Immunoglobulin Deficiencies: The B-Lymphocyte Side of DiGeorge Syndrome

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DiGeorge syndrome is associated with a T-lymphocyte immunodeficiency. The prevalence of hypogammaglobulinemia has not been reported. We found that 3% of patients with DiGeorge syndrome were receiving immunoglobulin replacement therapy and 6% of patients over the age of 3 years had hypogammaglobulinemia. We conclude that DiGeorge syndrome is associated with significant humoral immune deficiency. *(J Pediatr 2012;161:950-3).*

DiGeorge syndrome is a common syndrome occurring in approximately 1:3000 births. It is a clinical constellation of findings united by a common embryologic origin associated with cardiac anomalies, parathyroid gland hypoplasia, and thymus hypoplasia or aplasia.[1,2] Many infants have been found to have low circulating T-lymphocyte counts, with some improvement over the first year of life.[3] Not all T-lymphocyte subsets are affected equally by thymic hypoplasia, in part due to homeostatic expansion.[4,5]

A series of studies have hinted that humoral immunity may not be robust in patients with DiGeorge syndrome.[6-8] There have been case reports of patients who appeared to have common variable immunodeficiency,[9-11] immunoglobulin A (IgA) deficiency, immunoglobulin M (IgM) deficiency, and impaired vaccine response.[8,12,13] One study showed delayed B-lymphocyte maturation manifested with lower naïve and unswitched memory B lymphocyte.[4] Another study showed decreased memory B lymphocytes.[12] To better characterize humoral immunity in DiGeorge syndrome, we examined immunoglobulin levels in an international cohort of 1023 patients with DiGeorge syndrome.

Methods

The United States Immunodeficiency Network (USIDNET) and the European Society for Immunodeficiencies (ESID) registries and members were queried for cases categorized as DiGeorge syndrome. Both registries enroll patients with velocardiofacial syndrome and chromosome 22q11.2 deletion syndrome under the same umbrella designation. Members of the Latin American Society for Immunodeficiencies were sent an e-mail requesting their support of the same study. Data from 21 countries and 40 different contributors were compiled; 662 records were obtained from USIDNET, 381 from ESID, 327 from the Children's Hospital of Philadelphia, and fewer than 50 patients per institution from the remaining contributors. USIDNET and ESID collected information from subjects who consented for the study. The remainder of the patients' data were collected in an anonymous fashion in accordance with the local regulatory guidelines at each institution. Duplicate patients were removed manually and the final evaluable subject count was 1023. For patients with data from multiple points in time, data from the oldest age were utilized. Correlation coefficients were calculated using the Pearson method and linear regression analyses were performed within Prism. We defined a low serum immunoglobulin G (IgG) value as <500 mg/dL and a low $CD3^+$ count as <500 cells/mm^3 to stratify patients for the Pearson analysis. All *P* values were computed as 2-tailed *P* values.

ESID	European Society for Immunodeficiencies
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IGIV	Immunoglobulin intravenous
IgM	Immunoglobulin M
USIDNET	United States Immunodeficiency Network

Results

This cohort consisted of 1023 patients with DiGeorge syndrome. The mean age was 5.5 years and the median age was 3.0 years; 855 patients had immunoglobulin data available. Responses to vaccines were not available for most subjects; 42% of the cohort were identified as having a chromosome 22 deletion. For the remainder, no genetic basis was recorded.

We examined immunoglobulin levels according to age. The normal ranges are shown in grey in **Figure 1**. For the association of IgG, A, and M with age, the direct correlation coefficient was mild to moderate for IgG ($r = 0.4516$, $P < .0001$) and IgA ($r = 0.2828$, $P < .0001$); however, IgM levels

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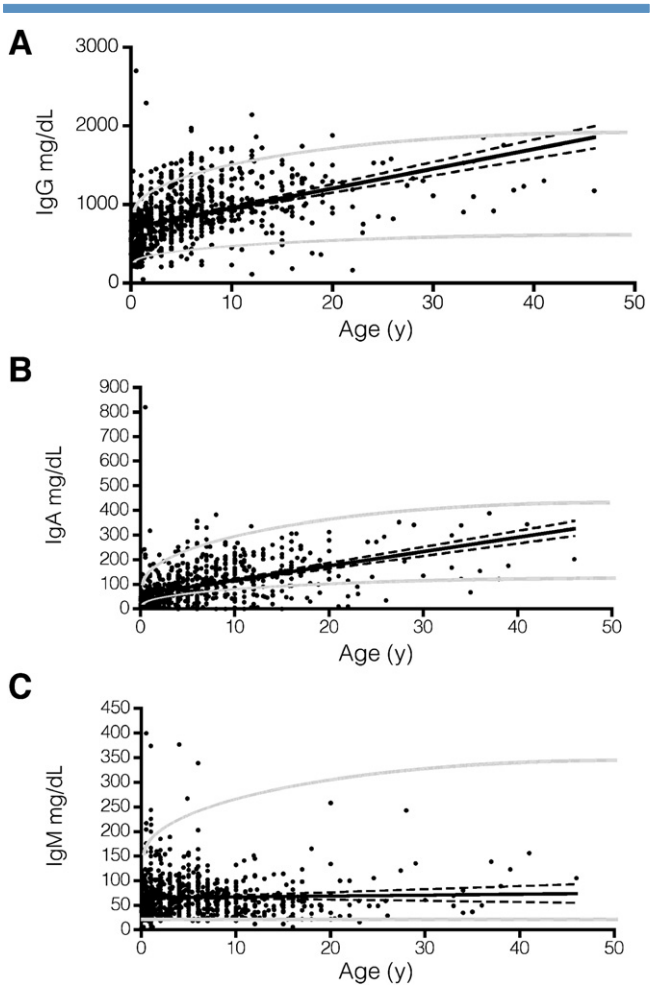

Figure 1. Immunoglobulin levels expressed as a function of age. **A,** IgG, **B,** IgA, and **C,** IgM levels are plotted according to the age in patients with DiGeorge syndrome. *Black line* indicates the trend and the *grey lines* represent the 95% CI for published normative data.[15] For each class of immunoglobulin, there are outliers both on the high and low end of the spectrum.

had no significant correlation with age (r = 0.3831, $P = .4283$) (Figure 1). We further evaluated immunoglobulin levels at older ages to exclude transient hypogammaglobulinemia of infancy. IgG and IgA levels had a moderate direct association with age for those over 3 years (r = 0.2694, 0.3615; $P < .0001$, <.0001 respectively). IgG levels also correlated with age for ages greater than 5 years (r = 0.1918, $P = .0004$). IgM levels did not correlate for ages greater then 3 years (r = 0.01, $P = .8317$).

We assessed associations between $CD3^+$ counts and immunoglobulin levels (Figure 2). The inverse correlation between age and $CD3^+$ count was moderate (r = −0.2543, $P < .001$). There was a weak association between $CD3^+$ count and IgG levels (r = −0.1071, $P < .0084$). We assessed IgG levels associated with low $CD3^+$ count ($CD3^+$ count <500 cells/mm^3) and found no clear association (r = 0.005331, $P = .9754$). Analysis of low IgG levels (IgG < 500 mg/dL) and $CD3^+$ count also showed no clear association (r = −0.07630, $P = .4414$). We similarly explored potential associations between $CD3^+$ count and IgA or IgM levels but found no association (data not shown).

A total of 2.7% (28 total) of the patient cohort was receiving immunoglobulin intravenous (IGIV) replacement therapy, with a broad age range of 2 months-17 years. A total of 3% of patients over the age of 3 years were receiving IGIV. The mean $CD3^+$ count was 1210 cells/mm^3 for patients receiving IGIV (range 130-4310 cells/mm^3). The mean IgG, A and M levels were 832 mg/dL, 77 mg/dL, and 103 mg/dL (ranges: 181-1740 mg/dL, 5-257 mg/dL, and 22-649 mg/dL, respectively). The registry data did not include information on whether the IgG levels were obtained on or off immunoglobulin replacement or treatment, however, we were able to analyze immunoglobulin levels and $CD3^+$ counts for the 28 subjects receiving immunoglobulin replacement and compare them with subjects not receiving immunoglobulin replacement therapy. Neither age, IgG, IgA, IgM, or $CD3^+$ count differed significantly between the 2 groups. Of the 28 subjects receiving immunoglobulin replacement, 9 were under 3 years of age. Of the 19 subjects over 3 years of age, 4 patients had an IgG <500 mg/dL.

Overall, 19% (150 total) of patients had IgG levels less then 500 mg/dL; 6.2% (28 total) of patients over the age of 3 and 5.6% (19 total) over the age of 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 4-15 years with the mean age of 8.7 years. A total of 10 patients (1.3%) had measurable levels below 5 mg/dL; all were greater than 3 years of age. 27% of patients (216 total) had IgM levels below 40 mg/dL; 23% (104 total) of patients greater than 3 years of age had IgM levels <40 mg/dL. Elevated IgG, IgA, and IgM levels were seen as well and we noted that these were observed primarily in the younger children.

Discussion

DiGeorge syndrome classically has been thought to be a T-lymphocyte disorder, however, recurrence and severity of infections have not always correlated with T-lymphocyte number.[8,14] There is now a growing body of evidence that B-lymphocyte functional deficit and hypogammaglobulinemia are associated with more severe infections in this syndrome,[8] thus, warranting more attention.

Our study is the largest report to date of immunoglobulin levels in this patient population. We showed that low levels of immunoglobulin are present in a significant minority of patients, and overall, between 2% and 3% of patients were receiving immunoglobulin replacement therapy. This study has several limitations imposed by the registry approach. The definition of DiGeorge syndrome was not uniform. Data sets were incomplete. There could be ascertainment bias due to the immunologic orientation of these registries and the data submitters. However, this study includes the largest collection of data on patients with DiGeorge

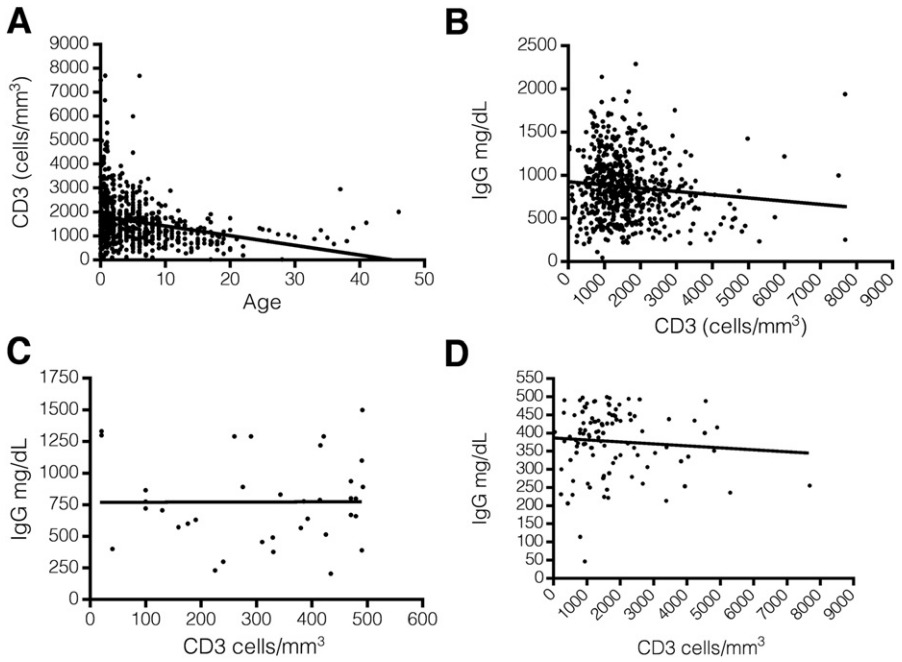

Figure 2. T-lymphocyte counts in patients with DiGeorge syndrome. These analyses express the $CD3^+$ T-lymphocyte count according to **A,** age and **B,** the IgG level according to the $CD3^+$ count. **A,** The expected age-dependent decrease in $CD3^+$ counts. There are no associations between $CD3^+$ counts and IgG levels in general or in those with lower levels of either (**C,** data for patients with low $CD3^+$ counts and **D,** those with low IgG).

syndrome and a registry approach is a valuable strategy to investigate features that are present in a small subset of patients.

There are multiple areas for further investigation including a better understanding of the indications for immunoglobulin therapy in these patients and how best to provide antimicrobial support for patients. Also, it would be useful to determine the impact of immunoglobulin replacement on the infection pattern. This study demonstrates the need for collaboration between groups to identify medically significant features present in a minority of patients. Although imperfect, a registry approach in this case revealed an unexpectedly high frequency of humoral immune deficiency. Greater attention to the humoral component of the immune deficiency could lead to additional beneficial therapies. Patients should be evaluated with this in mind.[8] Lacking comparative effectiveness data, a specific recommendation for evaluation can at best be considered tentative. One strategy would be to measure IgG, IgA, IgM levels; and diphtheria and tetanus titers in immunized patients, with recurrent sinopulmonary infections and to offer either prophylactic antibiotics or immunoglobulin replacement when humoral immunity is judged to be insufficient to provide protection. ■

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Appendix

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