

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-

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