

Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome)

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Objectives: To characterize immunologic function and clinical characteristics in patients with chromosome 22q11.2 deletion syndrome and determine whether there was significant change over time.

Methods: This study characterized the laboratory and clinical features of the immunodeficiency in a cohort of 195 patients with chromosome 22q11.2 deletion syndrome and used cross-sectional and analysis of variance to compare the findings in different age groups with control patients. Changes over time were also characterized by a model effect method in a subset of patients who were studied serially.

Results: Diminished T cell counts in the peripheral blood are common in patients with chromosome 22q11.2 deletion syndrome. The pattern of changes seen with aging in normal control patients was also seen in patients with chromosome 22q11.2 deletion syndrome, although the decline in T cells was blunted. Autoimmune disease was seen in most age groups, although the types of disorders varied according to age. Infections were also common in older patients, though they were seldom life threatening.

Conclusions: Slow declines in T cell populations are seen in chromosome 22q11.2 deletion syndrome. Clinical manifestations of immunodeficiency, such as recurrent infection and autoimmune disease, were common in this population but had little relationship to specific immunologic laboratory features. (*J Pediatr* 2001;139:715–23)

Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) is one of the most common chromosomal disorders

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Supported in part by the Wallace Chair of Pediatrics, the General Clinical Research Center (No. MO1-RR00240), Velocardiofacial (No. DC02027), Specialized Center of Research (No. HL62177), National Institute of Deafness and other Communication Disorders, Mental Retardation Research Center (No. HD26979).

Submitted for publication Nov 15, 2000; revisions received Feb 27, 2001, and June 19, 2001; accepted July 3, 2001.

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0022-3476/2001/\$35.00 + 0 9/21/118534

doi:10.1067/mpd.2001.118534

known, with an estimated prevalence of 1:4000 persons to 1:6000 persons being affected.¹⁻³ It is associated with conotruncal cardiac anomalies, hypocalcemia, dysmorphic facies, speech delay, and velopharyngeal incompetence.⁴⁻⁹ Studies have shown that the immunodeficiency is seen in many patients with the deletion without necessarily displaying the classic features of DiGeorge syndrome, originally described as a syndrome with a prominent component of immunodeficiency.^{10,11} In addition to these classical findings, there are many other phenotypic features that are seen less frequently in this population. None

AHA	Autoimmune hemolytic anemia
ANOVA	Analysis of variance
Con A	Concanavalin A
FISH	Fluorescent in situ hybridization
IBD	Inflammatory bowel disease
ITP	Idiopathic thrombocytopenia purpura
JRA	Juvenile rheumatoid arthritis
NK	Natural killer cells
PHA	Phytohemagglutinin
PWM	Pokeweed mitogen

of the phenotypic features is pathognomonic for the deletion, and the deletion does not predict end-organ effects or severity with any certainty. More than 90% of the patients carrying this hemizygous deletion have an identical 2.5 to 3 megabase deletion mediated by low copy number repeats.¹²⁻¹⁴ Therefore, the deletion size does not appear to be responsible for the phenotypic variation. Family studies in which parent-sibling pairs or sibling pairs had different phenotypic features confirm this.^{15,16} At

present, there is no satisfactory explanation for the differences.

Much of the variability in T cell production and function arises from the thymus itself. Some patients have no visible thymic tissue, whereas others have a small or hypoplastic thymus. Most of the former have microscopic rests of thymic epithelial cells that accounted for their ability to produce T cells.¹⁷ Studies of patients with DiGeorge syndrome showed decreased T cell numbers with variable functional deficits.¹⁸⁻²¹ The only large study of patients who all carried the chromosome 22q11.2 deletion analyzed both cellular and humoral immunity.²² The population in this study had relatively preserved T cell function and normal production of immunoglobulins.

The broad spectrum of immunodeficiency in chromosome 22q11.2 deletion syndrome makes it difficult to counsel patients and families regarding the morbidity or long-term consequences. This study was undertaken to characterize age-related changes in immunologic laboratory findings and possible clinical consequences.

PATIENTS AND METHODS

Patients

Patients (n = 195) in this study had chromosome 22q11.2 deletion syndrome, as defined by the presence of a hemizygous deletion found by using the ONCOR N25 probe (Intergen, Purchase, NY). They were excluded if they were acutely ill, had recently been transfused, or had significant weight loss. The diagnosis of juvenile rheumatoid arthritis was confirmed by physical examination performed by a pediatric rheumatologist. Idiopathic thrombocytopenia purpura was confirmed by a hematologist with the use of serial platelet counts (<80,000/mm³). Other diagnoses were clinically defined by appropriate subspecialists. The patients were divided into quartiles of (1)

0 to 6 months of age (n = 58), (2) 6 to 38 months of age (n = 44), (3) 38 to 109 months of age (n = 45), and (4) older than 109 months of age (9 years) (n = 45). The average age of those patients older than 109 months was 212 months, with a median age of 152 months. The initial evaluation was used for cross-sectional analysis when patients were evaluated multiple times. Sixty-two patients with serial evaluations (2-5 visits) were studied in the longitudinal analysis. In addition, 86 control patients were studied for comparison. They were also divided into the same age quartiles, 0 to six months (n = 16), 6 to 38 months (n = 23), 38 to 109 months (n = 23), and older than 109 months (n = 16). The average age of controls older than 109 months was 237 months, with a median age of 186 months. Institutional approval and informed consent was obtained. A small fraction of these patients and control patients, three of whom have JRA, had been involved in previous studies.⁹

Methods

Laboratory analyses were performed in the Clinical Immunology Laboratory at the Children's Hospital of Philadelphia, Pa. Two- or 3-color flow cytometry was performed on a Coulter EPICS XL (Beckman Coulter, Inc, Fullerton, Ca) to define the following lymphocyte populations: CD3+, CD3+/CD4+, CD3+/CD8+, CD3-/CD16/56+, CD19+, T cell receptor $\gamma\delta$ +, CD1+, CD38+. CD14 and CD45 were used to confirm the purity of the lymphocyte population. Absolute counts were obtained by multiplying the lymphocyte subset fraction by the absolute lymphocyte count obtained simultaneously. Proliferative responses phytohemagglutinin, pokeweed mitogen, and Concanavalin A were measured in triplicate cultures of 3 dilutions of stimulus harvested 72 hours after stimulation. Proliferative responses to *Candida*, tetanus, and diphtheria were measured in triplicate cultures of 3 dilutions of stimulus harvested at 5 days. Both raw counts per minute and stimu-

lation index were recorded for each patient. Tests with healthy control patients were run with each proliferative study and once per day for flow cytometry. Immunoglobulin levels and responses to recall antigens were performed in patients older than 8 months.

Statistical Analyses

Statistical analyses were performed by using SPSS version 10 for Windows (SPSS, Inc, Chicago, Ill). Group means were compared by using univariate analysis of variance followed by posthoc comparisons of pairs of means after a significant main effect for the group. Associations between continuous variables were examined by Pearson correlation (*r*). Skewed variables (proliferation results) were log-transformed to meet distribution assumptions. Multiple regression analyses with linear and quadratic terms for age were used to predict outcomes. To compare differences in laboratory findings in patients with and without clinical features, *t* tests or Mann-Whitney (a nonparametric test) analyses were used to identify differences between groups. A posthoc modified *t* test analysis was applied when the ANOVA indicated an overall statistically significant difference between any of the study subgroups. Results obtained from statistical analyses with a *P* value of <.05 were considered significant. We addressed the issue of multiple comparisons between control patients and patients with the deletion by performing a Bonferroni correction on the *P* values. Endpoint studies of independent variables incorporated into the initial study design were not corrected. Summaries of continuous variables are given as mean \pm SD.

RESULTS

Functional Analyses

To understand the association between changes that occur in patients' immune systems and with age, we analyzed our cohort data in age-stratified cross-sectional analyses. Lymphocyte proliferation in response to mitogens

and recall antigens was measured (data not shown). PHA, PWM, and Con A were used as polyclonal mitogens and *Candida*, tetanus, and diphtheria were used as recall antigens. The data were analyzed by using counts per minute of incorporated ^3H -thymidine because the early infancy group routinely exhibits a higher background proliferation. *P* values were reported on log-transformed data by using ANOVA. There were no statistically significant differences in mitogen responses between the different age groups for any stimulus. Similarly, there were no statistically significant differences in the specific antigen responses, although there appears to be a trend for decreasing responses with increased age. When patients with the deletion were compared with control patients, the only significant difference found was in the response to Con A with *P* = .009. The posthoc analysis demonstrated that the major difference occurs between the 2 groups of patients older than 109 months (*P* = .008).

Thymus-derived Lymphocyte Subpopulations

There are significant changes in lymphocyte populations over time in healthy children. Peripheral blood T cell counts decrease after 1 or 2 years, and this is presumed to be the result of thymic involution that progressively restricts thymic output. Therefore, we evaluated whether the age-related changes that occur in normal children are also seen in patients with chromosome 22q11.2 deletion syndrome. Fig 1 demonstrates the normal decline that is seen in control patients for CD3, CD4, and CD8 T cells. The patients with chromosome 22q11.2 deletion syndrome have fewer T cells in all age groups (corrected *P* < .020) with the exception of CD4 T cell counts in the group 38 to 109 months old. Despite having fewer T cells, the patients exhibited a progressive decrease in T cell counts, similar to that seen in the control patients, although the decline is blunted in the patients. The differences

in CD3 and CD4 T cell counts in the population with chromosome 22q11.2 deletion syndrome in the group 0 to 6 months old compared with the older than 109 month-old group are both significant with corrected *P* < .001. The difference in CD8 T cell counts in the 0 to 6 month-old group compared with the group older than 109 months is not significant after correction for multiple comparisons. To characterize the changes associated with age, linear regression was used to show that CD3 counts decline in control patients at 144 cells/mm³/year, whereas CD3 counts decline in the patients with the deletion at a rate of 25 cells/mm³/year. CD4 counts decline in the control patients at a rate of 118 cells/mm³/year, whereas they decline in the patients with the deletion at a rate of 23 cells/mm³/year. CD8 counts decline in the control patients at a rate of 24 cells/mm³/year, whereas they decline in the patients with the deletion at a rate of 3 cells/mm³/year. Although linear regression allows the generation of numbers that are easy to compare between groups, the age-related changes are not linear in nature. The declines seen early are more rapid than those seen later. To characterize the subset changes over time, a polynomial equation was determined to best represent the data. They are most accurate within our young population and may not represent the long-term T cell findings. These equations are given in the Appendix.

The rates of decline were also examined in a subset of 62 patients who had serial evaluations. These patients were generally less than 5 years old and are, therefore, not completely analogous to the group studied cross-sectionally. Rates of decline were derived by using a model effect method. Similar to the cross-sectional analysis, T cells, B cells, and natural killer cells increased in the first year of life. After 1 year of age, CD3 cells decreased at 44 cells/mm³/year, CD4 cells decreased at 41 cells/mm³/year, and CD8 cells decreased at 6 cells/mm³/year.

We also determined whether the limitation of thymic epithelium would lead to inappropriate appearance of phenotypically immature T cells in the peripheral blood. We defined CD1 and CD38 expression in the patients and control patients. These subpopulations were not increased in the patients with chromosome 22q11.2 deletion syndrome compared with control patients (data not shown).

Thymic-independent Lymphocyte Populations

We examined age-specific changes in 3 lymphocyte populations that were at least partially independent of the thymus for maturation (Fig 1). T cells bearing the $\gamma\delta$ T cell receptor may mature in the thymus or extrathymically.²⁴⁻²⁶ B cells require T cells for full function but are capable of maturation in the absence of T cells or thymic tissue. NK cells also are predominantly independent of T cell or thymic development. The $\gamma\delta$ T cell counts were lower in the population with chromosome 22q11.2 deletion compared with control patients at all ages, although this reached significance only in the 3 older groups. NK cell and B cell counts were higher in the population with chromosome 22q11.2 deletion compared with control patients; however, they exhibited a steeper age-related decline compared with control patients. The differences in NK cell and B cell counts in the group 0 to 6 months old compared with the group older than 109 months was significant, with *P* < .001 in both cases.

Humoral Immunity

Immunoglobulin levels were determined for each patient older than 1 year (Fig 2). Immunoglobulin levels rose throughout childhood and into adulthood. This is consistent with what is typically seen in childhood. Overall, IgG and IgA levels began somewhat lower than the published data from normal control patients and rose to levels above the published data from con-

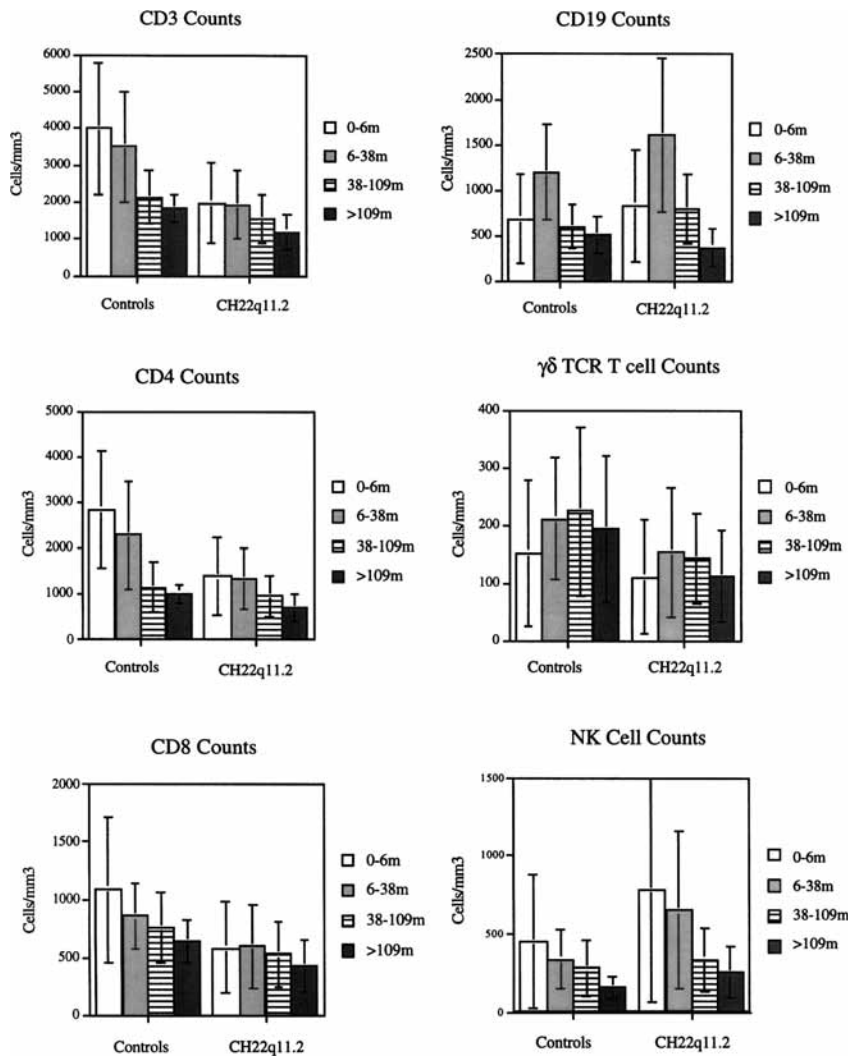


Fig 1. Peripheral blood lymphocyte counts analyzed according to age. The mean cell numbers \pm SD are shown. There is a fairly steep decline in CD3, CD4, and CD8 T cell counts in the control population. The patients with chromosome 22q11.2 deletion syndrome have fewer T cells than control patients in all age groups, except for CD4 counts in the group aged 38 to 109 months. Despite having fewer T cells, the patients exhibited a similar age-related decline in CD3 and CD4 T cells. Although less pronounced, even the CD8 T cell counts decreased over time. $\gamma\delta$ T cell counts were diminished in patients with deletion syndrome compared with control patients, which may reflect their partial requirement for thymic development. In the 3 older groups, chromosome 22q11.2 deletion syndrome patients had fewer $\gamma\delta$ T cells with $P < .05$. The changes over the age range were not significant. NK cells and B cells were higher in the patient population compared with control patients. NK cells were significantly higher in the group aged 6 to 38 months ($P < .01$). B cells were significantly higher in the 3 older age groups, with $P < .05$. Both B cells and NK cells decreased with age, and the differences between the group 0 to 6 months-old and the group older than 109 months were significant, with $P < .001$.

control patients. Five patients were IgA deficient.

Clinical Features Related to the Immunodeficiency

Four patients had JRA (50% female: 3 polyarticular, 1 pauciarticular), 8 patients had ITP (50% female), 2 of whom had chronic ITP. One patient with ITP

also had AHA at a separate time, one had vitiligo, one had psoriasis, and one had rheumatic fever with chorea. In addition, 2 young boys had intermittent ataxia that might have been autoimmune cerebellitis, but the diagnoses were never firmly established. The approximate prevalence values for each of the disorders in the study population is

given in Table I, as well as reference prevalence values for the general population. For disorders that occur predominantly in adults (psoriasis, vitiligo, rheumatoid arthritis), the prevalence in our adult population is also given. The median age of our study population was 17 months, which suggests that the prevalence values are minimal estimates.

Our previous evaluations of the 3 patients with JRA suggests that JRA is more common in those patients with the most disordered T cell function. Table II compares common immunologic studies from 3 populations with autoimmune disease with age-matched patients with the deletion but without autoimmune disease. The patients with JRA were all evaluated at a time when they had active JRA but were not taking disease-modifying drugs. The other patients had immunologic evaluations performed either after the acute illness (the acute ITP cases, chorea) or during the chronic illness (vitiligo, psoriasis, rheumatoid arthritis, chronic ITP). The 2 boys with intermittent ataxia were excluded from the analysis. The patients with autoimmune disease did not have decreased T cell counts or function compared with patients with chromosome 22q11.2 deletion syndrome who did not have autoimmune disease. None of the patients with autoimmune disease had markedly diminished T cell function as measured by proliferative responses to phytohemagglutinin, which can sometimes be seen in ITP and JRA (data not shown).^{27,28} The population with ITP had fewer T cells than the age-matched patients with chromosome 22q11.2 deletion syndrome without autoimmune disease, although the differences were not statistically significant. The most notable findings were all in the humoral compartment. The ITP patients had significantly lower IgG and IgA levels compared with age-matched control patients with the deletion. Two of the 4 patients with JRA had the known association of IgA deficiency,²⁹⁻³⁴ although typical prevalence val-

ues ranged from 1.7% to 4.3%. We also asked whether there were significant differences between the 3 groups by using one-way ANOVA and adjusting for age. In this analysis, only IgG levels were significantly different between the 3 groups with autoimmune disease, with the ITP patients having significantly lower levels of IgG ($P = .016$) than the other 2 groups. Therefore, there was no completely consistent finding among the patients with autoimmune disease. None of the patients with autoimmune disease had markedly increased numbers of CD5/19 B cells, nor CD3+/CD4-/CD8- T cells that can both sometimes be expanded in JRA and ITP (data not shown).^{27,35-38}

The frequency of infections in patients older than 9 years was determined. This age restriction was used to minimize the confounders of daycare, reflux, cardiac surgery, and upper airway issues related to velopharyngeal incompetence and bottle feeding. More than 3 episodes per year (treated with antibiotics) were required to define recurrent otitis, recurrent sinusitis, recurrent bronchitis, and recurrent pneumonia. Clinical information was recorded by interview for 55 of 58 patients older than 9 years. Recurrent infections during the past 2 years were recorded. Interviews were contemporaneous with laboratory studies. Of the 55 patients studied, 40% were considered as healthy as their peers. Twenty-seven percent had recurrent sinusitis, 25% had recurrent otitis media, 7% had recurrent bronchitis, and 4% had recurrent pneumonia. In addition, 7 patients had autoimmune disease (see previous), two had recurrent parotitis, two had extensive warts, one had mastoiditis, and one had osteomyelitis. CD3 counts, CD4 counts, CD8 counts, PHA stimulation, IgG, IgA, and IgM levels were examined for associations with the specific recurrent infections described previously. A *t* test that used unpooled variance was used in the analysis to account for the abnormal distribution of certain values. In no case was there any significant difference in the laboratory

values between patients with recurrent infections and those patients who were well.

DISCUSSION

Chromosome 22q11.2 deletion syndrome is associated with immunodeficiency, which is best described as a mild-to-moderate deficit in peripheral

blood T cells, although the spectrum includes patients with normal laboratory evaluations and patients with evidence of severe T cell dysfunction. Normal children produce progressively fewer T cells, which is the result primarily of decreasing thymic output as the thymus involutes.^{39,40} The pattern of changes seen over time in the patients with chromosome 22q11.2 deletion syndrome were similar to the pattern seen in con-

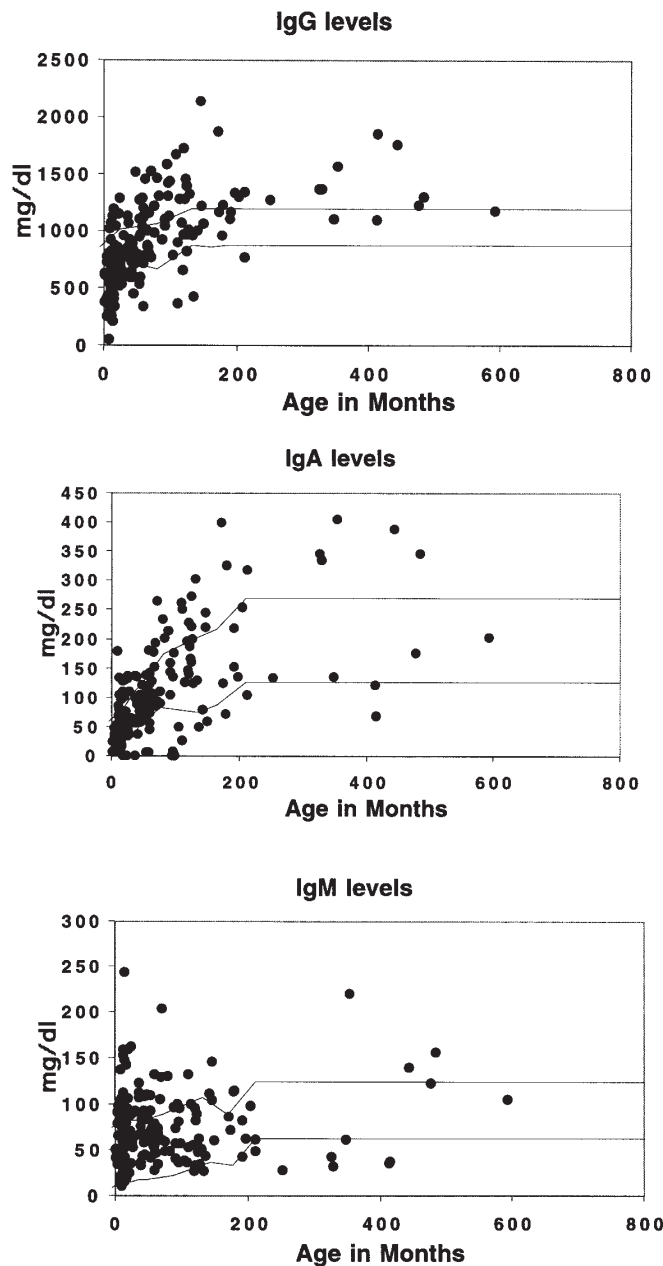


Fig 2. Immunoglobulin levels from each patient are plotted according to age. Normative data from a published source are given as solid lines. The IgG and IgA levels continue to rise in this population at a time when they are stable in the general population.

Table I. Autoimmune disorders in patients with chromosome 22q11.2 deletion syndrome

Autoimmune disorder	Prevalence in our population	Prevalence in general population	
JRA (onset 1.5-6 y)	4/195 (3 polyarticular)	0.021	0.001
ITP (onset 1-8 y)	8/195 (2 chronic)	0.041	0.0002
AHA (onset 8 y)	1/195	0.005	
Psoriasis	1/195	0.005	
Vitiligo	1/12 (adults)	0.083	0.04 (adults)
	1/195	0.005	
IBD	1/12 (adults)	0.083	0.01 (adults)
	1/195	0.005	0.004
Adult rheumatoid arthritis	1/195	0.005	
Rheumatic fever with chorea	1/12 (adults)	0.083	0.01 (adults)
	1/195	0.005	
Ataxia	2/195	0.010	

Sources of information for prevalence figures in the general population.⁵⁶⁻⁶²

trial patients, although the rate of decline of all T cell populations examined in the patients with chromosome 22q11.2 deletion syndrome was slower than that seen in the control patients.

There are potential explanations for the blunted decline in T cell counts in the patients with chromosome 22q11.2 deletion syndrome. Murine and human studies have demonstrated a powerful homeostatic mechanism to maintain peripheral blood T cell counts.⁴¹⁻⁴³ It is possible that this mechanism can override or modify thymic involution. Another explanation would be a mechanism controlling peripheral blood T cell counts that is independent of the state of the thymus, such as peripheral expansion. Studies of T cell repertoires in patients with chromosome 22q11.2 deletion syndrome suggest that the patients with the lowest T cell counts have the most restricted T cell repertoires, and this implies that peripheral expansion cannot regenerate a normal peripheral blood T cell count.⁴⁴⁻⁴⁶ This finding could be the result of ascertainment bias. Although only 2 patients in our cohort are deceased, it is possible that there were deaths in undiagnosed patients before referral that biased our re-

sults. Deaths in this syndrome are infrequent and unlikely to introduce substantial bias. Finally, it is possible that recurrent infections or other health issues, such as nutrition, have modified the normal T cell production changes. This is unlikely because patients were excluded from the study if they were ill or had significant weight loss in the month before the evaluation.

The IgG, IgA, and IgM analyses confirmed previous work²² demonstrating a largely intact humoral system. Although IgA deficiency and specific antibody defects have been identified,^{47,48} this analysis demonstrates that they occur in a minority of patients. Low IgG levels were seen in patients primarily in the youngest ages. In the older age group, immunoglobulin levels were above those levels seen in controls.

The clinical findings are not surprising; autoimmune disease and recurrent infections were expected. T cell disorders are often associated with autoimmune disease. In particular, autoimmune hemolytic anemia, ITP, autoimmune enteropathies, and arthritis are often seen in T cell dysfunction disorders of childhood.⁴⁹⁻⁵¹ Autoimmune diseases in immunodeficient adult pa-

tients are, more typically, ITP and rheumatoid arthritis.⁵² Autoimmunity is thought to result from disordered T cell regulation of tolerance.⁵³ A small number of patients with chromosome 22q11.2 deletion syndrome have been described as having autoimmune disorders.⁴⁻⁹ One survey of 20 patients indicated that as many as 10% of children with chromosome 22q11.2 deletion syndrome could have autoimmune disease. In this study, autoimmune cytopenias were specifically identified.⁵⁴ It is surprising that there is not a more obvious correlation with laboratory findings. Immunologists are accustomed to stratifying patients according to T cell numbers and level of function as a strategy to predict risk of infection. Although all of the patients with chromosome 22q11.2 deletion had lower T cell counts on average than the control patients, the patients with autoimmune disease did not have lower T cell numbers or proliferative responses compared with patients with the deletion but without autoimmune disease. Many of the patients were examined at a relatively late age. It is possible that immunologic perturbations earlier in life in some fashion predisposed to the development of autoimmune disease and these had resolved by the time of the evaluations in this study. It is also possible that immunodeficiency predisposes to autoimmune disease in a very general manner, and the ultimate development depends on a combination of other genetic susceptibility factors, infectious exposures, and stochastic processes. Consistent with this is our previous finding that 3 patients with JRA had human leukocyte antigen markers commonly seen in JRA.⁹ Our study suggests that impaired T cell production can predispose to autoimmune disease. Our study also argues against the deletion conferring a specific JRA phenotype.^{8,55}

The lack of an association of laboratory features with infections is difficult to explain. It is worth noting that none of our patients had absent T cells or died of infection. This study is representative

Table II. Immunologic evaluations in patients with autoimmune disease*

Patients (mean age)	CD3 cells/mm ³ (P value)	CD4 cells/mm ³ (P value)	CD8 cells/mm ³ (P value)	CD19 cells/mm ³ (P value)	NK cells/mm ³ (P value)	IgG mg/dL (P value)	IgA mg/dL (P value)	IgM mg/dL (P value)
JRA (80 m)	1188 (.4596)	728 (.5299)	418 (.7100)	314 (.5428)	291 (.4469)	1020 (.1745)	62 (2 IgAD) (.3576)	72 (.1334)
ITP (167 m)	980 (.7181)	618 (.7248)	290 (.2619)	300 (.8224)	147 (.1369)	662 (.0247)	74 (.0020)	86 (.4503)
Miscellaneous [†] (261 m)	1597 (.2869)	886 (.3009)	587 (.3518)	607 (.3160)	267 (.7420)	1146 (.8722)	203 (.3780)	103 (.3353)
CH22 q 38-109 m	1535	907	502	746	330	994	108	71
CH22 q older than 109 m	1187	677	417	358	250	1189	195	75
Healthy control patients	1800	800	800	400	300	1124	131	79

*P values reflect comparisons between JRA and age-matched (38-109 m) patients with chromosome 22q11.2 deletion syndrome, ITP patients and age-matched (older than 109 m) patients with the deletion, and miscellaneous patients and age-matched (older than 109 m) patients with the deletion. The published normative data from healthy controls are given for reference only.

[†]Miscellaneous includes autoimmune hemolytic anemia, vitiligo, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and rheumatic fever with chorea.

of patients with chromosome 22q11.2 deletion syndrome but cannot be extrapolated to the rare cases who have the most severe T cell defects. Within this context, the results are perhaps less surprising. The immunodeficiency is a risk factor for recurrent infections, but their basis is probably multifactorial with contributions from anatomy, colonization flora, and exposures. Immunologic laboratory studies are simply one tool in understanding the factors that predispose to infection and autoimmunity. A larger study including additional adults will be required to define the natural history of the immunodeficiency in adults and the relationship of the falling T cell counts to infection in this aging population.

We thank Leslie Davis, the patients, and their families for their enthusiastic support.

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APPENDIX

CD3 cells from patients with the deletion can be described as changing with age by $y = 2054 - 7.71(m) + 0.014(m)^2$, whereas control patients are described by $y = 3872 - 30.0(m) + 0.091(m)^2$. CD4 cells from patients with the deletion can be described as changing with age $y = 1376 - 6.65(m) + 0.012(m)^2$, whereas control patients are described by $y = 2705 - 26.8(m) + 0.086(m)^2$. CD8 cells from patients with the deletion can be described as changing with age by $y = 593 - 1.54(m) + 0.003(m)^2$, whereas control patients are described by $y = 1015 - 5.12(m) + 0.016(m)^2$. CD19 cells from patients with the deletion can be described as changing with age $y = 1170 - 5.95(m) + 0.008(m)^2$, whereas control patients are described by $y = 980 - 4.33(m) + 0.006(m)^2$.

m, Age in months.

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