Immunodeficiency

PRIMARY IMMUNODEFICIENCY

IMMUNODEFICIENCY AND INFECTIONS IN ATAXIA-TELANGIECTASIA


Purpose of the Study. To describe immunodeficiency in ataxia-telangiectasia (A-T) and its clinical manifestations and course.

Study Population. Patients with A-T who underwent multidisciplinary assessment at Johns Hopkins Hospital (Baltimore, MD).

Methods. Charts from the first 100 consecutive patients with A-T who were assessed at Johns Hopkins Ataxia-Telangiectasia Clinical Center were reviewed. Specific criteria for the diagnosis of A-T had to be met. Immunologic data were obtained by reviewing laboratory assessments of patients’ immune systems. Infections were determined by patient and family interviews and chart review.

Results. A large percentage of patients had immunoglobulin deficiencies at the time of first immunologic assessment: 65% had IgG4 deficiency, 63% had IgA deficiency, 48% had IgG2 deficiency, and 23% had IgE deficiency. Deficiencies did not correlate or progress with age. Lymphopenia occurred in 71% of patients. CD19 B lymphocytes were reduced in 75% of patients. CD4 T cells were decreased in 69% of the patients, and CD8 T cells were decreased in 51% of the patients. Patients had no untoward effects from live viral vaccines. Recurrent upper respiratory infections occurred in one third of the patients regardless of age. Lower respiratory tract infections increased with age. Viral and opportunistic infections were not common.

Conclusions. Patients with A-T have a wide array of laboratory-based immunodeficiencies. However, there seems to be no correlation between laboratory values and clinical manifestation of immunodeficiency in this population.

Reviewers’ Comments. This study confirms previously characterized immunodeficiencies in A-T patients. However, the large number of patients involved in this study allowed for a more extensive review of immunodeficiencies as well as clinical correlation of laboratory values. At this time it seems that clinical immunodeficiency is not common in A-T. Rather, the high rate of respiratory infections may be attributable to other factors of A-T such as neurologic deficits leading to aspiration.

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AUTOSOMAL RECESSIVE HYPERIMMUNOGLOBULIN E SYNDROME: A DISTINCT DISEASE ENTITY


Purpose of the Study. To describe the clinical and immunologic features of a distinct subgroup of patients with hyper-IgE syndrome (HIES) having autosomal recessive inheritance (AR-HIES) as distinct from the form having autosomal dominant inheritance (AD-HIES).

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CLINICAL AND IMMUNOLOGICAL EFFECT OF LOW-DOSE IFN-α TREATMENT IN PATIENTS WITH CORTICOSTEROID-RESISTANT ASTHMA


Purpose of the Study. To evaluate the clinical and immunologic effects of interferon (IFN)-α in patients with corticosteroid-resistant asthma with and without Churg-Strauss syndrome.

Study Population. Ten patients with severe steroid-resistant asthma, 3 of whom had Churg-Strauss syndrome, were studied.

Methods. Subjects were given 3 × 10^6 IU/day of recombinant IFN-α for at least 5 months. The prior systemic corticosteroid doses were maintained until clinical improvement was seen, and then they were decreased gradually. Spirometry, immunophenotyping of peripheral blood mononuclear cells, cytokine measurements, and lymphocyte proliferation assays were performed.

Results. IFN-α rapidly improved patient clinical status as assessed by improved lung-function parameters and decreased prednisone requirements. Immunologic changes included decreased leukocyte numbers, decreased numbers of eosinophils in patients with prior eosinophilia, increased relative numbers of CD4^+ T cells, increased differentiation of T-helper (Th)1 cells, and increased interleukin 10 and IFN-γ levels in peripheral blood mononuclear cells.

Conclusions. Treatment with IFN-α in patients with steroid-resistant asthma with and without Churg-Strauss syndrome was associated with clinical improvement. Possible mechanisms of action include induction of anti-inflammatory interleukin 10 and establishment of a correct Th1/Th2 balance.

Reviewers’ Comments. Although this study involved only a few patients and additional elucidation of the underlying mechanisms is needed, these patients with steroid-resistant asthma improved with IFN-α treatment. Although this study involved only adults, the use of IFN-α as a potential steroid-sparing medication for use in children may also prove beneficial, especially given justified patient, parental, and physician concerns about using long-term oral corticosteroids in children because of the potential for significant toxicity. The use of IFN-α, however, would have to outweigh its inherent potential adverse effects including influenza-like symptoms, nausea, and liver toxicity, to name a few. This preliminary study, however, does make a case for the need for additional, longer-term clinical trials.

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limitations to this study admitted by the authors in their discussion. For example, there is a small sample size in the individual strata, and as a result there are wide confidence intervals. Therefore, the authors could not exclude with certainty that long-term exposure to ICS might be associated with slightly increased fracture risk. More studies would be needed to better assess the impact of longer-term treatment and the use of concomitant oral steroids on fracture risks.
The clinical phenotype of HIES includes recurrent infections caused by atypical organisms, particularly Proteus mirabilis and Pseudomonas aeruginosa, and skin infections caused by unusual organisms such as Cryptococcus neoformans and unusual mycobacteria. The majority of reported mutations in NEMO affect exon 10. This report extends our understanding of the genetic basis of this disease and suggests that the majority of reported mutations are associated with 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 cytolyis 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.

Francisco A. Bonilla, MD, PhD
Boston, MA

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 cytolyis was markedly depressed in all patients tested (n = 5).

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# Autosomal Recessive Hyperimmunoglobulin E Syndrome: A Distinct Disease Entity

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