

ANTIBODY DEFICIENCY AND AUTOIMMUNITY IN 22q11.2 DELETION SYNDROME

Gennery A, Barge D, O'Sullivan J, et al. *Arch Dis Child*. 2002;86:422–425

Purpose of the Study. The aim of this study was to investigate humoral immunity, particularly antibody response to pneumococcal polysaccharide, and autoimmune anomalies in a cohort of patients with 22q11 deletion.

Study Population. Thirty-two patients from the Newcastle, United Kingdom (UK) Pediatric Immunology Clinic were identified based on referrals for the diagnosis of 22q11 deletion or because a patient with 22q11 deletion was suffering from recurrent infections.

Methods. A history of severe or recurrent bacterial infection and autoimmune symptoms were noted. Lymphocyte subsets, immunoglobulins, immunoglobulin G (IgG) subclasses, specific vaccine antibodies, and autoantibodies were measured. Subjects were vaccinated with appropriate antigens when specific antibodies were low.

Results. Twenty-six (81%) of the 32 patients had severe or recurrent infections, of which 13 (50%) had abnormal serum immunoglobulin levels and 11 of 20 (55%) ≥ 4 years old had an abnormal antibody response to pneumococcal polysaccharide antigen. Ten of 30 (33%) patients investigated had autoimmune phenomena, of which 6 were symptomatic, and all 10 had either low immunoglobulins or poor response to specific vaccine antigens.

Conclusions. Humoral immunodeficiency appears to be more common than has been previously recognized. Normal T cell function and normal immunoglobulin levels do not exclude poor specific antibody responses and susceptibility to severe or recurrent bacterial infections. Patients diagnosed with 22q11 deletion should be referred for formal investigation of both cellular and humoral immune function, including response to conjugated pneumococcal vaccines.

Reviewers' Comments. This study adds important information to our knowledge of the potential immune dysfunction in patients with 22q11 deletion. The exact mechanisms of the abnormalities in humoral immunity and the high incidence of autoimmune phenomena remain unclear and need to be determined. Although the authors state that there is reporting bias in the study based on whether patients were referred simply on the basis of their diagnosis or because of recurrent infections, they did not state how many patients were identified by which type of referral. Furthermore, there is likely more bias because this referral center may evaluate the most severe cases in the area. This study only involves a small group of patients from 1 center, and thus additional studies involving multicenter and multinational cohorts are necessary to see if the reported abnormalities occur as frequently.

DAVID FLEISCHER, MD
ROBERT A. WOOD, MD
Baltimore, MD

PLEIOTROPIC EFFECT IN LYMPHOCYTE ACTIVATION CAUSED BY CASPASE-8 MUTATIONS LEAD TO HUMAN IMMUNODEFICIENCY

Chun HJ, Zheng L, Ahmad M, et al. *Nature*. 2002;419:395–399

Purpose of the Study. Defects in genes involved in the apoptosis (programmed cell death) of lymphocytes have been shown to cause disorders characterized by significant adenopathy and autoimmunity. This study defines a new defect in that category and characterizes the clinical pre-

sentation. Mutations in the caspase-8 gene not only affect apoptosis but also affect host defense. This article describes a heretofore unrecognized function of caspase-8 in lymphocyte activation.

Study Population. The study relies on a single kindred with 2 affected children and the heterozygous parents and sibling. The carriers of the mutation were asymptomatic.

Methods. The authors carefully characterize the apoptosis of cells from the affected children as well as the activation of their lymphocytes. Traditional killing studies were performed to define the defect in apoptosis as well as flow cytometric determinations of T cell activation. Cytokine production and proliferation were also measured to delineate the defect in T cell function.

Results. The 2 patients with defects in caspase-8 had significant adenopathy and splenomegaly. These 2 features have been observed in all patients with defects in genes involved in lymphocyte apoptosis. In addition, these patients had several features that appear to be specific for caspase-8 defects. The patients had diminished CD4 counts, elevated CD8 T cell counts, poor responses to immunization, failure to thrive, recurrent herpes infections, and other recurrent infections. Mechanistic studies revealed defective apoptosis attributable to Fas-mediated signals but preserved apoptosis in response to mitochondrial-mediated signals. Western blots suggested that the Fas signal was intact up to recruitment of Fas-associated death domain, but that subsequent recruitment of caspase-8 was defective. Sequencing revealed a homozygous caspase-8 mutation. In addition to the defect in apoptosis, the authors describe a very significant defect in lymphocyte activation that probably accounts for the immunodeficiency phenotype. B cells, T cells, and NK cells are all defective in this disorder.

Conclusions. Caspase-8 mutations lead to a disorder characterized by expansion of lymphocytes in secondary lymphoid organs and abnormal lymphocyte activation.

Reviewer's Comments. This article is significant for introducing us to a new immunodeficiency and for the demonstration that caspase-8 is involved in lymphocyte activation. The 3 known defects of lymphocyte apoptosis, Fas deficiency, FasL deficiency, and caspase 10 deficiency all have a similar phenotype: the early presentation of significant adenopathy, splenomegaly, and autoimmune disease. Caspase-8 is now known to have an undefined but integral function in lymphocyte activation and the phenotype of patients with caspase-8 deficiency reflects this, with both lymphoid expansion and immunodeficiency.

KATHLEEN E. SULLIVAN, MD, PhD
Philadelphia, PA

CORRECTION OF ADA-SCID BY STEM CELL GENE THERAPY COMBINED WITH NONMYELOABLATIVE CONDITIONING

Aiuti A, Slavin S, Aker M, et al. *Science*. 2002;296:2410–2413

Purpose of the Study. To use improved gene therapy techniques to correct adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID).

Patient Population. Two patients (7 months old and 2.5 years) with ADA-SCID who lacked an HLA-identical sibling donor and for whom polyethylene glycol conjugated (PEG)-ADA was unavailable.

Methods. Patients underwent collection of autologous CD34+ cells (stem cells) from bone marrow that were corrected for ADA by transduction using a retroviral vec-

tor and infused 4 days later. Patients received nonmyeloablative treatment with busulfan.

Results. Both patients experienced immune reconstitution (although the infant showed a swifter and more complete response). Genetically corrected granulocytes, monocytes, megakaryocytes, and erythroid cells were detected, T cell responses normalized, antibody production was corrected, and specific responses to vaccination were documented. Infections also abated. Red blood cell toxic metabolites declined and liver enzyme abnormalities resolved. The less complete response of the older patient was attributed to a lower dose of transfected cells, less myeloablation, and possibly an effect of his older age.

Conclusions. A combined approach of using autologous genetically corrected stem cells and nonmyeloablative conditioning allowed more complete restoration of immune and metabolic functioning in ADA-SCID patients than has been previously achieved.

Reviewer's Comments. ADA leads to the accumulation of toxic metabolites that cause immune cell death and results in SCID. Previous studies of therapy using genetically corrected peripheral blood lymphocytes (PBLs) and exogenous ADA in the form of PEG-ADA to support immune function lead to poor engraftment of the corrected cells possibly because there was not a sufficient survival advantage for these cells in the presence of exogenous ADA. When PEG-ADA was not given, full correction was still not achieved, indicating that such correction may require a more global therapy, not just infusion of genetically corrected PBLs. This study shows that rather amazing immune reconstitution was possible with the successful engraftment of multipotent, genetically corrected stem cells, and provides hope for more definitive therapy for this and other disorders.

SCOTT H. SICHERER, MD
New York, NY

PREVALENCE OF MONOCLONAL GAMMOPATHY IN PATIENTS PRESENTING WITH ACQUIRED ANGIOEDEMA TYPE 2

Fremaux-Bacchi V, Guinnepain MT, Cacoub P, et al. *Am J Med.* 2002;113:194-199

Purpose of the Study. Acquired angioedema type 1 is characterized by a C1 inhibitor deficiency in patients with lymphoproliferative disorders, whereas acquired angioedema type 2 is characterized by anti-C1 inhibitor antibodies, and has not been thought to be associated with lymphoproliferative disease. We studied the clinical features, complement profiles, and associated diseases in 19 new patients with diagnosed acquired angioedema type 2.

Study Population and Methods. Plasma concentrations and functional activity of complement components were measured by conventional techniques. Functional C1 inhibitor activity was assessed by a chromogenic assay. Autoantibodies to C1 inhibitor were detected using an enzyme-linked immunosorbent assay.

Results. The 11 men and 8 women (median age: 60 years) presented with recurrent attacks of angioedema. All patients had detectable anti-C1 inhibitor antibodies in serum. A monoclonal gammopathy was detected in 12 patients (63%) at the time of diagnosis, 11 of whom had an immunoglobulin peak of the same heavy- and light-chain isotypes as the acquired anti-C1 inhibitor antibody. Three of these 12 patients developed a malignant lymphoproliferative disease.

Conclusions. As with type 1 disease, a large proportion of patients with acquired angioedema type 2 have a lymphoproliferative disorder.

Reviewer's Comments. These disorders present only rarely, so I'm always having to go back and refresh my memory. However, unlike the acquired chronic urticarias, the acquired C1 inhibitor deficiency syndromes are commonly associated with lymphoproliferative disorders, so we need to pursue things pretty aggressively. Don't be afraid to consult your friendly oncologist.

ALLEN ADINOFF, MD
Aurora, CO

HUMAN IMMUNODEFICIENCY VIRUS

CONTRIBUTION OF HUMAN α -DEFENSIN 1, 2, AND 3 TO THE ANTI-HIV-1 ACTIVITY OF CD8 ANTIVIRAL FACTOR

Zhang L, Yu W, He T, et al. *Science.* 2002;298:995-1000

Purpose of the Study. Since 1986, it has been known that CD8+ T-cells from human immunodeficiency virus (HIV)-infected, immunologic stable long-term survivors secrete a soluble factor that has been termed CD8 antiviral factor (CAF). The molecular identity of CAF has remained elusive. Some of the antiviral activity in CAF appears to be mediated by β -chemokines, MIP-1 α , MIP-1 β and RANTES; however, these factors do not account for all of the anti-HIV activity in CAF. The purpose of this study was to describe the anti-HIV activity of human α -defensins.

Methods. Protein chip technology was used to identify a cluster of proteins that were secreted when CD8+ T-cells from long-term nonprogressors were stimulated in vitro. After identification of these proteins, HIV suppressive activity was measured and the source of these molecules was identified.

Results. The proteins were identified as α -defensins 1, 2, and 3 on the basis of specific antibody recognition and amino acid sequencing. A significant proportion of CAF activity was eliminated or neutralized by antibody specific for human α -defensins. Synthetic and purified preparation of α -defensins inhibited the replication of HIV isolates in vitro. Finally, a subset of CD8+ T-cells express and secrete α -defensins.

Conclusions. These results indicate that α -defensins 1, 2, and 3 collectively account for much of the anti HIV activity in CAF that is not attributable to β -chemokines. The potential usefulness of α -defensins as therapeutic agents in patients with HIV remains to be demonstrated.

Reviewer's Comments. Defensins are members of a family of antimicrobial peptides that are particularly abundant in neutrophils. The demonstration that defensins constitute a component of CAF has important implications. Perhaps these defensins are causally involved in the reduction of HIV progression. If so, the administration of extrinsic defensins or the stimulation of in vivo production of defensins would be appropriate therapeutic goals. Alternatively, the presence of a subset of T cells capable of generating α -defensins may simply reflect the preservation of selected immune functions in individuals in which other mechanisms are responsible for this preservation. Importantly the amount of α -defensins produced by CD8+ T cells is tiny relative to the amount routinely expressed in neutrophils, including those of progressing HIV-infected patients.

JOSEPH A. CHURCH, MD
Los Angeles, CA

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COMBINED WITH NONMYELOABLATIVE CONDITIONING**

Scott H. Sicherer
Pediatrics 2003;112;489

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Scott H. Sicherer

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