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 (e.g., 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-
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