

cus in children, this study suggests that critically ill children with severe status asthmaticus may benefit from the addition of IV theophylline to  $\beta$ -agonist, anticholinergic, and corticosteroid therapies. Additional studies may examine the administration of theophylline to select patients in the ED unresponsive to conventional therapy or in patients known to be high risk for respiratory failure.

*Reviewer's Comments.* This is the first prospective randomized trial of IV theophylline limited to children admitted to the PICU. Other studies in hospitalized (noncritical care) asthmatic children failed to show a benefit with the addition of theophylline to conventional treatment. It is possible that the benefit of the addition of theophylline is dependent on the severity of their illness. Adult studies have shown the improvement in spirometry with the addition of a methylxanthine is related to the degree of airway narrowing. The addition of theophylline may serve to reduce the incidence of respiratory failure and mechanical ventilation in children with severe status asthmaticus. The authors note that not blinding the medical team to the treatment may have influenced the results to some degree, but for safety reasons, they did not feel that was warranted. The authors referred to this as a "controlled" study, but there was no reference to a placebo (ex: saline). It would be interesting to repeat this study with a placebo control and with some of the newer critical care treatments such as heliox.

MARY BETH BOLLINGER, DO  
Baltimore, MD

## Immunology

### IMMUNODEFICIENCY DISEASES

#### THE CARBOXYL TERMINUS OF THE GRANULOCYTE COLONY-STIMULATING FACTOR RECEPTOR, TRUNCATED IN PATIENTS WITH SEVERE CONGENITAL NEUTROPENIA/ACUTE MYELOID LEUKEMIA, IS REQUIRED FOR SH2-CONTAINING PHOSPHATASE-1 SUPPRESSION OF STAT ACTIVATION

Dong F, Qiu Y, Yi T, Touw IP, Lerner AC. *J Immunol.* 2001;167:6447–6452

*Purpose of the Study.* Some patients with severe congenital neutropenia harbor mutations in the carboxyl terminus of the granulocyte colony-stimulating factor (G-CSF) receptor. It is this subgroup of patients with severe congenital neutropenia that is markedly predisposed to acute myeloid leukemia. This predisposition poses a significant hurdle to management. Patients with severe congenital neutropenia are typically treated with G-CSF. In this subgroup, G-CSF could drive leukemogenesis and is contraindicated. This study examines the mechanism underlying the predisposition to malignancy.

*Methods.* Cell lines transfected with both wild-type and mutant G-CSF receptor cDNAs and SHP-1 negative cell lines were used to examine the effect of the mutation on signaling function. Electrophoretic mobility shift assays, Western blots, and transient transfections using reporter constructs were performed.

*Results.* The mutant receptors are paradoxically associated with an increased proliferative response to G-CSF despite the differentiative block in neutrophil development. The G-CSF receptor contains no intrinsic signaling activity, but activates Src family kinases, STAT 3/5, MAP

kinases, and PI3 kinase. SHP-1 acts as a negative regulator. The mutant receptors are unable to interact effectively with SHP-1. The consequences of this impaired negative regulation are prolonged responses in the STAT pathways but not other signaling pathways. The exaggerated responses in the STAT pathways would explain the survival advantage of these cells and their hyperproliferation.

*Conclusion.* Failure of the mutant G-CSF receptors to interact effectively with the negative regulator SHP-1 appears to underlie the predisposition to acute myeloid leukemia.

*Reviewer's Comments.* This study represents an important advance in our understanding of the secondary malignancies occurring in patients with severe congenital neutropenia. It should allow improved risk stratification for patients and could ultimately lead to improved management.

KATHLEEN E. SULLIVAN, MD, PhD  
Philadelphia, PA

#### MUTATION OF A NEW GENE ENCODING A PUTATIVE PYRIN-LIKE PROTEIN CAUSES FAMILIAL COLD AUTOINFLAMMATORY SYNDROME AND MUCKLE-WELLS SYNDROME

Hoffman HM, Mueller JL, Broide DH, et al. *Nature Genet.* 2001;29:301–305

*Purpose of the Study.* To identify the genes for familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

*Study Population.* Three families with FCAS and 1 family with MWS.

*Methods.* Genomic DNA isolation, identification of coding region, DNA sequencing, and mutation detection. Protein prediction programs were also performed.

*Results.* Four distinct mutations of the *CIAS1* Gene on chromosome 1q44 were identified. The gene encodes a newly identified protein called cryopyrin.

*Conclusion.* Mutations of the *CIAS1* Gene encoding cryopyrin cause at least two distinct but similar cold-sensitive diseases, including FCAS and MWS.

*Reviewers' Comments.* This exciting discovery has led to the identification of a new protein, aptly named "cryopyrin," that links cold temperature exposure to inflammation. In this report, mutations of the cryopyrin gene were identified in family members with 2 rare autosomal dominant conditions that are "autoinflammatory" disorders (ie, conditions with recurrent inflammatory symptoms in the absence of autoantibodies): FCAS and MWS. Recently, FCAS—also known as familial cold urticaria and familial polymorphous cold eruption—has been well-described by the same authors. The FCAS clinical picture includes: skin rash (100%), arthralgia (96%), fever (93%), conjunctivitis (84%), disease onset in the first 6 months of life (95%), an average time delay between cold exposure and the onset of symptoms of 2.5 hours, and an average episode duration of 12 hours (Hoffman HM, et al. *J Allergy Clin Immunol.* 2001; 108:615–620). In contrast, MWS leads to progressive sensorineural deafness, amyloidosis of the kidneys and other organs, fevers, chills, rigors, malaise, and chronic recurrent urticaria. The reason for the 2 distinct clinical entities associated with mutations in the same gene still need to be explored. For more discussion, see a brief editorial entitled "A fever gene comes in from the cold" by Kastner and O'Shea on pages 241–242 of the same issue.

AKALUCK THATAYATIKOM, MD  
ANDREW H. LIU, MD  
Denver, CO

# Mutation of a New Gene Encoding a Putative Pyrin-Like Protein Causes Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome

Akaluck Thatayatikom and Andrew H. Liu

*Pediatrics* 2002;110:466

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