Low Neonatal Toll-like Receptor 4-Mediated Interleukin-10 Production Is Associated With Subsequent Atopic Dermatitis


PURPOSE OF STUDY. To determine whether decreased Toll-like receptor (TLR)-mediated cytokine production at 1 month of age is associated with development of atopic dermatitis (AD) or respiratory syncytial virus lower respiratory tract infection (RSV LRTI). The first month of life is a period of rapid development of the TLR system, and disruption of this development early in life may lead to dysfunction of innate and adaptive immunity and predispose to atopy.

STUDY POPULATION. Healthy term neonates (N = 291) from a birth cohort study in the Netherlands. Subjects were enrolled prospectively and followed for 12 months.

METHODS. At 1 month of age, subjects’ serum concentrations of immune cells were measured by absolute leukocyte count and flow cytometry. After TLR stimulation in vitro, cytokine responses were measured via ELISA. Subjects were assessed for subsequent development of AD and RSV LRTI during the first year of life. AD diagnosis was determined by physician questionnaire at 1 year, and RSV LRTI was determined by reported respiratory symptoms and RSV-positive nasal-throat sample.

RESULTS. Overall, 15% of subjects developed AD and 14% developed RSV LRTI during the first year of life. AD was significantly associated with increased natural killer cells, decreased basophils, and dendritic cells and a 1.8-fold lower TL4-mediated interleukin (IL)-10 production (P < .001). RSV LRTI was not associated with either significant changes in the innate immune cell profile or TLR-mediated cytokine production.

CONCLUSIONS. This study found the development of AD, but not RSV LRTI, to be associated with distinct differences in the innate immune system early in life. Decreased TLR-4-mediated IL-10 production may have a causal role in development of AD.

REVIEWER COMMENTS. IL-10 is a key regulatory cytokine of the immune system. This study hypothesizes that decreased IL-10-mediated regulation of innate responses may contribute to development of atopic skin disease. Further studies are needed to validate these results and investigate the basic mechanisms of neonatal TLR-mediated IL-10 production, as doing so may identify potential targets for prevention and/or treatment of AD.


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Chronic Urticaria: Etiology and Natural Course in Children


PURPOSE OF THE STUDY. Chronic spontaneous urticaria (CSU) in childhood is infrequent, and information about the disease is limited. The study investigated its etiologic factors, natural course, and predictors of prognosis.

STUDY POPULATION. All children aged 18 years or younger in a cohort from Turkey who were diagnosed with CSU during during an 8-year period.
STUDY POPULATION. Three families with a dominantly inherited complex of cold-induced urticaria, antibody deficiency, and susceptibility to infection and autoimmunity.

METHODS. Immunophenotyping, including flow cytometry, analysis of serum immunoglobulins and autoantibodies, lymphocyte stimulation, and enzymatic assays, was used. Genetic studies, including linkage analysis, targeted Sanger sequencing, and next-generation whole-genome sequencing, were performed.

RESULTS. Cold-induced urticaria occurred in all affected subjects. Other, variable manifestations included atopy, granulomatous rash, autoimmune thyroiditis, antinuclear antibodies, sinopulmonary infections, and common variable immunodeficiency. Levels of serum IgM and IgA, circulating natural killer cells, and class-switched memory B cells were reduced. Linkage analysis led to the identification of an interval on chromosome 16q that included PLCG2, which encodes phospholipase Cγ2, a signaling molecule expressed in B cells, natural killer cells, and mast cells. Genomic sequencing identified 3 distinct in-frame deletions that co-segregated with disease. These deletions, located within a region encoding an inhibitory domain, result in protein products with constitutive phospholipase activity. PLCG2-expressing cells had diminished cellular signaling at 37°C but enhanced signaling at subphysiologic temperatures.

CONCLUSIONS. Genomic deletions in PLCG2 cause gain of function of phospholipase Cγ2, leading to signaling abnormalities in multiple leukocyte subsets and a phenotype that includes both deficient and excessive immune function.

REVIEWER COMMENTS. This is a very interesting “experiment of nature” that provides a great deal of insight into phospholipase-mediated signaling. It is fascinating that the PLCG2 mutations identified in this report could lead to both impaired and excessive immune function and that this can be affected by temperature.

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Cold Urticaria, Immunodeficiency, and Autoimmunity Related to PLCG2 Deletions


PURPOSE OF THE STUDY. To perform Mendelian analysis of 3 families with cold-induced urticaria and identify and elucidate immunologic pathways and mechanisms.

METHODS. Retrospective analysis of the medical records of these patients was performed, and the final outcomes were queried via a telephone interview.

RESULTS. One hundred patients (male/female ratio, 1.27) with a median age of 9.2 years (range, 0.7–17.2) at symptom onset were evaluated. The median follow-up was 2.5 years (range, 0.2–18.1). An autologous serum skin test was positive in 46.7% of the subjects (P < 0.001), with a female predominance (71.4%; P = .023). In 13.8% of the children, antinuclear antibody titers were >1:100. Food allergy (n = 1), thyroid autoantibodies (n = 3), possible collagen disease (n = 1), and drug use (deferroxamine) (n = 1) were found to be associated factors. Infections could not be confirmed as the cause of CSU. Recovery was seen in 16.5%, 38.8%, and 50.0% of the children after 12, 36, and 60 months, respectively. Though in multivariate analysis none of the factors, including age, gender, autologous serum skin test positivity, the presence of angioedema, or other allergic diseases appeared to predict the prognosis, in univariate analysis, being female and being older than 10 years predicted an unfavorable prognosis.

CONCLUSIONS. The etiology of CSU in children is mainly related to an autoreactive background, as in adults. CSU has a favorable prognosis, and resolution is seen in half of the children within 5 years. Girls older than 10 years may have an unfavorable prognosis.

REVIEWER COMMENTS. CSU is characterized by recurrent urticaria persisting for longer than 6 weeks. The disorder has a significant impact on the quality of life. While the diagnosis of CSU is based on clinical findings, identification of the etiologic factors responsible for this disease is often challenging. There are limited studies examining the etiology and natural history of CSU in children. The results of this study suggest that autoimmunity plays a role in a significant subset of children with CSU. Furthermore, this study provides long-term follow-up data on children with CSU, indicating a favorable prognosis.


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ALLERGIC RHINITIS

Natural Course and Comorbidities of Allergic and Nonallergic Rhinitis in Children


PURPOSE OF THE STUDY. To evaluate phenotypic variation of rhinitis in relation to natural course and comorbid allergic diseases in preschool and early school age children.

STUDY POPULATION. Subgroup of a Swedish population-based birth cohort (N = 4089) born from 1994 through 1996 in