Clinical Immunology
Vol. 92, No. 1, July, pp. 34–48, 1999
Article ID clim.1999.4725, available online at http://www.idealibrary.com on IDEAL®

Common Variable Immunodeficiency: Clinical and Immunological Features of 248 Patients

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Common variable immunodeficiency (CVI) is a primary immunodeficiency disease characterized by reduced serum immunoglobulins and heterogeneous clinical features. In these studies we describe the clinical and immunological status of 248 consecutively referred CVI patients of age range 3–79 years who have been followed for a period of 1–25 years. The median age at the time of onset of symptoms was 23 years for males and 28 years for females; the mean age at which the diagnosis of CVI was made was 29 years for males and 33 years for females. Forty percent of patients had impaired T cell proliferation to one or more mitogens; lymphocyte transformation to mitogens was directly related to the level of the serum IgG. Females at all ages had higher levels of serum IgM than males. Survival 20 years after diagnosis of CVI was 64% for males and 67% for females, compared to the expected 92% population survival for males and 94% for females. Parameters associated with mortality in this period were lower levels of serum IgG, poorer T cell responses to phytohemagglutinin, and, particularly, a lower percentage of peripheral B cells ($P < 0.006$). © 1999 Academic Press

Key Words: **common variable immunodeficiency; CVI; CVID; intravenous immunoglobulin; survival.**

INTRODUCTION

Common variable immunodeficiency (CVI) is a primary immunodeficiency disease characterized by hypogammaglobulinemia and recurrent bacterial infections (1–5). Although there have been a number of investigations into the nature of this defect since it was first recognized in 1953 (6), the fundamental cause of this disorder remains unknown. The phenotypic defect in CVI is a failure in B cell differentiation, with impaired secretion of immunoglobulins (7, 8), but T cell abnormalities, including decreased lymphocyte proliferation to mitogen and antigens, deficiency of antigen-primed T cells (9–12), and reduced production and/or expression of IL-2 and other cytokines, are common (13–16). An impairment in early signaling events following triggering of the T cell receptor has been suggested (17). Other studies have highlighted macrophage activation in this disease, demonstrating increased production of tumor necrosis factor, with biochemical evidence of oxidative stress, which could lead to some of the inflammatory manifestations of this disease (18, 19).

The clinical spectrum of CVI is quite broad, and symptoms of antibody deficiency may not become obvious until young, middle, or even late adult life. Chronic lung disease, particularly the development of bronchiectasis, is a common medical problem, leading to frequent hospitalizations and in some, severe respiratory impairment. Some patients with CVI present with classic or, more often, atypical inflammatory gastrointestinal disease resulting in diarrhea, malabsorption, and weight loss (20). For unknown reasons, autoimmune diseases, particularly autoimmune hemolytic anemia, autoimmune thrombocytopenia, rheumatoid arthritis, and pernicious anemia, are relatively common in this patient group. In other subjects, granulomatous infiltrations develop, mimicking sarcoidosis (21, 22). Patients with CVI also have an increased incidence of cancer, particularly lymphoma (23).

Because of the varied illnesses that may appear, patients with CVI tend to receive medical care from physicians in many clinical specialities; this can lead to delayed recognition of the antibody defect, and in some cases, suboptimum treatment. Standard treatment for CVI is periodic intravenous immunoglobulin (IVIg), a therapy available for 15–18 years. While a number of reports have demonstrated the efficacy of this treatment (24–27), the effect of long-term IVIg on the diverse clinical manifestations of CVI remains unknown. In these studies we have collected data on a large group of subjects with CVI in order to provide an updated view of the spectrum of illnesses which occur in this patient group over a long period of follow-up and the conditions and immunologic parameters which are associated with increased mortality.

METHODS

The Immunodeficiency Clinic at Mount Sinai Medical Center serves as a referral center for both adult and

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pediatric patients with known or suspected immune deficiency disease. Subjects with CVI have been referred to this clinic, located at Memorial Hospital in New York City, from 1973 to 1986 and at Mount Sinai Medical Center from 1986 until the present, over a 25-year period. The diagnosis of CVI was made by standard criteria, including reductions of serum IgG, IgA, and/or IgM by two or more standard deviations from the normal mean (1). Specifically, all subjects had reduced levels of at least two Ig isotypes. Subjects with reduced serum IgG alone, or just antibody deficiency, were excluded; no subject had an IgG of more than 600 mg/dl. For all subjects with IgG levels over 400 mg/dl, examination of antibody levels to tetanus, diphtheria, *Haemophilus influenzae,* and pneumococcal antigen after vaccination were determined and antibody deficiency was documented. In order to define a numerically defined population for study, this report is restricted to patients with CVI seen from 1973 until 1998. We excluded patients less than 2 years of age who had no further follow-up history to confirm continued hypogammaglobulinemia. Patients with known X-linked (XLA, Bruton-type) agammaglobulinemia, hypogammaglobulinemia with thymoma, and immunoglobulin deficiency due to secondary loss (intestinal loss, etc.) were excluded. For male patients with B cell numbers of 2% or less, molecular studies of the Bruton tyrosine kinase, Btk, were performed by Dr. M. E. Conley to further exclude XLA. Follow-up information for patients not currently receiving care at Mount Sinai Medical Center was obtained by contacting the patient, if possible, and/or the patient's physician to ascertain current health. For those who had died, the cause of death was determined by review of death certificate, autopsy report, and/or by contacting the attending physician.

Laboratory Testing

Blood samples were tested for immunoglobulin levels and other immunologic tests on the first clinic visit. For about half of the subjects, this was before treatment with IVIg was started; for all others, serum immunoglobulin levels obtained prior to IVIg treatment were obtained from referring doctors. Antibody deficiency was additionally verified in most cases for patients not yet on immunoglobulin treatment by quantitation of antibody responses to diphtheria and tetanus and/or immunization with a pneumococcal vaccine. Anti-IgA antibodies were sought in the sera of 30 patients, which included all patients who had a history of having a reaction to blood or blood products. Enumeration of T and B cells and the lymphocyte proliferative responses to mitogens phytohemagglutinin, concanavalin A, and pokeweed, and tetanus and candida were performed by standard methods (1, 3, 9). In cases where the history suggested that another family member might also have an immunodeficiency, this individual was also tested by us or by a family physician to determine whether the quantitative immunoglobulin levels were in the normal range. In some cases serum of parents, siblings, and/or children of the patient were also tested, despite the absence of a suggestive clinical history.

Further assessment was done by obtaining complete blood counts, chemistries, electrolytes, and other tests to define specific diseases (Coomb's test, hepatitis C RNA by polymerase chain reaction, thyroid hormones, thyroid autoantibodies, thyroid stimulating factor, antinuclear antibody, rheumatoid factor, sedimentation rate, folic acid, stool fat content, and xylose tolerance test). Chest and sinus X rays, cultures, gastrointestinal X rays, electrocardiogram, and complete pulmonary functions were obtained as medically required. Other procedures, such as endoscopies and biopsies, were performed where medically necessary.

Statistical Methods

Initial testing results were used for the evaluation of immunologic values. Differences between males and females in values of immunologic parameters and of ages were tested with Wilcoxon rank-sum tests. Since there was a wide range of immunologic values, ages and immunologic levels were grouped, and an association between age at diagnosis and immunologic values was tested by χ^2 tests of trend, stratifying on sex. Follow-up time was counted as the time between diagnosis and either the date of death or the date of last contact. Probabilities of survival after diagnosis of CVI were estimated from Kaplan–Meier life tables and compared with the expected survival in the general population based on U.S. mortality rates for 1990 for persons of the same age and sex (28, 29). The Cox proportional hazards model was used for the analysis of factors that might be associated with increased risk of death. For this analysis, the time between the age at diagnosis and the age at either death or last contact was used as the "time" variable; immune parameters of those who had died were compared to the immune parameters of all others of the same attained age (30).

RESULTS

From 1973 until 1998, there were 248 patients referred with or diagnosed as having CVI. The age range was 3–79 and there were 102 males and 146 females. Included are 11 subjects of Hispanic origin and 4 black Americans; the remainder are Caucasians of European descent.

There were differences in the male and female populations; a review of the charts showed that the mean

age at the onset of symptoms was 23 years for males and 28 years for females ($P = 0.06$) (Fig. 1). The mean age at the time of diagnosis was 29 years for males and 33 years for females ($P = 0.01$) (Fig. 1). By 1998, 57 of the patients had died (24%), 153 were known to be alive, and 38 could not be located. The mean age of the patient population at the end of 1998 was 41 for males and 45 for females.

Serum Immunoglobulins and Lymphocyte Studies

At the time of diagnosis, the baseline serum IgG was, by definition, two standard deviations below the normal level for age; the mean for this group was 246 mg/dl. The level of IgA was under 10 mg/dl in 70%. Serum IgM was less than 25 mg/dl for 82%. Mean serum immunoglobulin levels for the group are given in Table 1 and percentiles in Fig. 2. While the overall IgG levels are widely dispersed for the group, the level of serum IgG was closely correlated to the levels of both serum IgA ($r = 0.262$; $P = 0.001$) and IgM ($r = 0.334$; $P = 0.0001$). Initial levels of serum IgG were similar for males and females, but females had significantly higher levels of serum IgA at the time of diagnosis ($P = 0.05$) and significantly more serum IgM at all ages than males ($P = 0.01$) (Table 1). An inverse relationship was also found between the age of the subject and serum IgM, such that younger patients of both sexes were more likely to have lower levels of serum IgM at the time of diagnosis ($P = 0.03$) (Table 2). This is a linear and inverse association; for an illustration of the differences found, we show data for "younger" and "older" CVI subjects, arbitrarily distinguished as over or under age 30.

T cell abnormalities were common. Of the 176 patients who were tested, 40% had subnormal lymphocyte proliferative responses to one or more mitogens, phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) (Table 1; ranges considered normal are shown). A relative lack of CD4 T cells (less than 400 cu/mm) was found for 20% of subjects. The ratio of CD4/CD8 T cells and the number of CD4 T cells but not lymphocyte numbers were closely related to lymphocyte proliferation to PHA ($P = 0.006$) and to PWM ($P = 0.002$), but not clearly to proliferative responses to Con A ($P = 0.087$). The level of serum IgG was also significantly correlated to lymphocyte proliferative response to PHA ($r = 0.247$; $P = 0.002$), Con A ($r = 0.246$; $P = 0.0009$), and PWM ($r = 0.189$; $P = 0.04$). (Figure 3 shows this relationship for PHA.) In contrast to serum IgM and IgA, lymphocyte subsets and T cell functions were not related to the sex or age of the patient.

Associated Conditions

A number of diseases or conditions appear with increased frequency in CVI, the main categories being infections, autoimmune disease, hepatitis, granulomatous infiltrations, gastrointestinal or pulmonary disease, lymphoma, and cancer (Table 3). The frequency of these conditions is likely to be an underestimate since 38 subjects could not be currently located, but were not excluded from the total group, since at least a portion of their medical history could be included. It is also important to note that the true incidence of some conditions, for example, granulomatous disease, which was found in 21 of these subjects, many of whom were included in a prior report (22), would be particularly difficult to determine since many patients have never had biopsies.

Infections. Acute, chronic, or recurrent infections were found in almost all cases, particularly pneumonia, sinusitis, and otitis (Table 4). Bacterial meningitis occurred in 2 subjects prior to immunoglobulin treatment; we are not aware of any other cases in immunoglobulin-treated subjects in this group. Almost all of the patients had a history of recurrent episodes of bronchitis, sinusitis, and/or otitis. The majority (78%) had had pneumonia at least once prior to diagnosis. Many had noted chronic or recurrent conjunctivitis, culturing *H. influenzae* in most cases. By 1998, 68 subjects (27% of the total group) were known to have developed chronic lung disease (with or without bronchiectasis). Five patients of the 153 subjects for whom we have current information now require continuous or intermittent oxygen treatment. Due to advancing lung disease, 3 subjects have had a heart/lung or lung transplantation. Mycoplasma pneumonia or joint infection was diagnosed in 6 subjects of the group. Unusual, or opportunistic, infections were also found, including both viral and fungal pathogens (Table 4). *Pneumocystis carinii* infections developed in 7 subjects: a 10-month-old infant later found to have CVI, a 15-year-old on high-dose corticosteroids for hypersplenism, 1 subject who contracted HIV infection, and 4 others, only 2 of whom had extremely impaired T cell immunity.

Autoimmune disease and treatment. Fifty-six subjects (22%) developed one or more autoimmune conditions (Table 5). Excluding subjects with anti-IgA antibodies (7 subjects), there were 52 subjects with autoimmune disease. Female CVI subjects had more autoimmune disease (40 conditions) than males (26 conditions). Five subjects had one or more bouts of autoimmune hemolytic anemia (AHA) and idiopathic thrombocytopenia (ITP) (Evan's syndrome), episodes of which occurred before and after treatment with IVIg was initiated. For treatment of ITP and AHA, most

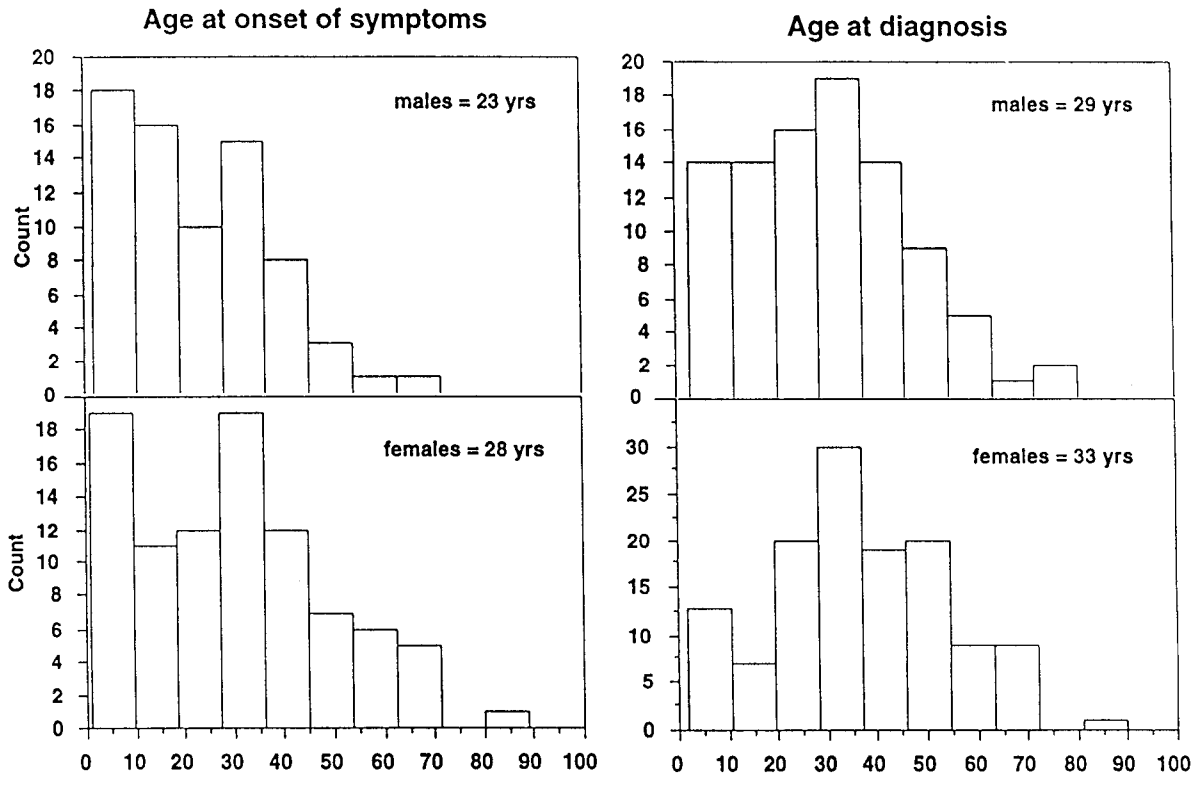

FIG. 1. The age at the onset of clinical symptoms of immunodeficiency and the age at diagnosis for males and females are shown in percentiles. The median ages for males and females for the ages at onset of symptoms and at diagnosis are given.

patients were given a high dose of IVIg coupled with short courses of corticosteroids; for RA, SLE, and vasculitis, corticosteroids were used for varying times. One subject given long-term corticosteroid treatment for chronic nephrotic syndrome developed an anaerobic leg infection requiring an amputation and then died of the infection. One patient with long-term JRA, who also had Hodgkin's disease at age 8, was given methotrexate; 11 years later at the age of 19, pulmonary Hodgkin's disease returned. Another patient with a past history of Hodgkin's disease was given methotrexate for primary biliary cirrhosis. Three years later he

TABLE 1

Immunologic Parameters

	Normal range[a] (mg/dl)	Males (n = 102) median (range)	Females (n = 146) median (range)	(Wilcoxon test)
Immunoglobulins				
IgG	800–1800	210 (8–600)	220 (0–591)	0.65
IgA	90–450	6.5 (0–202)	7 (0–255)	0.05*
IgM	80–300	22 (0–227)	30 (0–645)	0.01**
Lymphocyte markers (%)				
T cells	65–95	77 (39–94.5)	79 (27–97.6)	0.65
B cells	3–25	8 (0–30)	8 (0–29)	0.55
CD4 T cells/CD8 T cells	1.7 average	1.5 (0.29–5.5)	1.48 (0.3–5)	0.92
Lymphocyte proliferative response (cpm)				
Phytohemagglutinin (PHA)	16,000–29,000	20,100 (190–118,300)	21,697 (183–127,990)	0.43
Concanavalin A (Con A)	10,000–24,000	10,488 (220–53,400)	11,087 (269–122,780)	0.98
Pokeweed mitogen (PWM)	5,000–13,000	5,401 (63–29,982)	4,249 (100–81,851)	0.22

[a] Taken as the range including two standard deviations above and below the mean for normals of age range for subjects 18–45 years.
* Differences significant, $P < 0.05$.
** Difference significant, $P < 0.01$.

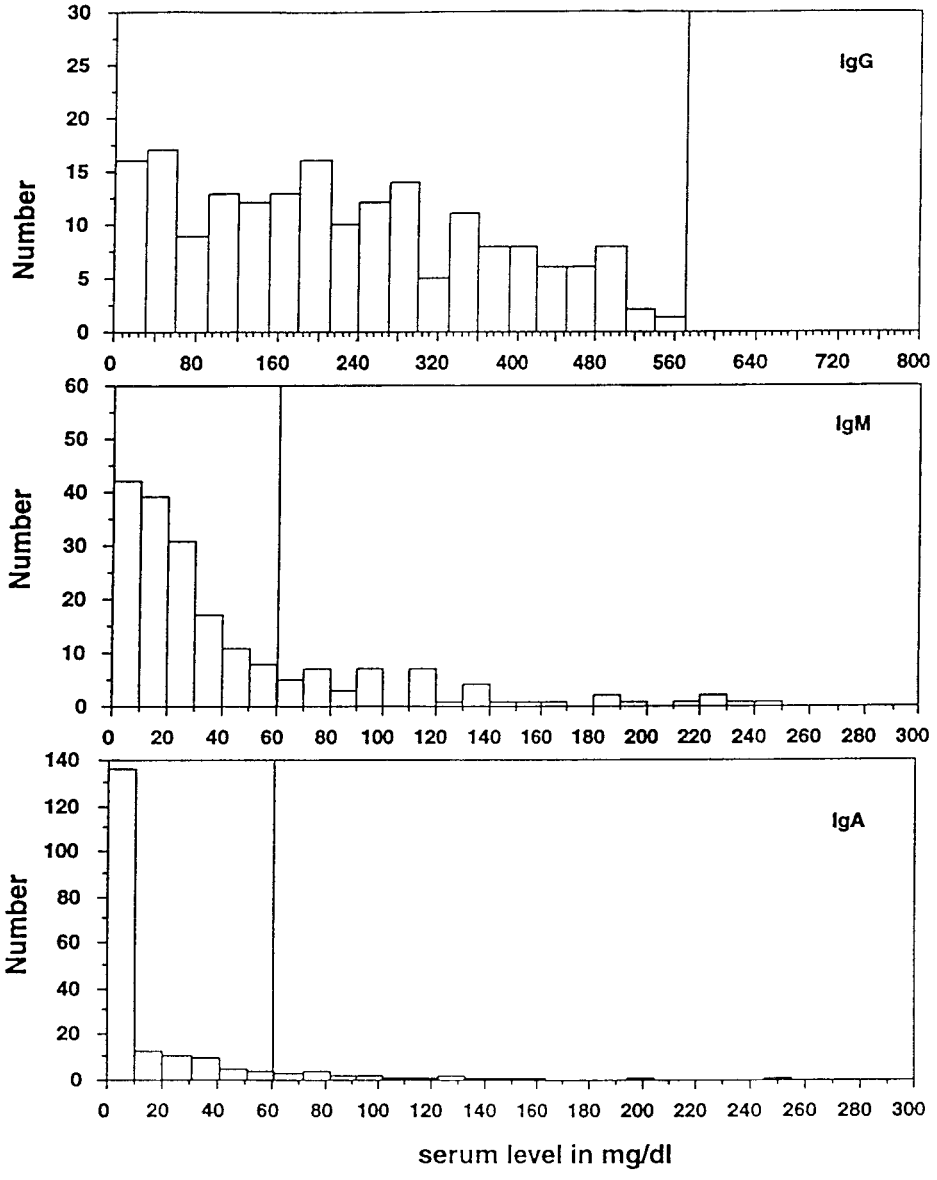

FIG. 2. The range for serum IgG, IgA, and IgM for the group at the time of diagnosis, prior to start of IVIg. The number of individuals having the indicated serum values is given.

developed a primary brain lymphoma and died after an autologous bone marrow transplant.

Hepatitis. Twenty seven (11.9%) patients had significant liver dysfunction (Table 6). In 5 cases, this was diagnosed as non-A non-B hepatitis; PCR testing was not available at that time. For 10 others, hepatitis C was diagnosed by PCR. Non-A, non-B hepatitis C was acquired from plasma infusions, IVIg, or unknown sources. In 3 other subjects, liver biopsy demonstrated primary biliary cirrhosis. In 7 cases, the cause of liver dysfunction was unknown. Eight patients of this group have died of liver disease, 4 of these of non-A non-B or what in more recent cases was identified as hepatitis C.

Lymphoma and cancer. Non-Hodgkin's lymphoma (NHL) developed in 19 subjects (7.7%) (14 females and 5 males), in mostly extranodal locations. In all those studied, these lymphomas were B cell in type. The first 11 of these were described in a prior report (30). In 10 of these cases, it was the cause of death (Table 7). Another three subjects had Hodgkin's disease, and 1 had Waldenstrom's macroglobulinemia. Aside from NHL, there were 24 other cancers in this patient group, including 2 stomach cancers (Table 8).

Gastrointestinal disease. Gastrointestinal disease was found in 53 subjects of the group (Table 9). Ten subjects of this group were found to have nodular lym-

TABLE 2

Distribution of Serum IgM Levels for Females and Males by Age at Diagnosis[a]

	Age of females		Age of males	
	<30	≥30	<30	≥30
Serum IgM (mg/dl)	(%)		(%)	
0–25	50	41	67	46
25–75	35	28	27	38
≥75	15	32	7	15
Median IgM (mg/dl)	25.5	36	15	27

[a] There is a linear inverse association between age at diagnosis and serum IgM level, stratified for sex: $P = 0.03$. The age "30," chosen to separate older from younger CVI subjects, was chosen arbitrarily to point out differences for these groups of individuals.

phoid hyperplasia, but this is likely to be an underestimate of the prevalence of this condition, since asymptomatic subjects may have had nodular lymphoid hyperplasia, but did not have endoscopy or radiographic procedures. Inflammatory bowel disease (ulcerative colitis, ulcerative proctitis, or Crohn's disease) was found in 16, while 6 others had a sprue-like illness with flat villi, not responsive to wheat withdrawal. Ten additional subjects, with no specific gastrointestinal diagnosis, had significant malabsorption. Five subjects of the group have required total parenteral nutrition. Specific infectious agents have been sought for all cases in which diarrhea was the presenting symptom, but a specific organism was documented in only an occasional instance. These were some differences in intestinal diseases found in males and females; females were more often diagnosed with nodular lymphoid hyperplasia than males, while males were more often diagnosed as having Crohn's disease.

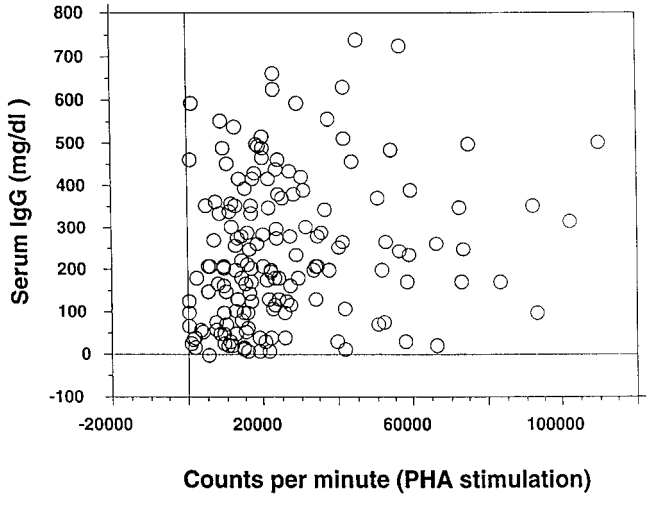

FIG. 3. The level of serum IgG (mg/dl) at the time of diagnosis of CVI is correlated to the lymphocyte proliferation responses to mitogens; here the relationship to PHA proliferation (given in cpm) is shown.

TABLE 3

Associated Conditions

Illness	Number of patients	%[a]
History of serious or recurrent infections	242	90
Chronic lung disease	68	27
Autoimmunity	55	22
Hepatitis	27	11
Granulomatous disease	21	8
Non-Hodgkin's lymphoma	19	8
Other cancers[b]	19	8
Inflammatory bowel disease[c]	16	6
Splenectomy	16	6
Malabsorption	10	4
Diabetes mellitus	6	2
Hodgkin's disease	3	<1
Schizophrenia	3	<1
Mucocutaneous candidiasis	3	<1
Presentation with hives and angioedema	3	<1
Cerebral atrophy	3	<1
XXY	1	<1
DiGeorge syndrome	1	<1
Amyloid of thyroid	1	<1
Demyelinating disease	1	<1
Waldenstrom's macroglobulinemia	1	<1

[a] Of the total group of 248 CVI subjects, 38 were not currently located; however, for calculations of frequency the total group was used.

[b] Breast, 6; stomach, 2; colon, 3; mouth, 2; prostate, lung, vagina, ovary, skin, and melanoma, 1 each.

[c] Crohn's disease, ulcerative colitis, ulcerative proctitis.

Splenectomy. Sixteen subjects of the group had a splenectomy, in most cases for autoimmune disease not controlled by corticosteroids. In all but 1, splenectomy successfully resolved the autoimmune disease, but 3 subjects had significant postoperative surgical complications (Table 10).

Transplantation. Four organ transplants have been performed in this patient group, one heart and bilateral lung transplantation, two bilateral lung transplants, and one liver transplantation. Two stem cell transplants were also done. The outcome of these procedures is shown in Table 11.

Family Members with Immunodeficiency

As reported previously, relatives of CVI patients may also be found to be immunodeficient. In this series, 10 of the women had 1 or more IgA-deficient children (9.6% of the 104 females who had children and have been followed here); no male CVI subject in this group has been found to have an IgA-deficient child, although

TABLE 4
Infections

	Number of patients	%
Recurrent bronchitis, sinusitis, otitis	243	98
Pneumonia	190	76.6
Viral hepatitis	16	6.5
History of severe *Herpes zoster*	9	3.6
Giardia enteritis	8	3.2
Pneumocystis carinii infections	7	2.8
Mycoplasma pneumonia	6	2.4
Chronic mucocutaneous candidiasis	3	1.2
Salmonella diarrhea	3	1.2
Sepsis (Pseudomonas, pneumococcus, *H. influenzae,* Listeria	3	1.2
Campylobacter enteritis	3	1.2
Meningitis (*H. influenzae,* pneumococcus, and pseudomonas)	2	<1
Osteomyelitis	2	<1
Septic arthritis	2	<1
Recurrent parotitis	1	<1
Pyoderma gangrenosum	1	<1
Nocardia brain abscess	1	<1
Anaerobic leg infection leading to amputation	1	<1
HIV infection	1	<1
Cryptococcal lung abscess	1	<1
Viral myocarditis	1	<1
Cytomegalovirus, intestinal infection	1	<1
Microbacterium avium, lung	1	<1
Fatal measles encephalitis	1	<1
Mycoplasma joint infection	1	<1
Psoas abscess (*Escherichia coli* and Bacteriodes)	1	<1
Pelvic abscess after appendectomy, unknown organism	1	<1

1 man had 2 daughters diagnosed as having CVI by standard criteria. In both cases the prolonged immunodeficiency in the daughters resolved, as described below. This group also contains 2 sibling immunodeficient pairs with unaffected parents and 1 male whose older brother (not part of this series) had CVI, but died of a carcinoid tumor.

Treatment with Immunoglobulin

While a number of the older patients had been treated with plasma infusions in the past, only three subjects in this patient group now receive plasma, one because of intolerance to IVIg solutions and two others who have not wanted to switch from this treatment to IVIg. Two subjects have received subcutaneously infused immunoglobulin for extended periods, one because of medically unmanageable reactions to intravenous delivery and the other due to poor venous access. Only one patient in this group has required an indwelling catheter for administration of IVIg. The only other exceptions are patients who have required infusions of parenteral nutrition or antibiotics in a home care setting; IVIg was occasionally given on a temporary basis via the same indwelling line. Two subjects of the group received no immunoglobulin treatment.

Transient Immunodeficiency

For almost all CVI subjects studied, the degree of immunodeficiency has remained stable over long intervals. However, four subjects originally been found to be panhypogammaglobulinemic had resolution of immunodeficiency. Two of these were daughters of a profoundly hypogammaglobulinemic man who died at the age of 48, of lymphoma of the stomach. Both children, having low levels of immunoglobulins, at ages 4 and 10, were treated with intramuscular immunoglobulin but serum levels of immunoglobulin slowly normalized and eventually immunoglobulin treatment was stopped when the girls were 18 and 24, respectively. (At age 4, one sister had IgG = 50, IgA = 12, IgM = 53 mg/dl; the other sister, at age 10, had IgG = 249, IgA = 55, IgM = 51 mg/dl). Both have remained healthy with normal serum immunoglobulins. The third subject, referred with intestinal disease, had a bowel biopsy suggestive of lymphoma and was found to have no plasma cells in the intestinal tract; he had total IgA deficiency, and a low serum IgG. He was diagnosed as having CVI, and IVIg was started. After being treated with IVIg for 2 years, immunoglobulin levels rose to normal and immunoglobulin replacement was discontinued.

TABLE 5
Autoimmunity

Type	Numbers	
	Male	Female
Idiopathic thrombocytopenia purpura (ITP)[a]	8	7
Autoimmune hemolytic anemia (AHA)[a]	6	6
Rheumatoid arthritis	0	5
Juvenile rheumatoid arthritis	2	2
Anti-IgA antibody	1	6
Sicca syndrome	0	2
Primary biliary cirrhosis	1	2
Alopecia totalis	2	2
Pernicious anemia	0	3
Hyperthyroid disease	0	2
Autoimmune neutropenia	1	1
Nephrotic syndrome	2	0
Systemic lupus erythematosus	1	1
Vasculitis	2	1
65 autoimmune diseases in 56 patients[b]		

[a] Five patients had both ITP and AHA, Evan's syndrome.
[b] Sixty-five total conditions: 26 of these were found in males, 40 were found in females.

TABLE 6

Liver Disease

Patient			
Age	Sex	Type of hepatitis	Outcome
14	M	Granulomatous disease	Stable, has granulomata in lymph nodes
16	M	Unknown, hepatitis C later	Chronic hepatitis from age 2, died of other problems at age 16
21	F	Non-A, non-B,[a] from plasma?	Chronic hepatitis, died of other problems
22	F	Hepatitis C, source?	Chronic liver disease
27	M	Hepatitis C, source?	Died liver disease, respiratory insufficiency, and inflammatory bowel disease
28	M	Unknown	Died, unknown degenerative cerebral disease
33	M	Non-A, non-B,[a] from plasma?	Died at age 38, liver failure
34	M	Non-A, non-B,[a] from plasma?	Died at age 38, liver failure
34	M	Hepatitis C, from plasma	Died of colon cancer; also had Nocardia brain abscess
35	M	Hepatitis C, from plasma?	Died liver failure
35	F	Granulomatous	Died post lung transplantation
35	F	Hepatitis C, from IVIg	Chronic hepatitis
38	M	Hepatitis C, source?	Chronic, low grade
39	M	Unknown	Stable
39	F	Autoimmune? Unknown	Died liver disease
40	M	Hepatitis B, from plasma?	Recovered, died of lung disease
40	M	Primary biliary cirrhosis	Died of CNS lymphoma, post autologous stem cell transplantation
42	F	Autoimmune? Unknown	Died of liver disease, respiratory insufficiency
45	F	Primary biliary cirrhosis	Chronic hepatitis, died of other problems at age 61
45	F	Hepatitis C, from unknown source? IVIg	Stable, cirrhosis
49	M	Hepatitis C, from experimental IVIg	Recovered
53	F	Hepatitis C, from experimental IVIg	Chronic hepatitis, died after transplant? cause
54	F	Primary biliary cirrhosis	Died of respiratory insufficiency; pneumonia
57	M	Unknown	Healthy
58	F	Non-A, non-B,[a] from plasma?	Recovered
60	F	Granulomatous?	Stable, has granulomatous lung disease
69	M	Non-A, non-B,[a] from plasma	Stable
73	M	Unknown, autoimmune?	Liver failure, died
60	F	Granulomatous?	Stable, has granulomatous lung disease

[a] Non-A, non-B hepatitis was diagnosed in these subjects prior to availability of PCR for hepatitis C; these cases were not proven to be hepatitis C; all others indicated to have hepatitis C were tested and found positive by PCR.

Quality of Life

In spite of the number and variety of medical conditions that have been found in this patient group, 77 of the 116 individuals (66%) between the ages of 21 and 66 for whom we have current information hold full-time jobs. While 28 individuals of this group (24%) are disabled, in 6, the disability is not due to CVI or directly related problems. Twelve women of the group have had 14 pregnancies after the diagnosis was made and IVIg was started. The deliveries were uncomplicated in all, but 2 women who had previously established lung disease had worsened lung function after pregnancy and now require continuous oxygen treatment.

Mortality and Survival: Relationship to Sex and Immune Functions

The median follow-up time for these patients was 7 years (range 0–25), during which 57 subjects died, from 1 to 32 years after their diagnosis, at ages ranging from 5 to 90 (median age 43). Excluding the 38 subjects who could not be located, this represents a mortality of 27%. If none of the 38 subjects who were not found have died, the mortality for the group would be 23%. Thus the true mortality lies between 23 and 27%. Of those who died, there were 32 females and 25 males (Table 12). The mean age of females at the time of death was older (45.5 years) than the mean age for males (40 years). The major single cause of death was lymphoma (10 cases). Another important cause of death was chronic pulmonary infections resulting in cor pulmonale (6 patients).

To compare the survival of CVI subjects to that expected for males and females living in the United States, survival analyses were performed. Figure 4 shows the estimated probability of survival after diagnosis of CVI, for males and females, compared to the expected survival in the general population, based on U.S. mortality rates for persons of the same age and sex (28, 29). The probability that males with CVI will

TABLE 7

Non-Hodgkin's Lymphomas[a]

Non-Hodgkin's lymphoma				
Age	Sex	Location	Treatment	Outcome
13	F	Cervical node	Chemotherapy (CHOP)	Died, age 13
31	F	Parotid	Surgery	Alive, 1 year later
41	M	Brain	Chemotherapy, autologous stem cell transplant	Died, age 41
44	F	Proximal jejunum	Surgery	Unknown, alive 8 years later
45	M	Chest	None	Alive, 1 year later
46	F	Pelvis	Chemotherapy (Type?)	Died
48	M	Stomach	None	Died, age 48
52	F	Pelvis, recurrent buccal mucosa	Chemotherapy (CHOP)	Died, age 56
52	F	Pleura	Radiation	Alive, 2 years later
54	F	Parotid, axilla; chest wall	Surgery, surgery, chemotherapy	Alive, but 10 years later relapsed, now on chemo., age 68
54	F	Inguinal node	Surgery	Died other causes, 15 years later, age 69
56	F	Pelvic nodes	Chemotherapy (M-BACOD, CHOP, RT, CP)	Alive, 12 years later
63	M	Bone marrow, ascites	Plasmapheresis (CHOP, M-BACOD, M2)	Died, age 65
67	F	Diffuse, supratavicular area, abdomen	Chemotherapy (C-MOPP)	Died, age 68
67	F	Diffuse	Chemotherapy (CHOP)	Alive, stable 8 years later
71	F	Chest lymph nodes, lungs	Chemotherapy (C-MOPP)	Died, age 72
72	F	Cervical lymph nodes	Alpha interferon	Died, age 73
75	F	Chest	Radiation	Alive, stable, 2 years later
77	M	Chest	Chemotherapy (Type?)	Died, age 77

Note. Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; M-BACOD, methotrexate, doxorubicin, cyclophosphamide, vincristine, dexamethasone; RT, radiation therapy; CP, *cis*-platinum; C-MOPP, cyclophosphamide, oncovin, procarbazine, prednisone; M2, vincristine, cyclosphosphamide.

[a] Eleven of these cases were previously reported (28).

survive 20 years after the diagnosis of CVI is estimated to be 64%, compared to an expected 92% survival of males at the same ages in the general population. Similarly, the probability that females with CVI will survive 20 years after diagnosis is estimated to be 67%, compared to an expected 94% survival for females of similar ages in the general population.

TABLE 8

Other Cancers

	Number of cases	
	Males	Females
Waldenstrom's macroglobulinemia	1	0
Hodgkin's disease	2	1
Adenocarcinoma of stomach	0	2
Adenocarcinoma of ovary	0	1
Adenocarcinoma of colon	2	1
Breast cancer	0	6
Prostate cancer	1	0
Squamous cell carcinoma of vagina	0	1
Squamous cell carcinoma of skin	1	0
Squamous cell carcinoma of mouth	2	0
Squamous cell carcinoma of lung	0	1
Squamous cell carcinoma	1	0
Melanoma	1	0
Invasive basal cell carcinoma	0	1

TABLE 9

Gastrointestinal Diseases

	Female	Male
Nodular lymphoid hyperplasia[a]	9	1
Ulcerative colitis	2	2
Ulcerative proctitis	2	1
Crohn's disease	1	8
Malabsorption, no other diagnosis	7	3
Giardiasis	4	4
Protein loosing enteropathy	2	1
Sprue-like disease	3	3
Malnutrition requiring total parenteral nutrition	2	3
Cytomegalovirus enteritis	1	0
Interstitial lymphangiectasia	1	0
Intestinal granulomatous disease	1	0
Campylobacter	3	2
Salmonella infection	2	1

[a] Most likely underdiagnosed.

TABLE 10

Reasons for Splenectomy and Outcome

Age at splenectomy (years)	Sex	Reason	Operative complications	Outcome
8	M	Hodgkin's disease	None	Relapsed, Hodgkin's disease 11 years later after chemotherapy
14	M	Hypersplenism	None	Died of lymphoid pulmonary infiltrates 12 months later
15	M	ITP	None	Alive and well 21 years later
18	F	Idiopathic thrombocytopenia purpura	None—pneumococcal sepsis 1 year later	Alive and well 4 years later
19	M	ITP	None	Alive and well 6 years later
30	F	Hypersplenism	None	Died unknown liver disease 8 years later
33	F	Hemolytic anemia, granulomata in spleen	Splenic granulomata LUQ abscess, bowel obstruction, temporary colostomy, gastrocutaneous fistula, large abdominal hernia	Stable 4 years later; had reconstructive abdominal wall surgery
35	M	Presumed lymphoma	None	
35	F	ITP	None	Alive, 10 years later
36	M	Autoimmune hemolytic anemia	Draining fistula to back, closed in 2 years	Alive and well 14 years later
38	M	Presumed lymphoma	None	Alive and well 6 years later
40	M	Abscesses in spleen (*E. coli* plus Bacteriodes)	Postoperative fever due to collection of fluid drainage performed successfully	Alive and well 9 years later
55	M	Uncertain	Pneumococcal sepsis 2 years after splenectomy	Died at age 63 of lymphoma
55	F	Hypersplenism	None	Alive and well 5 years later
56	F	Hemolytic anemia	None	Alive and well 1 year later
60	F	Hemolytic anemia	None	Hemolysis continued, died vasculitis, lymphopenia

To identify an immunologic parameter which might be associated with an increased risk of death, the Cox proportional hazards model was used. For this analysis, the age attained after the age at which the diagnosis of CVI was made was used as the time variable. The immune parameters of all subjects of comparable age known to be alive were compared to the parameters of the subjects or subject who had died. A separate test was done for each immune parameter. The percentage of peripheral B cells showed a highly significant association with the risk of death ($P < 0.006$), as did the PHA response ($P < 0.04$) and initial level of serum IgG ($P < 0.05$). When the various immune parameters as well as gender were combined in a multi-

TABLE 11

Transplantation

Age	Sex	Procedure	Reason	Outcome
27	M	Heart and lung	Respiratory insufficiency	Good condition for 3 years, chronic rejection for 1; developed bleeding disorder, platelet dysfunction
26	M	Bilateral lung	Respiratory insufficiency	Good condition for 2 years, low-grade rejection, developed bleeding disorder, platelet dysfunction
32	F	Bilateral lung	Granulomatous lung disease	Difficult procedure due to scarring of pleural surfaces, died 3 days after transplantation, of surgical complications
54	F	Liver	Liver failure to hepatitis C	Developed dementia posttransplantation
5	F	Placental stem cell	T and B cell defects, chronic anemia	Died 6 months posttransplant of infections
38	M	Autologous stem cell	CNS lymphoma, past history of Hodgkin's disease; had primary biliary cirrhosis, on methotrexate	Died posttransplant of infection

TABLE 12
Causes of Death

Cause of death	Cases
Lymphoma	10
Cor pulmonale	6
Unknown	5
Hepatitis (viral, 4; autoimmune, 1)	5
Respiratory insufficiency, malnutrition	4
Post lung transplant, chronic or acute rejection	3
Carcinoma of stomach	2
Arteriosclerotic heart disease	2
Carcinoma of colon	2
Bone marrow aplasia, malabsorption	1
Fetal measles infection	1
Cerebral vascular accident	1
Suicide	1
Accident	1
Malnutrition	1
Post stem cell transplant	1
Viral meningitis → paraplegia, suicide	1
Cerebral atrophy → neurologic degenerative disease	1
Severe rheumatoid arthritis	1
Bone marrow aplasia	1
Metastatic squamous cell carcinoma of mouth	1
Adenocarcinoma of ovary	1
Anerobic leg infection 2° steroids for renal disease	1
Pneumocystis carinii pneumonia 2° steroids for hypersplenism	1
Lung cancer	1
PML (progressive multifocal leukoencephalopathy)	1
Vasculitis	1
	57

variate analysis, the percentage of B cells remained an independent predictor of death. In fact, for each percentage decrease in the number of B cells, the risk of death in this follow-up period increased by a factor of 0.92 (95% confidence interval: 0.87–0.98).

DISCUSSION

Common variable immune deficiency is a complex immunological disease because of the variety of associated immunological defects and clinical manifestations. In a 1976 report of 50 cases of CVI, the average age at the time of diagnosis was 41.9 years (31). In our prior report in 1989, the average age at the time of diagnosis was 28 (3). In the current group, the average age at the time of diagnosis was 31 years for the group, but for males was 4 years earlier than for females. For both males and females there remains a period averaging 4–6 years during which symptoms of immune deficiency are present, but the diagnosis of CVI has not yet been made.

The hallmark of CVI is hypogammaglobulinemia, and the standard treatment is IVIg. While this form of treatment has altered the spectrum of illnesses, a large number of medical conditions continue to appear in this patient population. Previously, bacterial meningitis, sepsis, and recurring pneumonia were commonly seen in hypoglobulinemic patients (1–6, 32, 33). However, in our series, no cases of bacterial meningitis or sepsis have occurred in CVI subjects given standard amounts of IVIg; recurrent bacterial pneumonias have developed in one subject who has severe bronchiectasis and only rarely for other CVI subjects on IVIg. On the other hand, significant lung disease remains a characteristic of this patient population, with at least 27% of the group affected by bronchiectasis, restrictive, or obstructive lung disease. This may be due to damage sustained before IVIg treatment was started, continued inflammatory changes not treated by IVIg, or both. Due to severe lung disease, three subjects of this group have required lung transplantation, and five others require continuous oxygen treatment.

While most patients with CVI are particularly susceptible to infections with pneumococcus and hemophilus, mycoplasma infections, previously found to be an important pathogen in CVI (34, 35), were documented in seven instances, but were probably underdiagnosed. Other infections, suggestive of severe T cell defects, including *Pneumocystis carinii*, scarring *Herpes zoster*, chronic candidiasis, cryptococcal lung abscess, *Mycobacterium avium*, and cytomegalovirus enteritis, were found in a few subjects, not all of whom had reduced CD4 T cell counts or exceptionally poor T cell proliferation. Opportunistic infections such as these have been previously reported in a rare patient with CVI (4, 36, 37).

Nineteen non-Hodgkin's lymphomas (NHL) have appeared in this patient group, 14 of these being in women. The first 11 of these were previously described (31). The association between NHL and congenital immunodeficiency is well established, with most cases appearing in patients with T cell defects such as ataxia–telangiectasia, Wiskott–Aldrich syndrome, and severe combined immune deficiency, as well as CVI (38). As for other congenital immunodeficiency diseases, the lymphomas that occur in subjects with CVI tend to be extranodal in origin and B cell in type. Unlike the NHL found in other immunodeficiency disorders, which are often poorly differentiated, the lymphomas in CVI tend to be well differentiated and secrete immunoglobulin. The female predominance remains unexplained, except to note that our older CVI subjects are predominantly female; the increased appearance of NHL in these older female subjects may be due to a relative lack of older males with CVI in our group. Six lymphomas were previously reported in a CVI patient group of 240 subjects in the United Kingdom (4); the age and sex were not given. The true incidence of NHL in CVI would be difficult to determine from the current population; however, in our prior study we estimated that females with CVI had 438-fold increased likelihood of

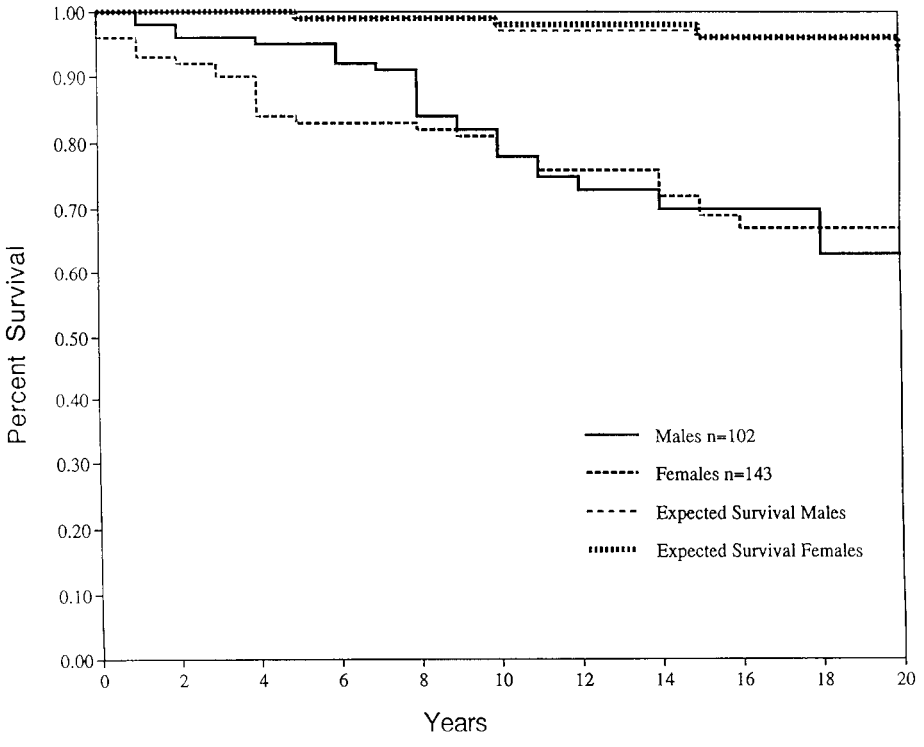

FIG. 4. Survival curves for male and female CVI subjects are given in comparison to the expected survivals at the same ages for male and females in the United States (28).

developing NHL compared to the age-adjusted expected incidence (23). Two stomach cancers were noted in this patient group, while in another large survey, three stomach cancers were found in 240 CVI subjects (4).

Data presented here suggest that chronic immunosuppression in CVI, using corticosteroids or methotrexate, may result in medical complications. Two subjects receiving methotrexate for autoimmune disease (both of whom had a prior history of Hodgkin's disease) developed an additional malignancy or recurrent disease. Prolonged corticosteroid treatment in another case was followed by *Pneumocystis carinii* pneumonia in one, a Nocardia brain abscess in another, progressive multifocal leukoencephalopathy in a third, and a severe anaerobic leg infection, leading to amputation, in a fourth. These data suggest that prolonged immunosuppressive therapy should be used with caution in patients with CVI. Whether the chronic long-term immunosuppression required after organ transplantation is safe for this patient group is not yet settled. Two subjects of our group had prolonged graft survival (2.5 to 4 years) after bilateral lung transplantation without severe infections, but both developed chronic rejection and an undiagnosed bleeding disorder, characterized by platelet dysfunction and pulmonary bleeding. Successful liver and lung transplantation has been reported in CVI (38, 39) but long-term follow-up is not available.

In this group, although 10 CVI women are known to have children with IgA deficiency, this is not likely to reflect the true incidence of IgA deficiency in these families, since family screening was not done on the majority of subjects. The predominance of female transmission of IgA deficiency in this setting has been previously reported (41). While several prominent major histocompatibility haplotypes have been found in both CVI and IgA deficiency (41, 42), most CVI subjects studied here have not had tissue typing. Whether one or more genetic elements located in the MHC region contribute to the development of these immune defects remains uncertain; however, for 16 multiplex families with dominant transmission of IgA deficiency and CVI, no MHC linkage was discovered (43).

Almost all patients in this group have had a stable immunodeficiency, with serum immunoglobulins remaining similarly reduced over very long periods of time; however, four subjects included here displayed a different course. For each of these individuals, serum immunoglobulins (IgG, IgA, IgM) have become normal over a period of 18 months to 14 years. Two were girls diagnosed in childhood after their father was found to be profoundly hypogammaglobulinemic; the other two were adults. In all four cases, antibody production and

immunoglobulin levels are now normal. Spontaneous resolution of immunodeficiency such as this has been noted previously (44), suggesting that this immunodeficiency is not always an intrinsically permanent B cell defect, or that this more transient form cannot currently be distinguished from CVI.

The mortality in this CVI group is high, between 23 and 27% over a median follow-up period of 7 years. In our previous report, we found that the mortality was 22% over a 13-year period (3). This prior report reflected more data for a period during which intramuscular immunoglobulin was the standard treatment than the currently compiled information which includes data collected 15–18 years after IVIg was introduced. While the currently presented data seem to suggest that IVIg has not made an impact on mortality in CVI, a number of subjects referred to this medical center in the past decade have been in poor medical condition. These CVI subjects, with more systemic disease, have most likely increased the overall mortality rate for this patient group. In fact 16 subjects, included in this series, died within 1 year of their first visit to this medical center. An older report demonstrated a 22% mortality over a 13-year period, 1960–1973, (30); a more recent report showed a 30% mortality for a group of 240 CVI subjects followed over a 30-year period (4). These mortality rates appear to exceed that for XLA, where the mortality in one study was 17% (45). The reasons for the apparently increased mortality in CVI compared to XLA are unknown, although gastrointestinal disease, lymphoma, and autoimmune disease are not commonly found in XLA (45). A potential explanation for these differences could be that the additional T cell defects in CVI may lead to immune dysregulation and perhaps additional medical complications.

Additional studies were done to determine if any specific immune parameters were associated with earlier diagnosis or poorer survival. Although females tended to have a later onset of symptoms and to be diagnosed later than male CVI subjects, after the diagnosis of immunodeficiency was made, the survival of males and females was similar, both being significantly reduced at all ages compared to U.S. population survival statistics (28). Similarly reduced survival curves were found for another group followed in the United Kingdom, although comparisons of CVI subjects to that expected for age-matched individuals in the same population were not determined (4).

Since females had a later onset of symptoms and tended to be diagnosed later than males, immunological differences between males and females were sought; females were found to have higher levels of serum IgA, and especially serum IgM, than males at the time of diagnosis. In addition, serum IgM levels for females exceeded that for males at all ages. Serum levels of IgM have been noted previously to be higher in normal females than in males; earlier studies found that the level of serum IgM appears related to the number of X chromosomes (46, 47). Whether the X chromosome influence is related to the higher IgM levels in CVI females is unknown; however, the higher serum levels of IgM (and IgA) might afford females with some additional degree of antibody protection, leading to a delay in onset of symptoms. Perhaps related to this is the observation that younger patients of both sexes had significantly reduced levels of serum IgM compared to older CVI subjects; this is consistent with the view that more significant immune impairment in these individuals resulted in the earlier appearance of illnesses requiring immunologic investigation and earlier diagnosis. However, these higher levels of serum IgM in females appear not to enhance survival after diagnosis, since survival curves for males and females were similar. Perhaps as another feature of retained B cell function, females were also more likely to develop autoimmune disease; whether the immune differences between males and females may relate to the greater numbers of B cell lymphomas, or in the apparent excess of nodular lymphoid hyperplasia, in females is unknown.

The immunologic differences between the subjects who died, as opposed to those who survived during the follow-up period, were also sought. The subjects who died were more likely to have lower levels of serum IgG at the time of diagnosis and poorer T cell proliferative responses to PHA. Serum IgG and proliferative responses to PHA were also closely associated with each other, suggesting that these immune functions are both interdependent and predictive of survival. However, the parameter most strongly associated with better or worse survival was the percentage of peripheral B cells. Reduced percentages of peripheral B cells have been previously noted in some subjects with CVI (1–8, 48); in male subjects, exclusion of XLA is important. The reason for the B cell deficiency in these CVI subjects is unknown; however, accelerated peripheral B cell apoptosis has been demonstrated for some CVI subjects and may be involved in B cell depletion (49). Our data suggest that the immune mechanisms leading to a lack of circulating B cells signify an immune impairment associated with reduced survival.

At this point in time, the genetic causes of CVI and the reasons for the widely differing clinical manifestations remain unknown. While pronounced antibody deficiency is the unifying parameter, there is accompanying immune dysregulation, with T cell deficiency and poorly controlled inflammation leading to additional organ damage and reduced survival.

ACKNOWLEDGMENTS

We gratefully acknowledge the administration skills of Mrs. Lydia Lopez, the nursing skills of our nurses, Sarah Martin, Monica-Reiter-Wong, and Vivian Badami, and the help of Marilyn Guichardo, the laboratory skills of Erica Sapira, and Dr. Loraine Miller and Kevin Kelliher for statistical management. We also are grateful to Dr. M. E. Conley for testing subjects for the presence of mutations of Btk, and to a large number of referring physicians including Dr. Dan Adelman, Dr. Andrea Apter, Dr. Dennis Cooper, Dr. Janet Cuttner, Dr. Bruce De Cotiis, Dr. Gerald Hellman, Dr. Howard Lederman, Dr. Savita Pahwa, Dr. Kenneth Prager, Dr. Robert Rabinowitz, Dr. Fred Siegal, Dr. Mark Stein, and Dr. Jerry Winkelstein.

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Received January 21, 1999; accepted with revision March 26, 1999

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