

Letter to the Editor

Autoimmunity in a cohort of 130 pediatric patients with partial DiGeorge syndrome*To the Editor:*

Partial DiGeorge syndrome (pDGS) is a condition characterized by conotruncal cardiac anomalies, hypocalcemia, and a variable, although not severe, T-cell immunodeficiency. A microdeletion of chromosome 22q11 is associated with more than 90% of cases.¹ Reports of autoimmunity in patients with pDGS have been sporadic, with the exception of 2 studies that yielded very different prevalences of this complication (8.7%² and 33%³). We examined our cohort of 130 pediatric patients with pDGS for the prevalence of autoimmunity and associated laboratory findings, suggesting that higher numbers of naive CD4⁺ T cells (CD4⁺CD45RA⁺ cells) measured in early childhood might be associated with a lower risk of autoimmune disease.

T-cell lymphopenia is hypothesized to increase the risk of autoimmunity because of impaired balance between regulatory T cells and autoreactive T cells for specific self-antigens, whereby activated autoreactive T cells produce disease when regulatory T cells are limited by low numbers.⁴ This is a particular scenario for patients with pDGS, who have a varying degree of T-cell lymphopenia.

We performed a chart review of the patients with pDGS in the Allergy and Immunology Clinic at Texas Children's Hospital who were evaluated between 1987 and 2011. Informed consent was obtained from the patients' caregivers, and the study was approved by the Institutional Review Board of Baylor College of Medicine. All patients included have the chromosome 22q11 deletion and are without severe immunodeficiency (complete DiGeorge syndrome) or other chromosomal abnormalities. Four patients were excluded: 3 had complete DiGeorge syndrome, and 1 had additional chromosomal abnormalities. The mean age of this cohort was 8.2 years (median, 7.5 years; range, 5 months to 23 years), and it consisted of 67 male and 63 female patients. The mean follow-up was 5.3 years (range, 2 months to 21 years).

Autoimmune diseases were identified as follows: immune thrombocytopenic purpura (ITP) by the presence of anti-platelet antibodies and thrombocytopenia and by means of peripheral blood smear; autoimmune hemolytic anemia (AIHA) by means of history and peripheral smear and a positive Coombs test result; hypothyroidism by anti-thyroglobulin and peroxidase anti-thyroid antibodies with a low serum thyroxine (T4) level and an increased thyroid-stimulating hormone level; juvenile idiopathic arthritis by means of clinical diagnosis by a pediatric rheumatologist; autoimmune neutropenia by neutropenia with anti-neutrophil antibodies; and vitiligo by the results of a clinical examination. No other autoimmune conditions were identified. Immunophenotyping by means of flow cytometry was done at the Clinical Immunology Laboratory, Texas Children's Hospital.

Eleven (8.5%; 95% CI, 6.1% to 10.9%) patients had an autoimmune disease (Table I), with a mean age of presentation of 5 years (range, 8 months to 11 years), 8 (72%) of whom were female (72%). The mean follow-up was 6.8 years (range, 1.6-19 years). Three patients had autoimmune hypothyroidism, 1 patient had monoarticular arthritis with a positive antinuclear antibody result, 1 patient had juvenile idiopathic arthritis, 1 patient

TABLE I. Demographic characteristics of the 11 patients with pDGS and autoimmune diseases

Patient no.	Sex	Disease	Age at disease (y)
1	F	Hypothyroidism	8
2	M	Hypothyroidism	7
3	F	Hypothyroidism, vitiligo	11
4	M	ITP	4
5	F	ITP	6
6	F	ITP, autoimmune neutropenia, AIHA	7
7	F	ITP, AIHA	5
8	M	Autoimmune neutropenia	0.7
9	F	Monoarticular arthritis, ANA ⁺	4
10	F	Polyarticular JIA	3
11	F	Psoriasis	5

ANA, Antinuclear antibodies; F, female; ITP, immune thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; M, male.

had vitiligo, 1 patient had psoriasis, 1 patient had autoimmune neutropenia, and 4 patients had ITP and AIHA.

In comparison with the 2 previous discordant reports,^{2,3} the prevalence of autoimmunity in this cohort is similar to that in the study by Jawad et al.² The discrepancy with the report by Genery et al.³ might be explained by their definition of autoimmunity because it included patients with evidence of autoantibodies but without other laboratory changes or clinical disease. When these patients are excluded, the prevalence of autoimmunity in that series is 10%.

Overall autoimmune disease, and specifically ITP and autoimmune hypothyroidism, were identified at a higher prevalence than in the general population. Between the ages of 1 and 8 years, ITP occurs at a prevalence of 0.02% in the general population,⁵ whereas in this cohort the prevalence was 3.1%. Of the 49 patients tested for thyroid disease in our cohort, 3 (6.1%) had autoimmune hypothyroidism, which is 2½ times the prevalence in the general population.⁶ In contrast to previous published reports in patients with autoimmunity and pDGS,^{2,3} we did not identify any patients with inflammatory bowel disease and had a lower proportion of patients with arthritis.

We then compared lymphocyte subset measurements at different ages of the 11 patients with autoimmune disease and a subgroup of our cohort of patients with pDGS who were all older than 6 years and were without autoimmune disease. This subgroup consisted of 74 patients, 30 female and 44 male patients, with a mean age of 10.7 years and a mean follow-up of 6.9 years. Naive T-cell percentages measured in early childhood of these patients were lower in those with autoimmunity compared with those in the rest of the cohort; however, the difference in the average medians did not reach statistical significance, likely because of the small number of patients with pDGS with autoimmunity. When broken down by age range, patients with autoimmune disease had the lowest naive T-cell numbers at age 48 to 120 months (Fig 1). There were no statistical differences between the 2 groups in the absolute number of CD3⁺CD4⁺CD8⁺ T cells or CD19⁺ B cells. (see Figs E1 and E2 in this article's Online Repository at www.jacionline.org).

Our hypothesis was that patients with pDGS with the highest levels of naive T cells would not have autoimmune disease.

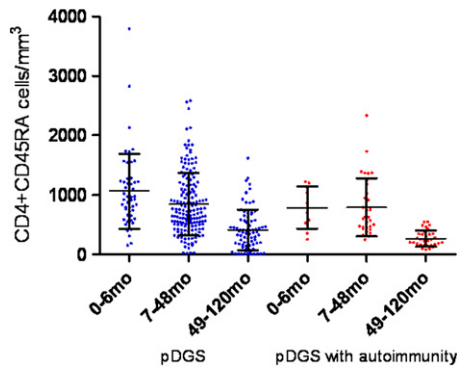


FIG 1. Comparison of CD4⁺CD45RA⁺ (naive T cells) cells/mm³ by age range in months between patients with pDGS older than 6 years without autoimmune disease (blue) and patients with pDGS with autoimmune disease (red).

We found that all of the patients who presented with autoimmunity had a naive CD4⁺ T-cell count of less than 1218 cells/mm³ at age less than 6 months and less than 550 cells/mm³ at age 48 to 120 months (see Fig E3 in this article's Online Repository at www.jacionline.org). Although two thirds of patients without autoimmune disease fell in the above category, there were no patients with autoimmune disease with naive CD4⁺ T-cell counts of greater than the values noted. Looking forward, 11 (20%) of the 54 patients less than 6 years of age in our cohort had counts greater than these cutoff levels and might be at a lower risk of autoimmune disease.

In conclusion, our data confirm that the prevalence of autoimmune disease in the pDGS cohort is 8.5% (95% CI, 6.1% to 10.9%). The most common autoimmune diseases identified were cytopenias (ITP, AIHA, and autoimmune neutropenia) and then hypothyroidism and autoimmune arthritis. High values of naive CD4⁺ T cells (>1218 cells/mm³ for those <6 months of age and >550 cells/mm³ at 48-120 months of age) might indicate a reduced risk of autoimmune disease. Our data also suggest that thyroid function testing and routine complete blood counts, in

addition to the history and physical examination, would be advised as screening for the most prevalent autoimmune diseases in this condition and especially for those children with pDGS who do not have high naive T-cell counts.

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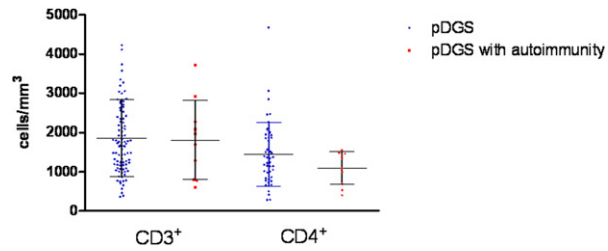


FIG E1. Absolute numbers in cells per cubic millimeter of CD3⁺ and CD4⁺ cells at age less than 6 months among patients with pDGS with autoimmune disease (*red*) compared with a subgroup of the cohort of patients with pDGS without autoimmune disease (*blue*) shown with means and SDs.

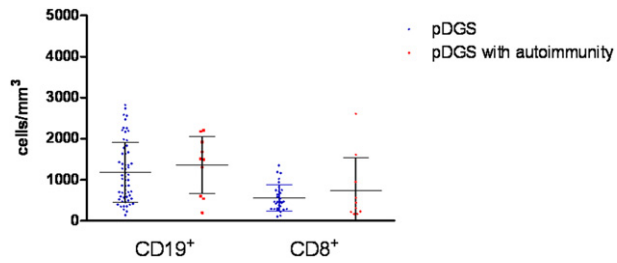


FIG E2. Absolute numbers in cells per cubic millimeter of CD19⁺ and CD8⁺ cells at age less than 6 months of patients with pDGS with autoimmune disease (*red*) compared with a subgroup of the cohort of patients with pDGS without autoimmune disease (*blue*) shown with means and SDs.

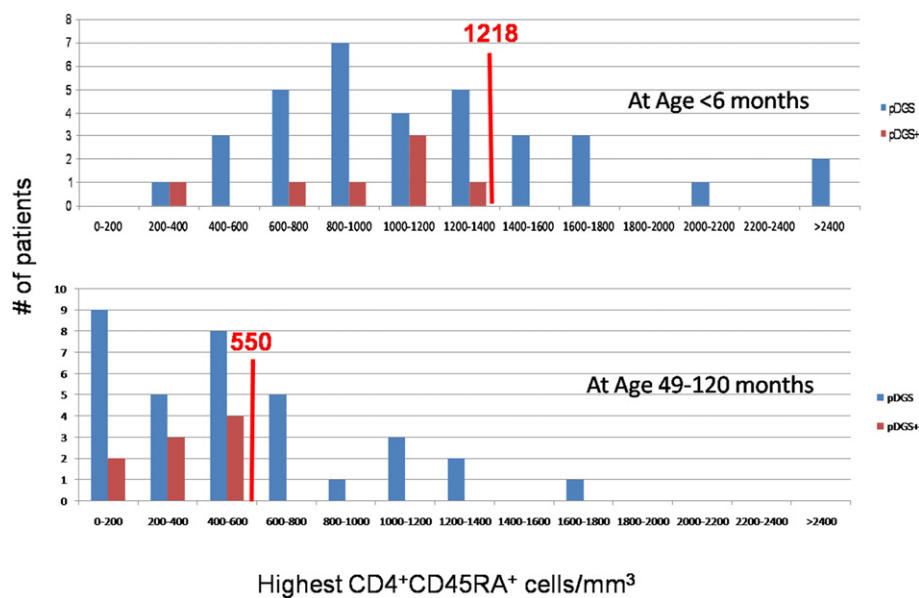


FIG E3. Number of patients whose highest CD4⁺CD45RA⁺ count fell within the designated ranges (in cells per cubic millimeter), as shown for patients less than 6 months and 49 to 120 months of age. Patients with pDGS with autoimmune disease are shown in *red*, and those in a subgroup who were without autoimmune disease are shown in *blue*. No patient had autoimmune disease who had greater than 1218 cells/mm³ at less than 6 months of age or greater than 550 cells/mm³ between 49 and 120 months of age.