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)

by using a lentiviral vector (LV) to introduce a functional WAS gene into hematopoietic stem and progenitor cells (HSPCs) for autologous transplantation.

STUDY POPULATION. Three patients who had WAS with a severe clinical condition or severe mutation/absent WAS protein expression without a suitable matched donor for allogeneic transplant or ineligible for HSPC transplantation were enrolled.

METHODS. Patients were pretreated with a reduced-intensity myeloablative regimen. Afterward, they received autologous HSPCs that were transduced with an optimized LV carrying the WAS gene. Patients were monitored for up to 2.5 years after gene therapy, and the genomic distribution of LV integration sites in bone marrow and peripheral blood lineages was investigated.

RESULTS. Researchers were able to administer autologous HSPCs transduced with LV with high efficiency (>90%). This technique resulted in robust (25%–50%) and long-term engraftment in bone marrow, as well as detection of WAS protein expression in peripheral blood. All 3 patients experienced improved platelet counts, protection from bleeding and severe infections, and resolution of eczema. Analysis of LV integration resulted in highly polyclonal multilineage hematopoietic reconstitution with no in vivo selection of clones carrying integrations near oncogenes, as had been seen with previous γ-retroviral gene therapy.

CONCLUSIONS. The authors concluded that gene therapy using lentiviral HSPCs results in hematopoietic reconstitution and restoration of WAS expression to near physiologic levels in patients with resultant clinical benefit. There was no increased risk of malignant transformation as seen with γ-retroviral gene therapy in the same disease setting.

REVIEWER COMMENTS. Infusion of autologous HSPCs that have been genetically corrected ex vivo is an alternative therapeutic strategy for patients with WAS for whom a fully matched allogeneic donor is unavailable. Previous gene therapy in WAS patients using the γ-retroviral vector showed initial clinical benefit but was later associated with development of leukemia or myelodysplasia. This study addresses a potentially safer alternative with the use of the LV carrying the WAS gene under the control of its endogenous promoter to ensure that the transgene is expressed in a physiologic manner. Because there is currently no curative treatment of WAS other than a fully matched allogeneic HSPC transplant, LV gene therapy could be an attractive treatment option for patients. It would be of particular interest because of its safety profile compared with previous therapies because WAS patients are already innately prone to developing malignancies. Future studies with the use of a larger patient population will likely provide information about indications for LV gene therapy as an alternative to traditional stem cell transplantation.

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Absence of Detectible HIV-1 Viremia After Treatment Cessation in an Infant

Persaud D, Gay H, Ziemniak C, et al. *N Engl J Med*. 2013;369(19):1828–1835

PURPOSE OF THE STUDY. Until very recently, the only patient "cured" of HIV was the "Berlin patient," an adult male treated for HIV-associated acute myeloid leukemia with stem cell transplantation from a donor who was intrinsically resistant to HIV. The donor carried homozygous mutations (delta32) in the chemokine receptor 5 gene, which is an essential co-receptor for HIV entry into most target cells. The present study reports on an infant who also may be cured with early, highly active antiretroviral therapy (ART) after documented perinatal infection.

STUDY POPULATION. A 35-week gestational age infant was born by normal vaginal delivery to an HIV-infected woman who received no prenatal care and who was not taking ART. ART was initiated in the infant at 30 hours of age with zidovudine, lamivudine, and nevirapine. At 1 week of age, this regimen was adjusted to zidovudine, lamivudine, and ritonavir-boosted lopinavir. The infant remained on ART for 18 months and was then lost to follow-up until 23 months of age. ART has been discontinued and, because of results from subsequent studies, has not been restarted.

METHODS. Standard HIV polymerase chain reaction (PCR) assays and HIV antibody testing were used to diagnose and monitor the HIV-exposed infant. Peripheral blood mononuclear cell cultures were analyzed with PCR for virus DNA and with co-culture techniques for replication-competent virus. Lymphocyte subset analysis was conducted with standard flow cytometry, and HIV-specific T-cell responses were evaluated with intracellular cytokine generation assays.

RESULTS. During the first month of life and while receiving ART, the infant had elevated quantitative HIV RNA PCR measurements that declined to undetectable levels and remained there. Subsequently, although proviral DNA was detected at the limits of the assay at 26 months of age, plasma viral RNA was undetectable, and replication-competent virus could not be cultured at age 24 months. HIV antibody assays were not detected in the infant at or after 24 months of age, when maternal antibody would not confound the assays, and HIV-specific T-cell responses

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