Original Article

Autosomal Dominant Hyper-IgE Syndrome in the USIDNET Registry

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What is already known about this topic? Hyper-IgE syndrome (HIES) is a rare autosomal-dominant (AD) immune defect associated with lung, skin, and other infections, usually due to bacteria or selected fungi. Lung infections and hemoptysis are the major cause of mortality and morbidity.

What does this article add to our knowledge? We report clinical, immunologic data as well as quality of life for a large cohort of patients with AD-HIES entered into the USIDNET Registry.

How does this study impact current management guideline? Knowledge of the course and complications of a large group of patients provides critical information for providers caring for those affected with this rare condition. The use of immune globulin replacement on prevention of infections remains to be clarified.

BACKGROUND: Autosomal dominant hyper-IgE syndrome (AD-HIES) is a rare condition.

OBJECTIVE: Data from the USIDNET Registry provide a resource to examine the characteristics of patients with rare immune deficiency diseases.

METHODS: A query was submitted to the USIDNET requesting deidentified data for patients with physician-diagnosed AD-HIES through July 2016.

RESULTS: Data on 85 patients diagnosed with AD-HIES (50 males; 35 females) born between 1950 and 2013, collected by 14 physicians from 25 states and Quebec, were entered into the USIDNET Registry by July 2016. Cumulative follow-up was 2157 years. Of these patients, 45.9% had a family history of HIES. The complications reported included skin abscesses (74.4%), eczema (57.7%), retained primary teeth (41.4%), fractures (39%), scoliosis (34.1%), and cancer (7%). Reported

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Abbreviations used
AD-HIES- Autosomal dominant hyper-IgE syndrome
HIES- Hyper-IgE syndrome
HSCT- Hematopoietic stem cell transplantation
Ig- Immunoglobulin
NIH- National Institutes of Health
STAT- Signal transducer and activator of transcription signal

allergic diseases included food (37.8%), environmental (18%), and drugs (42.7%). The mean serum IgE level was 8383.7 kU/mL and was inversely correlated to the patient's age. A total of 49.4% had eosinophilia; 56% were known to be on trimethoprim-sulfamethoxazole, 26.6% on antifungal coverage, and 30.6% on immunoglobulin replacement therapy. Pneumonias were more commonly attributed to *Staphylococcus aureus* (55.3%) or *Aspergillus fumigatus* (22.4%); 19.5% had a history of lung abscess; these were most often associated with *Pseudomonas aeruginosa* (*P* Fisher's exact test = .029) or *A. fumigatus* (*P* Fisher's exact test = .016). Lung abscesses were significantly associated with drug reactions (*P* χ^2 = .01; odds ratio: 4.03 [1.2-12.97]), depression (*P* Fisher's exact test = .036), and lower Karnofsky index scores (*P* Mann-Whitney = .007). DISCUSSION: Data from the USIDNET Registry summarize the currently reported clinical characteristics of a large cohort of subjects with AD-HIES. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Buckley-Job syndrome; Chronic mucocutaneous candidiasis; Immunodeficiency; Pneumatocele; Quality of life*

Autosomal dominant hyper-IgE syndrome (AD-HIES) first described and named Job syndrome in 1966 is characterized by the triad of pulmonary infections, eczematoid dermatitis, and recurrent skin infections or localized abscesses. The "cold" abscesses initially described by Davis et al may occur, but inflammatory symptoms, such as tenderness and warmth, are more common. On aspiration, there is frank pus, and *Staphylococcus aureus* is usually cultured.[1] In 1972, Buckley et al recognized the multisystem nature of this syndrome, and that elevated serum IgE was an integral part of the spectrum,[2] although IgE levels may decrease with age.[3] Patients often have characteristic facial features, including a wide nasal bridge, high palate, and/or wide or deep-set eyes and prominent forehead; other common features are mucocutaneous candidiasis, usually onychomycosis and thrush,[4] and fractures with minor trauma.[5] Bone abnormalities such as scoliosis and osteoporosis are common[5]; children may not shed primary teeth easily, requiring surgical extraction.[6] The prognosis of AD-HIES is largely determined by the degree of lung disease.[7] Recurrent pyogenic pneumonias commonly occur in childhood and lead to the formation of pneumatoceles, followed by fungal infections and other secondary infections, and the potential for hemoptysis, which are major causes of mortality and morbidity.[7,8] The extent of pulmonary infections may be out of proportion to the systemic signs of illness such as fever, leading to failure of early recognition of lung infections.

The multisystem involvement in AD-HIES may be accounted for by the widespread role played by the underlying genetic defect, heterogeneous mutations in signal transducer and activator of transcription 3 (STAT3).[7,9,10] STAT3 is a transcription factor that transmits signals to the nucleus after activation by a number of cytokines and growth factors, including IL-2, IL-6, IL-10, IL-12, IL-15, IL-21, IL-23, and IL-27.[11-14]

As AD-HIES is a rare disease (annual incidence is estimated at 1/1,000,000), physicians in Allergy/Immunology are likely to see only a few patients with this syndrome in their practice. In this report, we outline the immunologic and clinical aspects of 85 patients with AD-HIES as reported to the research consortium USIDNET Registry. As for the French National Survey of 60 patients,[15] the data from this registry provide a useful broad description of the clinical and immunologic features of this rare syndrome.

METHODS

The USIDNET Registry was formed in 1992 by the Immune Deficiency Foundation, and converted to an online electronic format in 2008 with standardized case report forms.[16] The online patient-consented Registry is funded by the National Institutes of Health (NIH), and maintains clinical, laboratory, molecular, treatment, and quality-of-life data for patients with a number of primary immune defects, including those with an unclear diagnosis. Data are entered from enrolling institutions in the North America as well as via a new link allowing patients to self-enroll and transfer medical records for entry into the Registry. Deidentified data available for research purposes were used for the current study, for which a query was submitted to the USIDNET requesting all data for patients with physician-diagnosed HIES through July 2016. The data fields surveyed included demographics, criteria used to render diagnosis, pedigree evaluation, clinical features, laboratory findings, treatment, and transplant records. The underlying genetic mutations for this cohort were not recorded. All statistical tests were 2-sided and computed using IBM SPSS Statistics 20.0 (IBM, New York, NY).

RESULTS

Demographics

As of July 2016, the USIDNET Registry contained data for 85 patients (50 males and 35 females) with HIES, entered by 14 physicians. The patients come from 25 different US states and Quebec, and the longest reported follow-up is 15 years (from 2001 to 2016). Considering the age of the patients at the last encounter, the total number of years of medical history encompassed totals 2157 years. For subjects with incomplete entries, the data available are included here. The median age at the onset of symptoms was 2 years (range: newborn to 18 years old); the mean age at diagnosis was 13.8 and at data entry 27.3 years (Table I). Of the total patients, 62.4% (53/85) were Caucasian, 11.8% (10/85) Hispanic, 11.8% African American, and 5.9% (5/85) Asian. Of the entered patients, 45.9% (39/85) had family histories of HIES: amongst the group were 8 affected mothers, 4 affected fathers, 1 affected sister, 3 affected brothers, 2 affected sons, and 1 affected daughter.

Laboratory data

The mean serum IgE for these patients was 8,383.7 kU/mL (range 3,600-53,399). As previously reported,[3] the levels of serum IgE were inversely correlated with the age of the patients (analysis of variance, N = 66; *P* = .03). Patients had normal levels of other serum immunoglobulins. Of the group, 54.9%