Summary and General Discussion

Introduction

Adverse reactions to cow's milk, indicated as cow's milk protein allergy or intolerance (CMPA/CMPI), are one of the most common adverse reactions to foods in infancy and early childhood with an incidence ranging from 2% to 5%, when strict diagnostic criteria are used. The diagnosis CMPA/CMPI has to be based on the clinical response to cow's milk. Following dietary elimination of cow's milk protein, the prognosis of CMPA/CMPI is good with a remission rate of 90% at three years of age. Only a few long-term prospective follow-up studies have focused on the prognosis of CMPA/CMPI with respect to the development of additional allergic disorders later in childhood. These studies demonstrate that the development of asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, and food intolerance later in childhood is substantial. It has been hypothesized that early dietary intervention and environmental measures may influence the development of subsequent allergic symptoms. Primary preventive effects of dietary intervention during lactation and in the neonatal period on the development of allergic symptoms have been demonstrated in high-risk infants, i.e., infants with at least one parent or sibling with an atopic disorder. It has been hypothesized that secondary prevention, including early dietary intervention with a protein hydrolysate-based formula, could modulate the "atopic march" in infants with CMPA/CMPI. However, it is still a matter of debate whether there is a preventive effect of dietary intervention on the development of additional allergic disorders in children with CMPA/CMPI in infancy, due to the absence of controlled studies. Moreover, in the few long-term follow-up studies which focused on the prognosis of CMPA/CMPI with respect to the development of subsequent allergic disorders, the age at which the diagnosis was made, and consequently the age at which dietary intervention was started, varied widely. Furthermore, it is not clear, due to the character of these uncontrolled studies, whether early treated CMPA/CMPI may be a risk factor for the development of allergic symptoms. Additionally, the outcome of allergy in children with CMPA/CMPI in infancy is not clear due to a lack of uniform diagnostic definitions, and standardized methods in assessing the presence or severity of an allergic disorder in this young age group.

The studies described in this thesis aimed to fill in these hiatuses in the field of CMPA/CMPI. In this thesis the first controlled prospective follow-up study on the development of allergic disorders in children with CMPA/CMPI in...
infancy is presented. In this follow-up study through a mean age of 7 years all infants with CMPA/CMPI were diagnosed by a strict well defined elimination and provocation procedure during the first three months of life. Consequently, this is the first follow-up study in which all infants with CMPA/CMPI received dietary intervention with an extensively hydrolysed whey protein based formula starting before the fourth month of age.

**Summary of the studies**

Chapter one contains a concise review of the literature including, definitions, diagnostic criteria, clinical manifestations, treatment, aetiology, pathogenesis, and prognosis of CMPA/CMPI. Furthermore, the aims of the studies are described. The aim of this thesis was to investigate, in a prospective follow-up study through age 7 years, the subsequent development of allergic disorders in children with CMPA/CMPI diagnosed by elimination and challenge of cow's milk protein during the first three months of life, and treated with an extensive protein hydrolysate based formula. Furthermore, to investigate the clinical outcome of allergy in children in whom the diagnosis CMPA/CMPI was suspected but could be rejected on the basis of the same elimination and challenge procedure during the first three months of life. Moreover, to determine risk factors for the development of additional allergic disorders later in childhood. Additionally, to develop and study alternative methods to assess bronchial hyperresponsiveness in children, in order to apply these methods in the young children participating in the follow-up study. Furthermore, to critically review and study some of the available, and in research most used atopic dermatitis severity scoring systems in order to give information about the advantages and disadvantages of these scoring systems, and therefore, to contribute to a more informed choice in which severity scoring system to use in research concerning atopic dermatitis.

In Chapter two (A) we presented a study in which we determined whether a change in lung sounds in asthmatic children corresponded with a 20% fall in forced expiratory volume in one second (FEV₁) after methacholine challenge, and whether the occurrence of wheeze was the most important change. This study showed that changes in lung sounds correspond well with a 20% fall in FEV₁ after methacholine challenge. In contrast with previous studies in which wheeze was the indicator of bronchial responsiveness, we found wheeze by itself to be a poor indicator for assessment of bronchial responsiveness, rate, and prolonged...
Summary and General Discussion

In Chapter two (B), we investigated the agreement between the total cumulative histamine dose causing a fall in FEV\(_1\) of 20% or more and the detection of a change in lung sounds after two bronchial challenges at different occasions in asthmatic children. In this study we found good agreement between the total cumulative histamine dose causing a fall in FEV\(_1\) of 20% or more and the detection of a change in lung sounds after two bronchial challenges at different occasions. The observation that not only the appearance of wheeze was an indicator of bronchial responsiveness, but also the appearance of cough, increase in respiratory rate, and a prolonged expiration, was in accordance with the first study presented in this chapter. We conclude that for routine clinical assessment of bronchial responsiveness in asthmatic children changes in lung sounds can be used provided that attention is paid, not only to the occurrence of wheeze, but also to cough, increase in respiratory rate, and a prolonged expiration.

In Chapter three a study is presented in which we investigated whether an increase in transcutaneous measured electromyographic (EMG) activity of the diaphragm and intercostal muscles corresponds with the concentration of histamine that induces a 20% fall in FEV\(_1\) in asthmatic children. We found that an increase of the transcutaneous diaphragmatic and intercostal EMG activity ratio (EMGAR) corresponds closely to a histamine induced 20% fall in FEV\(_1\) in asthmatic children. In all children reaching a 20% fall in FEV\(_1\) after histamine challenge, an increase in the EMG activity of the diaphragm and intercostal muscles was observed. In these children, no increase in diaphragmatic and/or intercostal EMGAR was found at the dose step before the PC\(_{20}\)-histamine was reached. This study is the first study which investigated the use of diaphragmatic and intercostal EMG after histamine- or methacholine-induced bronchoconstriction in the assessment of bronchial responsiveness in humans. We conclude that the assessment of bronchial responsiveness by measuring the transcutaneous diaphragmatic and intercostal muscle activity during the inhalation challenge could be a method for younger children who are not able to perform spirometry reliably.

In Chapter four we presented an overview of available atopic dermatitis severity scoring systems in which we focused on the usefulness and validity of the different scoring systems. We determined whether a fall of 20% or more in FEV\(_1\) after histamine or methacholine challenge, and the occurrence of bronchial responsiveness, was a good indicator for assessing bronchial responsiveness. Cough, increase in respiratory rate, and prolonged expiration were more frequently found.

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ent scoring systems. A number of scoring systems are being used for clinical and research purposes. However, assessing the severity of atopic dermatitis in a reproducible manner by this scoring systems is difficult. Even after training, and by dermatologically experienced physicians, it is demonstrated that a considerable interobserver variation exists in assessing the severity of atopic dermatitis by most scoring systems. We conclude that the choice for a certain scoring system needs to depend on the purpose of its use, the feasability, the accuracy, the sensitivity, and whether or not the scoring system has been validated. A scoring system with a minimum intraobserver and interobserver variation has the preference. We recommend that a simple, rapid, and reproducible scoring system will suffice, when only a rough estimation of the severity of atopic dermatitis, as in longterm follow-up studies, is needed. A more elaborating system is recommended if subtle modifications in the severity of atopic dermatitis needs to be detected. However, we warn that one should be aware of significant interobserver variation in the assessment of isolated intensity items, the extent, as well as in subjective patient symptoms. Furthermore, we advise to use a scoring system in which the interobserver variation is minimized, and this can be accomplished by a system in which the intensity items, the extent, and the subjective symptoms are scored separately. For clinical trials it is necessary to use a scoring system, which is primarily designed for this purpose. It is recommended for research purposes to have the atopic dermatitis severity scores assessed by a single observer, in order to avoid interobserver variation.

Furthermore, a study is presented in this chapter in which we compared three atopic dermatitis severity scoring systems. In this study we investigated agreement between observers in the assessment of the overall severity of atopic dermatitis, and interobserver variation in the assessment of severity of atopic dermatitis for each scoring item separately, with the Simple Scoring System (SSS), the Scoring Atopic Dermatitis Index SCORAD, and the Basic Clinical Scoring System (BCSS). Moreover, we investigated agreement between these three scoring systems in the assessment of the overall severity of atopic dermatitis. We found good agreement between observers assessing the overall severity of atopic dermatitis in the lower and higher scoring rates by the SSS and the SCORAD, and excellent agreement by the BCSS. Furthermore, we found significant interobserver variation on the isolated intensity items scales, excoriations, edema/papulation, and erythema. Moreover, we found poor agreement between the three scoring systems in assessing the overall severity of atopic dermatitis, indicating that the SSS, the SCORAD, and the overall severity of AD, because we did not use the intensity items. Moreover, we recommend that a single observer is used to assess the severity of AD, because we did not use the intensity items. Moreover, we recommend that a single observer is used to assess the severity of AD, because we did not use the intensity items. Moreo
The SSS, the SCORAD, and the BCSS cannot be used interchangeably to assess the overall severity of atopic dermatitis. We conclude that the BCSS is an excellent and simple score to detect the development of atopic dermatitis, whereas the SSS, and the SCORAD are suitable to follow-up the severity of atopic dermatitis. A single observer is essential for studies assessing the modifications in the severity of AD, because we demonstrated significant interobserver variations in scoring intensity items. Moreover, atopic dermatitis severity scoring systems should not be used interchangeably.

In Chapter five and Chapter six we presented the results of the prospective follow-up study on the development of allergic disorders in children with and without cow’s milk protein allergy or intolerance (CMPA/CMPI). In this follow-up study we investigated the prevalences of allergic disorders, total IgE, specific IgE against inhalant and food allergens, bronchial hyperresponsiveness (BHR), and risk factors for the development of allergic disorders in children with CMPA/CMPI diagnosed by elimination and provocation test during the first three months of life, and treated with an extensive protein hydrolysate based formula. Moreover, these parameters were investigated in children in whom the diagnosis was suspected, but could be rejected on the basis of the same standardized elimination and provocation procedure during the first three months of life (non-CMPA). In chapter five cross-sectional data are presented at a mean age at follow-up of 4.9 years. In chapter six cross-sectional as well as longitudinal data are presented from a mean age of 3.8 years through a mean age of 6.8 years. We found that the prevalence of allergic disorders at a mean age of 4.9 years as well as at a mean age of 6.8 years was substantial. However, no statistical significant difference in prevalences of any of the allergic disorders was found between these two age periods. At a mean age of 6.8 years, at final follow-up, 31% of the children with CMPA/CMPI in infancy had developed asthma, 37% atopic dermatitis, 17% allergic rhinitis, 19% allergic conjunctivitis, and 31% food intolerance. However, no significant statistical differences were found at a mean age of 4.9 years, nor at a mean of 6.8 years, in the prevalences of allergic disorders, total serum IgE, specific IgE against food and inhalant allergens, BHR, and severity of atopic dermatitis between children with and without CMPA/CMPI. No significant statistical difference was found in the course of the reported prevalences of asthma, atopic dermatitis, and allergic conjunctivitis between children with and without CMPA/CMPI during the follow-up period from a mean age of 3.8 years to a mean age
of 6.8 years. Food intolerance was significantly more reported, and allergic rhinitis was significantly less reported in the CMPA/CMPI than in the non-CMPA/CMPI group at a mean age of 3.8 years. However, the point prevalences of allergic rhinitis increased significantly in the CMPA/CMPI group from a mean age of 3.8 to 6.8 years. In contrast, the point prevalences of allergic rhinitis in the non-CMPA/CMPI group decreased significantly from a mean age of 3.8 to 6.8 years. In chapter five we showed by cross-sectional logistic regression analysis that CMPA/CMPI is not a significant risk factor for the development of any of the allergic disorders at a mean age of 4.9 years. Other well known factors, as atopy among first degree relatives, wheeze during the first year of life, and passing through a serious lower respiratory tract infection before the age of 4.9 years, were significant risk factors for allergic disorders at a mean age of 4.9 years. Furthermore, total serum IgE, and sensitization to inhalant and food allergens were significantly associated with allergic disorders at a mean age of 4.9 years. Performing longitudinal data analysis over the total follow-up period from a mean age of 3.8 years to a mean age of 6.8 years, as described in chapter six, we could confirm the results as found at a mean age of 4.9 years. Again, CMPA/CMPI was not a significant risk factor for asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and food intolerance. Atopy among first degree relatives, wheeze during the first year of life, a serious lower respiratory tract infection, sensitization to food and inhalant allergens, and bronchial hyperresponsiveness appeared to be independent significant risk factors for the presence of allergic disorders in our study population.

General discussion

Due to an worldwide increase in the prevalence, and morbidity of allergic disorders there is a need to identify allergy prevention strategies. Several studies have been performed in “high risk for atopy infants”, and have focused on the primary prevention of allergic disorders, including food allergen avoidance during lactation, and in the neonatal period. Extensive, and partial hydrolysed protein based formulas have been proven to be effective in the primary prevention of allergic disorders in high risk infants, particularly in the prevention of food intolerance, including CMPA/CMPI, atopic dermatitis, and asthma. However, some of these studies have demonstrated that dietary intervention during infancy did not prevent the development of asthma and allergic rhinitis later in childhood. Only one study investigated the combination of food allergen and house dust mite sensitization to prevent the development of additional sensitization to food allergens, and sensitization to foods in infants. In this study, atopic dermatitis, and food intolerance and sensitization to foods were significantly reduced in the intervention group compared to the control group at 2 years of age. Asthma was only significantly reduced in the intervention group. The combination of dietary intervention and environmental measures have influenced the development of allergic disorders.

To our knowledge, there have been no studies investigating the effects of this combined approach on the development of asthma and allergic rhinitis later in childhood. Furthermore, the long term effects of this combined approach on the development of allergic disorders have not been investigated. The studies in this field need to be performed, and there is a need for the development of new methods to reliably assess bronchial hyperresponsiveness, and atopy among infants with CMPA/CMPI. The studies in this field need to be performed, and there is a need for the development of new methods to reliably assess bronchial hyperresponsiveness, and atopy among infants with CMPA/CMPI. The studies in this field need to be performed, and there is a need for the development of new methods to reliably assess bronchial hyperresponsiveness, and atopy among infants with CMPA/CMPI.