which the involvement of specific IgE and immunoglobulin free light chains (Ig-fLC) in clinical allergic responses to casein and whey was investigated. In a murine model mice were orally casein- or whey-sensitized after which mice exhibited acute clinical reactions upon challenge with the specific antigen. We show that after sensitization serum whey-specific IgE levels were elevated in whey-sensitized mice, while in casein-allergic mice casein-specific IgE levels were not measurable. Instead Ig-fLC levels were increased in serum from casein-sensitized mice. Furthermore, by using a specific antagonist for the immunological actions of Ig-fLC(F991) allergic skin reactions in casein-sensitized mice strongly diminished, while whey-induced skin reactions were unaffected. In addition, in a human model we found significant higher kappa and lambda free light chain levels in serum of CMA infants as compared to non-allergic infants. We conclude that sensitization to CMPs may lead to both IgE-dependent and Ig-fLC-dependent clinical allergic reactions and suggest that measurement of Ig-fLC may be important in the diagnosis of allergy.

In **Chapter VI** a study is presented in which plasma cytokine levels in food allergic children were compared with food tolerant children to attain more insight in the factors that contribute to a food allergic response and the development of tolerance. Plasma levels of IL-25 (or IL-17E), a recently identified member of the IL-17 family of cytokines, were highly elevated only in children with a proven clinical peanut allergy. These high levels of IL-25 were not measured in non-peanut allergic children, or in CMA infants. We did not find differences in the conventional Th2 cytokines, IL-4, IL-5 and IL-13. We conclude that that IL-25 is a prominent secreted cytokine in peanut allergic children. In combination with the finding that IL-17 is more secreted in peanut tolerant children, this study suggests that the IL-17 cytokine family plays an important role in peanut allergy.
In Chapter VII we responded to a paper from Eigenmann that was published in Pediatric Allergy and Immunology.\(^{(1)}\) In this educational review, Eigenmann proposed a diagnostic flow chart for the diagnosis of CMA on which we commented. The presented diagnostic flow chart showed that in children with symptoms suggestive of non-IgE mediated CMA a successful avoidance diet is sufficient to establish the diagnosis CMA. However, in previous studies it has been clearly demonstrated that only 64-81% of food challenges in children with symptoms suspected for food allergy are positive. Therefore, we aimed to illustrate the importance of performing a DBPCFC to confirm the diagnosis CMA after a successful completion of an avoidance diet.

In Chapter VIII we commented on a paper by Van den Plas and colleagues that was published in Archives of Disease in Childhood.\(^{(2)}\) In this paper, the authors presented guidelines for the diagnosis and treatment of CMA on which we commented. The guidelines implied that children suspected of CMA with initial immediate symptoms such as urticaria and angioedema do not necessarily need to perform a food challenge to CMP in a hospital setting. Because of the increased risk of anaphylaxis in this subset of children, we replied to this paper to describe the importance of performing a food challenge in a hospital with specialized facilities and experience in performing food challenges.
REFERENCES