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 (n = 45), 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 (defereroxamine) (n = 1) were found to be associated factors. Infections could not be ascribed 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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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.

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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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
# Cold Urticaria, Immunodeficiency, and Autoimmunity Related to PLCG2 Deletions

Brian A. Smart

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