3.14 Relation of infectious diseases within the first year of life, development of immune response, and risk of atopy within pre-school age: a prospective birth cohort study

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**Background:**
The incidence of atopic diseases such as atopic dermatitis and asthma is currently increasing dramatically in industrialized countries. A reduced microbial exposure and, as a result, a different development of the Th1/Th2 immune response is discussed as one possible explanation for the observed increase of atopic diseases in early childhood (1).

Former epidemiologic studies have consistently shown an inverse relation between number of siblings and allergic diseases. Strachan formulated the hygiene hypothesis, suggesting that the risk of allergic disease is reduced by infectious diseases in infancy transmitted by older siblings (1). Children are born with a tendency to show allergic-type (type 2 cytokine) immune reactions, a pattern that disappears in the first years of life. However, this maturation might be delayed if infants are predisposed to allergy (e.g. by parental history) and in children with reduced exposure to lipopolysaccharides (the latter resulting mainly from exposure to gram-negative bacteria). The dominant Th2 immunity may then cause a higher risk for allergic reactions.

However, with respect to the so called “hygiene hypothesis” conflicting evidence exists. Some recent studies could not confirm that early infections protect against allergic diseases as the number of early infections did not protect against allergic diseases. Instead Benn and colleagues found an increased risk with number of manifest infections within the first 6 months of life and risk of atopic dermatitis (2). In contrast, the risk of atopic dermatitis decreased with each additional exposure to three or more siblings, day care, pet ownership, and farm. The authors suggested that the tendency for a reduced risk for atopic diseases associated with number of siblings, early day care or pet keeping or farm residence may be associated with a higher degree of microbial exposure and a respective stimulation of the immune system in early life and not necessarily reflect the number of clinically manifest infectious diseases.

However, further prospective studies in population based groups of children are needed to clarify these issues. The success of such population based epidemiologic studies in children will also depend on the future development of less invasive methods to determine the respective long-term endpoints (a different development of the Th1/Th2 immune response and/or the atopic outcome) in a non-clinical setting and link it to the infectious diseases patterns within the first year of life. The non-invasive diagnosis of parameters of interest (as in analogy successfully done by our group in a previous study with respect to whole-saliva-based IgG antibody testing (3)) might be a promising research tool for such an epidemiologic study. This way it would be possible to screen a large number of children with a non-invasive method with high acceptance and very good practicability. In addition, this would allow to elucidate an important part of the hypothesized underlying pathway between infectious diseases, respectively microbial exposure and immune development.

**Aim:**
- To investigate the means of a non-invasive ELISA test for measurement of salivary markers of atopy (e.g. immunoglobulin A or others) and the inflammatory response (e.g. C-reactive protein or others) in school children.
To investigate whether number of manifest infections within the first year of life are associated with risk of physician diagnosed atopic diseases at school age independent from markers of microbial exposure (number of siblings, early day care or pet keeping or farm residence),

To investigate whether the number of manifest infections within the first year of life and/or markers of microbial exposure are associated with salivary markers of atopy or the inflammatory response at school age.

Study plan: The work will be performed within a prospective birth cohort study ("Ulmer Säuglingsstudie") which was initiated in November 2000 (4, 5). Overall 1060 women who came to the Department of Gynecology and Obstetrics at the University of Ulm between November 2000 and November 2001 for the delivery of their baby, their partners, and their offspring were recruited for the study (the supervisor is among the principal investigators of this study).

The study was primarily initiated to investigate the epidemiology of \textit{H pylori} infection. However, as \textit{H pylori} infection is supposed to reduce the risk of atopic diseases, the development of atopic disease was also recorded in this study population to allow additional analyses.

Active follow-up was conducted at various points in time (at age one, two, three and age four, five and six are already successfully completed with a response around 90%) in which the parents and in addition, the caring pediatricians of the children provided information about the medical history and other relevant information. (During the last follow-up saliva was collected also). In addition, both parents and pediatricians gave a detailed medical history (number of fever episodes, number and diagnosis of bacterial and/or viral diseases) during the first year of life and a detailed history about the development of atopic diseases during follow-up.

The doctoral student shall do a literature review to identify suitable biologic markers to define the respective endpoints of interest and initiate an evaluation study in which results from measures of serum and saliva will be compared to determine their accuracy (as already approached for some salivary markers of atopy in children (6) or for salivary markers of the inflammatory response in animal studies (7), both with promising results).

If markers with an adequate accuracy will be identified, saliva will be collected in the whole cohort of the meanwhile 8 year old children of the birth cohort study and the respective laboratory measurements will be performed. The doctoral student will also participate in the follow-up. Beside the inclusion of this salivary markers the data analysis will also include physician reported main endpoints (atopic diseases during follow-up).

References