common in the groups receiving SLIT than in comparator groups. There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated subjects.

CONCLUSIONS. According to published trials, there is moderate strength of evidence supporting the effectiveness of SLIT for allergic rhinoconjunctivitis and asthma. There were significant limitations in the reporting of safety data, but no life-threatening adverse events were noted in the published trials.

REVIEWER COMMENTS. As per the accompanying editorial, several unanswered issues remain regarding the use of SLIT. Insufficient data were available to identify optimal dosing strategies. The optimal duration of therapy remains unclear, and the relative benefits of single versus multiple allergen therapy are unclear. These issues must be answered before the Food and Drug Administration is likely to approve SLIT in the United States.

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PRIMARY IMMUNODEFICIENCY

Selective IgA Deficiency: Clinical and Laboratory Features in 118 Children in Turkey

PURPOSE. To investigate the clinical and laboratory features of children with selective immunoglobulin (Ig)A deficiency followed in a tertiary children’s hospital.

STUDY POPULATION. The medical records of 118 children (63 boys, 55 girls), median age 7 years (range 4–18 years), seen over a 5-year period were retrospectively reviewed.

METHODS. Patients with IgA levels <7 g/L and normal or elevated IgG and IgM were included in this study. Medical records were reviewed and laboratory studies included quantitative immunoglobulins, IgG subclasses, IgE, and autoantibodies. Medical history was evaluated for evidence of infections, allergic disease, and autoimmunity.

RESULTS. Sixty-one percent of these patients had been followed for > 6 months, with 99 (84%) of the 118 patients with a history of recurrent infections, primarily upper respiratory infections. In addition, 51 (43%) of 118 had a history of allergic disorders, including predominantly rhinitis, asthma, and atopic dermatitis. Finally, 20 (17%) of 118 had a history of autoimmune disease with a wide range of disorders, including celiac disease and type 1 diabetes being the most prevalent.

CONCLUSIONS. Children with selective IgA deficiency may be more prone to upper respiratory infections, allergic disease, and autoimmunity.

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Immunoglobulin Deficiencies: The B-Lymphocyte Side of DiGeorge Syndrome

PURPOSE OF THE STUDY. To better characterize humoral immunity in patients with DiGeorge syndrome.

STUDY POPULATION. An international cohort of 1023 patients with DiGeorge syndrome was used in this investigation. This included data from 21 countries and 40 different contributors, including 662 records from the US Immunodeficiency Network, 381 from the European Society for Immunodeficiencies, 327 from the Children’s Hospital of Philadelphia, and fewer than 50 patients per institution from the remaining contributors.

METHODS. The investigators defined a low serum immunoglobulin G (IgG) value as <500 mg/dL and a low CD3+ count as <500 cells/mm3 to stratify patients for the
RESULTS. The cohort consisted of 1023 patients with DiGeorge syndrome. The mean age was 5.5 years and median age was 3.0 years; 855 patients had immunoglobulin data available. Overall, 19% (150 total) of patients had IgG levels <500 mg/dL; 6.2% (28 total) of patients older than 3 and 5.6% (19 total) older than 5 years had levels of IgG <500 mg/dL. A total of 7 patients had undetectable IgA levels (IgA = 0 mg/dL); ages ranged from 4 to 15 years with the mean age of 8.7 years. A total of 10 patients (1.3%) had measurable IgG levels <5 mg/dL; all were older than 3 years. Twenty-seven percent of patients (216 total) had IgM levels <40 mg/dL; 23% (104 total) of patients older than 3 years had IgM levels <40 mg/dL.

CONCLUSIONS. The investigators found that 3% of patients with DiGeorge syndrome were receiving immunoglobulin replacement therapy and 6% of patients older than 3 years had hypogammaglobulinemia. The investigators concluded that DiGeorge syndrome, which is typically thought of as a T-lymphocyte disorder, was associated with significant humoral immune deficiency.

REVIEWER COMMENTS. There has been a growing body of evidence that B-lymphocyte functional deficit and hypogammaglobulinemia are associated with more severe infections in DiGeorge syndrome. This investigation directly addresses this clinical issue and is the largest report to date of immunoglobulin levels in this patient population. The investigators clearly identified limitations of their registry approach to collect data. For example, the definition of DiGeorge syndrome was not uniform, the data sets were incomplete, and there may have been ascertainment bias in the overall analysis. Although imperfect, this registry approach was helpful in identifying an unexpectedly high frequency of humoral immune deficiency in patients with DiGeorge syndrome. A reasonable clinical strategy, as mentioned by the investigators, would be to measure IgG, IgA, and IgM levels and diphtheria and tetanus titers in immunized patients with DiGeorge syndrome with recurrent sinopulmonary infections. If humoral immunity is determined to be insufficient, additional beneficial therapies, such as immunoglobulin replacement therapy, should be considered.

Impaired Intrinsic Immunity to HSV-1 in Human iPSC-Derived TLR3-Deficient CNS Cells

PURPOSE OF THE STUDY. Toll-like receptors (TLR) are innate immune receptors that recognize pathogen-associated molecules and are critical for the development of proper antimicrobial responses. Children with defects in the TLR3-signaling pathway are specifically susceptible to developing herpes simplex virus (HSV) encephalitis but not disseminated infections with HSV or other viruses. Therefore, the authors investigated whether TLR3 activity in neuronal cells was necessary for controlling HSV infection in the central nervous system (CNS).

STUDY POPULATION. Studies were performed by using cells from patients with inherited defects in TLR3 or UNC93B, a protein necessary for TLR3-mediated signaling.

METHODS. The authors used an elegant strategy of generating inducible pluripotent stem cells (iPSC) from patients. This innovative technique involves obtaining skin fibroblasts and genetically modifying them to assume an undifferentiated and self-renewing phenotype similar to embryonic stem cells. The iPSC were cultured with certain molecules and are critical for the development of proper antimicrobial responses. Children with defects in the TLR3-signaling pathway are specifically susceptible to developing herpes simplex virus (HSV) encephalitis but not disseminated infections with HSV or other viruses. Therefore, the authors investigated whether TLR3 activity in neuronal cells was necessary for controlling HSV infection in the central nervous system (CNS).

The authors verified that neurons and glial cells derived from patient iPSC resembled primary CNS cells both molecularly and functionally. As expected, neurons and oligodendrocytes generated from patient iPSC were defective in TLR3 signaling, as these cells were unable to secrete antiviral interferon after treatment with a TLR3 agonist. When the CNS cells were infected with HSV, viral replication was significantly greater in cells generated from TLR3- or UNC93B-deficient iPSC than those from normal subjects. The enhanced viral replication in neuronal cells was associated with impaired secretion of TLR3-dependent interferon production.

CONCLUSIONS. TLR3 activity in neurons and glial cells is critical for controlling HSV infection in the CNS.

REVIEWER COMMENTS. This intriguing study addresses multiple issues relevant to human disease pathogenesis. First, it introduces the power of using iPSC for studying the biology of human cells that are difficult to obtain or culture ex vivo. This strategy could prove useful for studying organ systems that are generally prohibitive for analyzing at the cellular level, such as the CNS or cardiovascular system. Second, it illustrates the obvious but sometimes overlooked reality that humans and rodents are not identical. Unlike humans, mice deficient in TLR3 are susceptible to systemic infections with multiple viruses, thus highlighting the importance of verifying genetic phenotypes observed in animals with patient samples. Finally, this study provides an example that antimicrobial signaling pathways in neurons and glial cells were examined in vitro to determine their role in controlling HSV infection.
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