Primary and Secondary Immunodeficiency

Pyogenic Bacterial Infections in Humans With MyD88 Deficiency


PURPOSE OF THE STUDY. Myeloid differentiation protein 88 (MyD88) is a key downstream adapter for receptors of the innate immune system, including most Toll-like receptors (TLRs) and interleukin 1 receptors (IL-1Rs). MyD88 deficiency in mice leads to susceptibility to a broad range of pathogens, and the goal of this study was to determine whether there are children with recurrent infections who have a deficiency in MyD88.

STUDY POPULATION. Nine children with MyD88 deficiency were identified from those evaluated for recurrent infections in immunodeficiency clinics in several different tertiary care centers.

METHODS. Fibroblasts, peripheral blood mononuclear cells, and Epstein-Barr virus-transformed B cell lines were evaluated with a number of molecular techniques, to evaluate responsiveness to stimulation via MyD88-dependent pathways such as IL-1Rs and multiple TLRs. Genetic analyses were also performed for patients and family members.

RESULTS. Nine children with autosomal recessive MyD88 deficiency suffered from life-threatening, often recurrent, pyogenic bacterial infections, including Streptococcus pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa. However, these patients were otherwise healthy, with normal resistance to other microbes. Their clinical status improved with age, but not because of any cellular leakiness in MyD88 deficiency. Cells from affected subjects were not responsive to IL-1R or TLR stimulation, and this responsiveness was restored by transfecting MyD88-deficient fibroblasts from the patients with a normal copy of the gene (complementary DNA). Genetic analysis revealed several defects associated with loss of function.

CONCLUSIONS. The authors conclude that MyD88-dependent TLRs and IL-1R are essential for protective immunity to a small number of pyogenic bacteria but are redundant for host defenses to most natural infections.

REVIEWER COMMENTS. There has been an explosion in information describing the innate immune system. The primary purpose of the innate immune system is to recognize microbial components. One major mechanism involves the binding of pathogen-associated molecules (eg, endotoxin or bacterial DNA) to innate immune receptors such as the TLR group. These receptors, which were first discovered in fruit flies, initiate intracellular signaling pathways that direct the synthesis of a wide variety of cytokines and antimicrobial pathways. MyD88 is a particularly important because it is involved in several TLR signaling pathways. These findings identify a specific pattern of increased bacterial infections associated with MyD88 deficiency. One of the advantages of identifying this disorder is that the clinical course improves with time, perhaps because elements of the adaptive immune system can compensate for the defect in innate immunity. In addition, now that the genetic defect is known, family members of affected individuals can be screened. Treatment is currently limited to supportive care, but identification of the molecular defect raises the possibility that specific therapies for MyD88 deficiency will be developed in the future.

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Common Variable Immunodeficiency: 20-Yr Experience at a Single Centre


PURPOSE OF THE STUDY. To describe and to classify children with common variable immunodeficiency (CVID) according to presentation, familial incidence, infections, and memory B (MB) cell classification.

STUDY POPULATION. Participants were children <18 years of age with CVID (N = 22) at a National Health Service referral center for immunodeficiency in Barcelona, Spain.

METHODS. A retrospective chart review was used to obtain clinical and immunologic data for pediatric patients with CVID monitored between 1985 and 2005. Clinical data included documentation of infections, onset of allergic diseases, autoimmune diseases, bronchiectasis, or cancer, and familial cases of CVID and other primary immunodeficiencies. Immunologic data included immunoglobulin levels, lymphocyte subsets, and classification of MB cells in patients with >2% CD19+ cells, to determine whether they were naive or mature. Patients with normal MB cells were classified as MB2, those with low MB cells but normal nonswitched MB cells were classified as MB1, and those with no MB cells were classified MB0.

RESULTS. The median age at diagnosis was 7.8 years (range: 2.5–16 years), with the exception of 1 outlier who was diagnosed at 6 months of age on the basis of family history and infectious manifestations. There were 15 boys and 7 girls, and follow-up periods ranged from 1 to 18 years. Infections were the most common manifes-
tations before diagnosis, with respiratory and gastrointestinal symptoms being the most common. Infection rates improved with γ-globulin replacement therapy. Bronchiectasis secondary to respiratory infections was present in 7 of 22 patients and was the presenting finding for 5 of 7 patients. Allergy was diagnosed in 11 of 22 patients, but only 3 patients had positive specific allergen prick test results. CVID was diagnosed in 3 girls after they were found to have an autoimmune disease, which delayed the diagnosis for 1 patient who subsequently developed severe lung disease. Four patients had other family members with CVID or other primary immunodeficiency. Immunoglobulin G (IgG) levels (range: 80–552 mg/dL; median: 332 mg/dL) at the time of diagnosis did not correlate with the severity of clinical manifestations in children. Although results were not statistically significant, patients without MB cells (MB0 group) had more-severe complications, including bronchiectasis, persistent positive culture results, or autoimmune manifestations, compared with MB2 and MB1 groups.

CONCLUSIONS. Early diagnosis and treatment are important for patients with CVID. IgG levels at diagnosis did not correlate with the severity of clinical manifestations in pediatric patients with CVID; however, there was a trend suggesting that lack of MB cells might correlate with clinical severity and outcomes.

REVIEWERS COMMENTS. Contrary to findings among adult patients with CVID, IgG levels did not correlate with disease severity among children with CVID. Bronchiectasis was diagnosed in one third of pediatric patients with CVID and presented as early as 2.5 years of age. Providers should consider CVID in the differential diagnosis for young children with recurrent infections. The authors were able to demonstrate that MB cell classification correlates with the severity of clinical manifestations and may be an important marker to aid in the determination of prognoses for patients with CVID in the future.

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

PURPOSE OF THE STUDY. To investigate the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) attributable to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

STUDY POPULATION. The study evaluated 10 children with SCID attributable to ADA deficiency who lacked a HLA-identical sibling donor. These patients had early manifestations of the deficiency (median age: 2 months) and underwent gene therapy at a median age of 1.7 years (range: 0.6–5.6 years).

METHODS. After nonmyeloablative conditioning with busulfan, the subjects received infusions of autologous CD34+ bone marrow cells that had been transduced with a retroviral vector containing the ADA gene. Enzyme-replacement therapy polyethylene glycol-modified bovine ADA (PEG-ADA) was not given after infusion of the cells.

RESULTS. All patients were alive after a median follow-up period of 4.0 years. Transduced hematopoietic stem cells had stably engrafted and differentiated into myeloid cells containing ADA and lymphoid cells. Eight patients did not require enzyme-replacement therapy, their blood cells continued to express ADA, and they had no signs of defective detoxification of purine metabolites. Nine patients had immune reconstitution with increases in T-cell counts and normalization of T-cell function. In the 5 patients for whom intravenous immunoglobulin replacement was discontinued, antigen-specific antibody responses were elicited. Serious adverse events included prolonged neutropenia (2 patients), hypertension (1 patient), central venous catheter-related infections (2 patients), Epstein-Barr virus reactivation (1 patient), and autoimmune hepatitis (1 patient).

CONCLUSIONS. Gene therapy, combined with reduced-intensity conditioning, is a safe, effective treatment for SCID in patients with ADA deficiency.

REVIEWER COMMENTS. This group previously reported gene therapy for ADA deficiency in 2 patients, and this article includes the long-term outcomes of those patients as well as 8 others. Because the mortality rates for patients with ADA deficiency who receive transplants from unrelated or haploidentical donors are quite high, this report represents a significant advance. Because, with gene therapy for ADA deficiency, there is less selective pressure for the survival of stem cells that may have vector integrations that may lead to activation of oncogenes, it is less likely that these patients will experience the T-cell lymphoproliferative syndrome that affected some of the patients in the previously reported trials of gene therapy for X-linked SCID. It is hoped that the principles learned in these trials of gene therapy for children affected with SCID will be used in the further development of gene therapy for these and other genetic diseases.
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