Study Population. Thirteen patients from 6 families having AR-HIES and 68 of their relatives.

Methods. Patients were identified based on exhibiting a classic triad of features of HIES: recurrent skin abscesses, recurrent pneumonias, and elevated serum IgE. Medical records were reviewed, and patients and family members underwent uniform immunologic evaluations.

Results. All families were consanguineous. Five are from Turkey and 1 is from Mexico. According to a previously developed scoring system (>20, HIES possible; >40, HIES highly likely), all 13 patients had scores ranging from 19 to >50. All relatives had scores of <20, supporting an autosomal recessive mode of inheritance. Eight of the 13 patients died between the ages of 6 months and 12 years. Features that are common to both forms of HIES include a chronic eczematous skin eruption with staphylococcal superinfection and upper and lower respiratory tract bacterial infections caused by common pathogens as well as unusual organisms (Proteus mirabilis, Pseudomonas aeruginosa, Cryptococcus neoformans) and chronic mucocutaneous candidiasis. Features that are found in AD-HIES that are not shared in AR-HIES include failure to shed primary dentition, bone fragility, coarse asymmetric facies, and pneumatocoele formation. Features found only in AD-HIES include susceptibility to severe infection with molluscum contagiosum and herpesviruses. Patients with AR-HIES also have a high rate of life-threatening inflammatory cerebrovascular complications leading to stroke and/or hemorrhage. Serum IgE in patients with AR-HIES ranged from 4500 to 45 000 IU/mL (similar to AD-HIES). In general, serum immunoglobulin levels were elevated because of general stimulation resulting from infectious burden; specific antibody formation appeared normal. Eosinophil counts in patients with AR-HIES were from 2 500 to 18 000 cells per mm³, somewhat higher than in patients with AD-HIES. There were no major abnormalities of lymphocyte subpopulations, although in vitro T-cell responses to recall antigens and to a B-cell mitogen were depressed. Some patients with AD-HIES have impaired neutrophil chemotaxis and killing; this was not observed in those with AR-HIES. AD-HIES has been linked to a region on chromosome 4q. This linkage has not been observed in patients with AR-HIES.

Conclusions. AR-HIES is similar to but distinct from AD-HIES and most likely arises from an altogether different genetic basis.

Reviewer’s Comments. HIES is among the earliest described syndromes of immunodeficiency, originally named Job’s syndrome because of the prominence of skin infections in the clinical phenotype. The genetic basis of this disease still eludes investigators. The description of an apparently distinct but very similar entity raises the exciting possibility that we may be seeing the results of defects in molecules that have a functional interaction in vivo. One may hope that defining the genetic bases of these diseases may lead to the same kinds of advances in our understanding of immune system biology, as have resulted from the study of other primary immunodeficiencies, with a potential for novel therapies.

Francisco A. Bonilla, MD, PhD Boston, MA

THE PRESENTATION AND NATURAL HISTORY OF IMMUNODEFICIENCY CAUSED BY NUCLEAR FACTOR κB ESSENTIAL MODULATOR MUTATION


Purpose of the Study. To describe the clinical and immunologic natural history of patients with immunodeficiency associated with mutation in nuclear factor κB modulator (NEMO).

Study Population. Seven boys who presented to Children’s Hospital Boston (Boston, MA) for immunodeficiency evaluation between 1984 and 2002 and were diagnosed to have a NEMO mutation with immunodeficiency (NEMO-ID).

Methods. Patients with recurrent bacterial infection and ectodermal dysplasia (ED) or atypical mycobacterial infection were evaluated by sequence analysis for NEMO mutation. Functional analyses of these mutations have been described previously. Genomic and complementary DNA from patient leukocytes were sequenced and compared with 40 healthy individuals. Serum immunoglobulin concentrations, leukocyte enumeration, lymphocyte subset numbers and function, nitroblue tetrazolium reduction, total hemolytic complement, and natural killer cell cytotoxicity were measured by using standard assays. Data were obtained both retrospectively and prospectively. NEMO-ID incidence rates were approximated by using US census data for the catchment area of Children’s Hospital Boston. Immunologic measurements were compared with laboratory-specific age-related norms, and significance of differences was assessed by Student’s t test.

Results. The estimated incidence of NEMO-ID is 1 in 250 000 live male births. Four of the 6 independent mutations described (2 patients were half-siblings) affected the C-terminal zinc-finger domain encoded by exon 10. Six of 7 patients presented with ED. All patients had serious pyogenic bacterial infections early in life (median age at first infection: 8.1 months; range: 0.1–60.9 months). Immunodeficiency was diagnosed before ED in all patients. Five of 7 patients had infection with atypical mycobacteria (median: 84 months old; range: 14–168 months old). The most severe clinical phenotype was seen in the 2 sibling patients with a mutation resulting in truncation of >50% of the final exon. That mutation was also associated with a pattern of immunoglobulin dysregulation consisting of hyper-IgM and hypo-IgA. All but 1 patient (patient 5) was hypogammaglobulinemic, and all were deficient in specific antibody production. However, 5 of 6 mutations were associated with hyper-IgA. Patient 5, who has an unusual mutation causing deletion of exon 9, was also uniquely unaffected by ED. Lymphocyte subsets and in vitro function were variable, although natural killer cell cytosis was markedly depressed in all patients tested (n = 5).

Conclusions. NEMO-ID is an X-linked combined immunodeficiency characterized by early susceptibility to pyogenic bacteria and later susceptibility to mycobacterial infection.

Reviewer’s Comments. The majority of reported mutations in NEMO affect exon 10. This report extends our knowledge of NEMO-ID and suggests genotype-phenotype correlations, including for the first time a description of NEMO-ID without ED. The striking incidence of early pyogenic infections deserves emphasis and suggests defects in innate immunity. Severe pyogenic bacterial infection should prompt consideration of nuclear factor κB-activation disorders, especially when accompanied by hyper-IgA.

Wayne G. Shreffler, MD, PhD New York, NY
The Presentation and Natural History of Immunodeficiency Caused by Nuclear Factor κB Essential Modulator Mutation
Wayne G. Shreffler
Pediatrics 2005;116;569
DOI: 10.1542/peds.2005-0698UUU

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/116/Supplement_2/569

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Allergy/Immunology
http://www.aappublications.org/cgi/collection/allergy:immunology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml
The Presentation and Natural History of Immunodeficiency Caused by Nuclear Factor κB Essential Modulator Mutation

Wayne G. Shreffler

Pediatrics 2005;116;569
DOI: 10.1542/peds.2005-0698UUU

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/116/Supplement_2/569