Immunology

IMMUNODEFICIENCY DISEASES

CUTANEOUS MANIFESTATIONS OF HYPER-IgE SYNDROME IN INFANTS AND CHILDREN


Purpose of the Studies. Hyper-immunoglobulin E (HIE) syndrome is an immunodeficiency disorder characterized by recurrent skin abscesses, pneumonia, elevated serum IgE, and increased incidence of dental abnormalities (retained primary teeth), bone fractures and scoliosis. X-linked agammaglobulinemia (XLA) is characterized by a mutation in the gene for Bruton’s tyrosine kinase (BTK) typically resulting in recurrent bacterial infections in the first few years of life. These studies reviewed the clinical features of patients with these diagnoses and report clinical features that could lead to earlier diagnosis.

Study Populations. Eight children with hyper-IgE syndrome were identified from 5 pediatric dermatology practices through a retrospective chart review. Eighty-two patients with clinical features leading to the diagnosis of XLA, and proven mutations in the BTK gene culled from 53 institutions were evaluated.

Methods. The clinical history, laboratory results and clinical photographs were obtained from chart review (hyper-IgE) or from structured survey forms completed by referring physicians or genetic counselors (XLA).

Results. The 8 children recruited from dermatology practices had been evaluated for a papulopustular eruption on the face and scalp in the first year of life and were not diagnosed with HIE until an average of 18 months later. Six developed the rash by 1 month of age and most were diagnosed before 1 year of age. Seventy-three males with a definite diagnosis of XLA constituted the study population. An enrollment questionnaire was sent in 1994 and annual reports have been filed on each patient since that time.

Conclusions. A papulopustular eruption with the described features and distribution, along with additional findings such as early infections, fractures, and/or eosinophilia, should prompt an evaluation for HIE. Children with 3 or more episodes of otitis media or sinusitis should be examined closely and if the tonsils or cervical lymph nodes are unusually small or absent, serum immunoglobulin levels should be screened with appropriate referral for additional studies if they are abnormal.

Reviewer’s Comments. Prompt diagnosis of immunodeficiency disorders allows for earlier treatment and can prevent sequela. Knowing the results of these 2 studies will allow pediatricians to increase the chance for early diagnosis. It must be kept in mind, however, that the presentations emphasized here are not the only ones that are possible with these disorders. Vigilance in keeping primary immunodeficiency disorders on the differential diagnosis of recurrent, refractory, and unusual infections is key.

Scott H. Sicherer, MD
New York, NY

CLINICAL, IMMUNOLOGICAL, AND MOLECULAR ANALYSIS IN A LARGE COHORT OF PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA: AN ITALIAN MULTICENTER STUDY


Purpose of the Study. This large Italian study was designed to investigate the natural history of X-linked agammaglobulinemia (XLA). Although it is among the more common of the primary immunodeficiencies, there is surprisingly little information on optimal management and outcome. This study was designed to characterize the long-term issues facing this patient population.

Study Population. Seventy-three males with a definite diagnosis of XLA constitute the study population. Thirty-nine Italian centers participated. This group is relatively old with a mean age of 14 years, and this allows the authors to perform certain longitudinal studies.

Methods. All male patients at the 39 centers with hypogammaglobulinemia and B cell numbers <1% were initially included. Mutation analysis of Bruton’s tyrosine kinase (BTK) was performed and 73 were identified as having “definite XLA” on this basis. These patients constitute the study population. An enrollment questionnaire was sent in 1994 and annual reports have been filed on each patient since that time.

Results. There are several surprises in this article. The immunoglobulin G (IgG) levels at enrollment ranged from a low of 7 mg/dL to a high of 891 mg/dL. Most patients, but not all, had very low immunoglobulin A (IgA) levels, and the 10 patients who had an IgA >20 mg/dL typically had normal or near normal immunoglobulin M (IgM) levels, but there was no correlation between IgA/IgM levels and IgG levels. All patients had <1% B cells because that was required for entry into the study. As one would expect, respiratory tract infections were observed in a majority of patients at the time of diagnosis. Other common infections were skin infections, gastrointestinal infections, and sepsis. These authors describe a high rate of chronic lung disease in their patients rising to 100% at 30 years of follow-up. There is a sharp increase in chronic lung disease between 12 and 20 years of follow-up, perhaps reflecting the introduction of intravenous immune globulin (IVIG) 15–20 years ago. The chance of having chronic lung disease also increases with delay in diagnosis. Half of the patients diagnosed at 10 years or age or later had chronic lung disease at the time of diagnosis. There was a single death and no malignancies, which is better than has been previously published.

Conclusions. The spectrum of XLA is clearly broader than was once imagined. Although patients have improved survival in this study compared with earlier studies of XLA patients, there are significant health issues for these patients. Chronic lung disease and sinusitis remain persistent problems.

Reviewer’s Comments. This is a wonderful study that will lead many people to revise their diagnostic work-up of
CLINICAL FINDINGS LEADING TO THE DIAGNOSIS OF X-LINKED AGAMMAGLOBULINEMIA
Scott H. Sicherer
Pediatrics 2003;112;487

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/112/Supplement_2/487.

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_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
CLINICAL FINDINGS LEADING TO THE DIAGNOSIS OF X-LINKED AGAMMAGLOBULINEMIA
Scott H. Sicherer
*Pediatrics* 2003;112;487

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/112/Supplement_2/487.2