

Of the remaining patients, 26 children (16%) were found to have an immunologic abnormality, and a primary immunodeficiency was identified in 17 of these patients (10%). The majority of the patients with an identified immunodeficiency had a defect associated with antibody production, whereas there were also patients with complement defects ($n = 3$), MyD88 deficiency ($n = 1$), and congenital asplenia ($n = 1$). Importantly, patients presenting with invasive pneumococcal disease aged >2 years had a much higher risk of having a primary immunodeficiency (26% vs 2% in patients aged <2 years at presentation).

CONCLUSIONS. Patients presenting with invasive pneumococcal disease should undergo an immunologic evaluation, particularly those who present with disease who are aged >2 years.

REVIEWER COMMENTS. This study is the first prospective evaluation of immunized children presenting with invasive pneumococcal disease. The incidence during the first 4 years of the study (2005–2008) was 23 per 100 000 for children aged <2 years and 5 per 100 000 for children aged >2 years. Universal immunization with 7-valent pneumococcal conjugate vaccine was initiated in France in 2006, and this was switched to 13-valent pneumococcal conjugate vaccine in 2010, with vaccination coverage reaching $\sim 93\%$ by 2011. The majority of the serotypes found in the patients with invasive pneumococcal disease were not found in the 7-valent pneumococcal conjugate vaccine, suggesting that “herd” immunity is at play regarding the serotype exposure among susceptible children. This study may actually underestimate the frequency of invasive pneumococcal disease because it did not include children missed who may have died of this infection. The take-home message from the study is that any child who develops invasive pneumococcal disease should undergo an immunologic evaluation focused on leukocyte count and differential, immunoglobulin levels, and complement (classic and alternative pathway) activity. In addition, these patients should be assessed for congenital asplenia as well as anatomic abnormalities that could be associated with infectious susceptibility. If results of all these studies are unrevealing, referral to a clinical immunologist with expertise in primary immunodeficiency disorders should be considered for evaluation of toll-like receptor function.

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Deficiency of Innate and Acquired Immunity Caused by an IKBKB Mutation

Pannicke U, Baumann B, Fuchs S, et al. *N Engl J Med*. 2013;369(26):2504–2514

PURPOSE OF THE STUDY. The goal of this study was to characterize a form of severe combined immunodeficiency (SCID) that has previously been described.

STUDY POPULATION. The study included 4 patients of Northern Cree ancestry from Canada, who presented with normal numbers of T cells and B cells but very low levels of immunoglobulins, as well as a severe defect in activation of immune cells, which affected both the innate and adaptive immune-receptor pathways. These patients presented with oral candidiasis, *Escherichia coli* septicemia, parainfluenza virus type 1 pneumonia, *Listeria monocytogenes* septicemia, parainfluenza virus type 3 pneumonia, and *Serratia marcescens* bacteremia.

METHODS. Immunologic phenotyping, genetic and protein analyses, and functional investigations were performed.

RESULTS. The patients all had hypogammaglobulinemia or agammaglobulinemia, and peripheral blood B and T cells were almost exclusively of naive phenotype. Regulatory T cells and $\gamma\delta$ T cells were absent. All 4 patients carried a homozygous duplication that led to loss of expression of IKK2, which is a component of the IKK-nuclear factor κ B pathway. Immune cells from these patients had impaired responses to stimulation through T-cell receptors, B-cell receptors, toll-like receptors, inflammatory cytokine receptors, and mitogens.

CONCLUSIONS. This form of SCID is characterized by normal lymphocyte development despite a loss of IKK2 function. This deficiency results in an impaired response to activation stimuli in a variety of immune cells, which leads to severe impairment of adaptive and innate immunity.

REVIEWER COMMENTS. SCID is rare, but most pediatricians will encounter this diagnosis sooner or later. It is important to be vigilant with children who have unusual, frequent, and persistent infections. In this case, the presence of normal numbers of T cells and B cells did not rule out the diagnosis of SCID.

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Autosomal Recessive Phosphoglucomutase 3 (PGM3) Mutations Link Glycosylation Defects to Atopy, Immune Deficiency, Autoimmunity, and Neurocognitive Impairment

Zhang Y, Yu X, Ichikawa M, et al. *J Allergy Clin Immunol*. 2014;133(5):1400–1409. e1–5

PURPOSE OF THE STUDY. The goal of this study was to investigate the clinical, laboratory, and molecular characteristics of patients with similar findings, including immunodeficiency, significant atopy, immune dysregulation, and neurocognitive developmental defects.

STUDY POPULATION. Eight patients from 2 different families underwent clinical, laboratory, and genetic evaluation.

METHODS. Patients were assessed clinically followed by an immunologic evaluation and whole-exome sequencing,

directed Sanger sequencing, and specific ex vivo biochemical studies.

RESULTS. All patients had a history of significant atopic dermatitis as well as other allergic findings, including asthma, food allergy, and/or environmental allergy. Staphylococcal soft tissue infections, recurrent sinopulmonary infections, low-level Epstein-Barr virus viremia, and other viral infections were characteristic of these patients. In addition, autoimmunity was found in the majority of the patients, primarily cutaneous leukocytoclastic vasculitis or membranoproliferative glomerulonephritis. Finally, neurologic impairment that developed early in life was present in all patients. Laboratory evaluation revealed elevated IgE levels, whereas IgG, IgA, IgM, and specific antibody production to vaccines were found to be normal. The patients also demonstrated varied degrees of cytopenias. Whole-exome evaluation in the affected patients from the first family revealed a large number of single nucleotide variants that after extensive software filtering yielded 1 candidate, an autosomal recessive defect in the gene encoding phosphoglucomutase 3 (PGM3). Application of the same strategy in the second family also yielded an autosomal recessive defect in the affected patients involving the same gene, and in both families, Sanger sequencing confirmed these results. The genetic results were followed by biochemical studies that demonstrated variable defects in O- and N-linked glycosylation, thus establishing that these genetic changes yielded functional abnormalities in glycosylation.

CONCLUSIONS. Patients with autosomal recessive defects in PGM3 have an immunologic disorder that includes severe atopic disease, autoimmunity, and intellectual disability as well as increased susceptibility to infection.

REVIEWER COMMENTS. This report adds to a growing list of immune defects associated with immune dysregulation that present clinically with elevated IgE levels, atopic disease, and autoimmunity together with increased susceptibility to infection. The link between immune dysregulation and atopy is providing valuable new information regarding the underlying immunologic processes involved in the development of allergic disease. In addition, defects in glycosylation have typically been associated with neurologic disease but generally have not been linked with immune disorders. Conversely, ~50% of the proteins in humans are glycosylated, and there is an evolving appreciation that protein glycosylation plays a role in immunologic development and response. This newly defined disorder provides support for this role, and an additional report of immunologic changes in the setting of genetic defects of glycosylation (Sadat MA, Moir S, Chun TW, et al. Glycosylation, hypogammaglobulinemia, and resistance to viral infections. *N Engl J Med.* 2014;370 [17]:1615–1625) strengthens this link.

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Glycosylation, Hypogammaglobulinemia, and Resistance to Viral Infections

Sadat MA, Moir S, Chun TW, et al. *N Engl J Med.* 2014;370 (17):1615–1625

PURPOSE OF THE STUDY. The goal of this study was to elucidate viral resistance despite immunodeficiency in a rare congenital disorder of glycosylation type IIb.

STUDY POPULATION. The study subjects were 2 siblings presenting with multiple neurologic complications and a paradoxical immunologic phenotype characterized by severe hypogammaglobulinemia but limited clinical evidence of recurrent severe infections.

METHODS. An 11-year-old boy and 6-year-old girl, first and third children, born to a young, healthy, non-consanguineous couple were evaluated. They are characterized by dysmorphic features, hypotonia, seizures, global developmental delay, cerebral atrophy, optic nerve atrophy, hearing loss, and recurrent bone fractures.

RESULTS. The siblings had normal or increased numbers of B cells in peripheral blood but severe hypogammaglobulinemia (317 mg/dL and 142 mg/dL) with significantly shortened half-life for IgG (6 days). The patients had normal specific antibody response to polysaccharide proteins, conjugated proteins, and polysaccharide antigens but did not respond to live virus vaccines such as measles-mumps-rubella (vaccine) or varicella, which are viruses with glycosylated envelopes. These patients did not have altered susceptibility to adenovirus or parvovirus 1, which are nonenvelope viruses, or to vaccinia virus, which is an envelope virus. In contrast, the patients did have markedly reduced susceptibility to infection with HIV and influenza viruses, which are glycosylation-dependent envelope viruses.

CONCLUSIONS. These data seem to suggest that altered glycosylation may modify the susceptibility to infection with viruses that must undergo protein glycosylation to complete their infection cycle.

REVIEWER COMMENTS. This study helps us to continue to expand our understanding of genetically determined permutations of host defense that could aid in explaining these unusual and unanticipated clinical presentations.

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Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients With Wiskott-Aldrich Syndrome

Aiuti A, Biasco L, Scaramuzza S, et al. *Science.* 2013;341 (6148):1233151

PURPOSE OF THE STUDY. The goal of this study was to develop a clinical protocol for Wiskott-Aldrich syndrome (WAS)

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