Immunodeficiency

PRIMARY IMMUNODEFICIENCY

STAT3 Mutations in the Hyper-IgE Syndrome

PURPOSE OF THE STUDY. To identify the genetic defect underlying the hyper–immunoglobulin E (IgE) (Job) syndrome.

STUDY POPULATION. Patients with hyper-IgE syndrome were ranked by a clinical scoring system. Fifty patients over the age of 16 years who had the highest scores (most features of the disease) were selected. Forty-eight family members also underwent genetic analysis.

METHODS. The authors used a combination of microarray screening of gene expression and analysis of cytokine production in vitro from lymphocytes subjected to various stimuli.

RESULTS. Lymphocytes from patients were found to have diminished response to the cytokine interleukin 6. The authors systematically analyzed the intracellular signaling molecules involved in the response to interleukin 6 and found that patients carried a mutation in 1 of the 2 copies of the gene encoding signal transducer and activator of transcription 3 (STAT3). They confirmed the biological importance of the mutations by showing that the STAT3 protein did not function normally within the cell.

CONCLUSIONS. STAT3 mutations are the genetic basis of the hyper-IgE syndrome.

REVIEWER COMMENTS. The first clinical description of hyper-IgE syndrome as a distinct entity was published in 1966. It was given the eponym “Job syndrome” as a biblical allusion because of the many severe skin abscesses that affect patients with the condition. This report is the culmination of >40 years of investigation by many groups around the world to find the molecular basis of this disease. A similar report was published by another group around the same time (Minegishi Y, Saito M, Tsuchiya S, et al. Nature. 2007;448[7157]:1058–1062). We are reminded again of the power of modern molecular biological methods and the tremendous insights we gain when such diseases are finally understood at their “source.”

Population Prevalence of Diagnosed Primary Immunodeficiency Diseases in the United States

PURPOSE OF THE STUDY. To measure the prevalence of primary immunodeficiency diseases (PIDs) in the United States.

STUDY POPULATION. A random sample of 10,005 American households (26,657 people) was included in the study.

METHODS. Households were selected by random-digit dialing stratified according to time zone. Calls were placed by trained interviewers with computer assistance. Eighty percent of the households contacted completed the interview. Respondents were asked, “Has anyone in your household ever been diagnosed with a primary immunodeficiency disease such as common variable immunodeficiency, IgA [immunoglobulin A] deficiency, IgG subclass deficiency, or any other immunodeficiency? (This is not acquired immunodeficiency—AIDS).” If they replied “yes,” they were further questioned with details of the diagnosis and limited demographic information about the affected individual(s).

RESULTS. Twenty-three individuals in 18 households were identified as having a specific PID (including common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, X-linked agammaglobulinemia, severe combined immunodeficiency, and chronic granulomatous disease). The calculated prevalence of diagnosed immunodeficiency was 1 in 2000 children, 1 in 1200 people of all ages, and 1 in 600 households. The 95% confidence limits for the estimate for all individuals were between 1 in 824 and 1 in 1956. Several of the identified individuals with primary immunodeficiency were not receiving therapy that is standard of care for their diagnoses (γ-globulin replacement).

CONCLUSIONS. Quoting the authors, “The current study suggests that these conditions are sufficiently common that primary care physicians are likely to see patients with underlying primary immunodeficiency disorders in their practice and should test for these disorders in patients with recurring, unusual or serious infections. In the absence of routine screening, physician awareness of the relative frequency of these disorders is critical to early diagnosis and treatment.”

REVIEWER COMMENTS. This is an extremely important message for all primary care physicians. These patients are in your practices now. The authors also pointed out that several studies have shown that many cases of PID are diagnosed late or are “mild” enough that they are never diagnosed and that patients suffer excess morbidity and mortality as a result. Some severe cases may be missed because children die before they are diagnosed. Thus, the true prevalence of PID is likely to be higher than

Francisco A. Bonilla, MD, PhD
Boston, MA
STAT3 Mutations in the Hyper-IgE Syndrome
Francisco A. Bonilla
*Pediatrics* 2008;122;S224
DOI: 10.1542/peds.2008-2139
STAT3 Mutations in the Hyper-IgE Syndrome
Francisco A. Bonilla
Pediatrics 2008;122;S224
DOI: 10.1542/peds.2008-2139EEEEE

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/122/Supplement_4/S224.1