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Clinical and Immunologic Analyses of 103 Patients with Common Variable Immunodeficiency

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Common variable immunodeficiency (CVI) or hypogammaglobulinemia is a heterogeneous primary immunodeficiency disease in which B cells produce little or no antibody. Since the disease is relatively rare and the spectrum of associated illnesses is broad, patients are given care by a variety of specialists. Thus it has been difficult to determine the incidence of specific complications. In these studies we analyzed 103 consecutively referred CVI patients of age range 3–71 years (average, 29 years) who were followed for a period of 1–13 years (total of 750 patient years). The average serum IgG was 174.4 mg/dl for untreated patients and 301 mg/dl for patients treated with intramuscular immunoglobulin at the time of the first visit. The average IgA was 14.5, and the average IgM was 80.7, with no difference between or after immunoglobulin treatment. About one-half of the patients had T-cell dysfunction, but lymphocyte stimulation responses were inversely related to age, which implies worsened T-cell immunity with age. Serum IgG and IgA levels were found to be statistically associated (P = 0.008), and serum IgG was related to lymphocyte stimulation with concanavalin A (P = 0.01). By 1986, 79 patients were alive, 23 had died, and 1 could not be located. Recurrent bacterial illnesses were common to all patients, and 22% had developed chronic lung disease, 22% autoimmune disease, 15% cancer, 13% hepatitis, and 9% malabsorption. Autoimmune disease was more common in females, and cancer was more likely to develop in the fifth and sixth decades. In 11% of the group, other family members were found to be immunodeficient (hypogammaglobulinemic or IgA deficient). Nine patients died of respiratory insufficiency (with or without other complications), and seven patients died of cancer. These data provide valuable information about the immunologic abnormalities and the spectrum and frequency of illnesses associated with hypogammaglobulinemia.

KEY WORDS: Common variable immunodeficiency; hypogamma globulinemia; B-cell defect; T-cell defect; malabsorption.

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INTRODUCTION

Common variable immunodeficiency (CVI) (acquired or adult-onset hypogammaglobulinemia) is a primary immunodeficiency disease in which B lymphocytes produce little or no antibody. Reduced levels of serum immunoglobulins and normal or decreased numbers of circulating B cells bearing surface immunoglobulin are the hallmarks of the disease (1). Patients who have this disorder are often afflicted by recurrent bacterial infections, particularly of the sinopulmonary tract. Chronic lung disease, particularly bronchiectasis, is a common sequel to such infections, and cor pulmonale may develop (2, 3). Gastrointestinal diseases, such as giardiasis, a sprue-like syndrome with severe malabsorption, and nodular lymphoid hyperplasia, are also common (4–7). Another major complication is the development of autoimmunity, particularly autoimmune thrombocytopenia, autoimmune hemolytic anemia, rheumatoid arthritis, sicca syndrome, or pernicious anemia (3, 8–10). Patients with CVI also have an increased incidence of cancer, particularly of the lymphoid system (11) or the gastrointestinal tract (12).

While the disease appears to be due to an intrinsic B-cell defect, about half of all hypogammaglobulinemic patients also have T-cell defects (13). These abnormalities include poor lymphocyte proliferation to mitogens, T-dependent or T-independent antigens, anti-OKT3 and interleukin-2 (IL-2), and allogeneic cells, as well as variable B-cell differentiation responses to IL-2 or B-cell differentiation factors (BCDF) (14–19). Autosomal dominant inheritance of the defect is present in a small percentage of patients. Probably somewhat more common is the presence of first-degree relatives with selective IgA deficiency. In most instances,

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however, other family members are not immunodeficient.

The clinical disease spectrum is quite broad and may become manifest within the first 10 years of life or in young, middle, or even late adulthood (2, 3). Because of this and the varied diseases which may appear, patients with CVI tend to receive care from physicians in many diverse specialties. This report summarizes the clinical and immunologic features of 103 children and adults with hypogammaglobulinemia referred over a period of 13 years. The emphasis of these analyses was to determine the spectrum of clinical illness which appeared in this large group over long-term follow-up and to evaluate the immunologic parameters of the group. We also wished to determine whether specific clinical illnesses could be related to immune status.

METHODS

Patients

The Immunodeficiency Clinic was originally established at Memorial Hospital in New York City in 1973. Adult and pediatric patients with CVI were referred for analysis and treatment until 1986, when the clinic was relocated at the Mount Sinai Medical Center. The diagnosis of CVI was made by standard criteria (20). Specifically, these include the reduction of serum IgG by two or more standard deviations, with levels of serum IgA and IgM which are often, but not always, similarly reduced. In order to have a numerically defined population for study, this report is restricted by patients with CVI who were registered at and attended the Immunodeficiency Clinic from 1973 until October of 1986. Therefore, for the purposes of this report, we excluded patients less than age 2 years who had no further follow-up history to confirm continued hypogammaglobulinemia (since such patients may have had transient hypogammaglobulinemia of infancy) and patients with X-linked (Bruton-type) agammaglobulinemia, hypogammaglobulinemia with thymoma, and immunoglobulin deficiency due to secondary loss (intestinal loss, etc.). In order to exclude patients who were hypogammaglobulinemic due to cancer, patients who had been diagnosed as having cancer either before or 2 years after the diagnosis of hypogammaglobulinemia was established were also excluded from this report. To determine the clinical conditions of each individual in 1986, patients not currently attending the clinic were contacted and interviewed using a standard questionnaire. In most cases, the patient's current physician was also interviewed. For those who had died, the cause of death was ascertained by contacting the attending physician and, in six cases, by examination of the autopsy report. The pathology slides for each patient who had developed a lymphoid malignancy were reviewed previously for a prior report (11).

Laboratory Testing

Blood samples were usually tested for immunologic parameters on the first clinic visit, at which time most (57) patients were not receiving immunoglobulin therapy. (Therapy was started after this evaluation in almost all cases.) For the remaining patients, tests were done at a maximum interval after intramuscular immunoglobulin treatment. No patient studied on this first visit was on intravenous immunoglobulin. Serum immunoglobulins were quantitated by radial immunodiffusion and examined for monoclonal proteins by immunoelectrophoresis. Antibody deficiency was additionally verified in many cases by determining the titer of isohemagglutinins, by Schick testing, or 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 as well as all patients seen after 1980. Enumeration of T and B cells and the lymphocyte proliferative response to mitogens, antigens, and allogeneic cells was performed by standard methods (21–24) on the first clinic visit. Control samples for these tests were taken from volunteers of age range 18–45 years. Fluorescence microscopy was performed on peripheral blood in order to determine the percentage of B cells bearing various immunoglobulin isotypes (23). T-cell subset analyses were first performed using monoclonal antibodies and fluorescence microscopy; after 1981, flow cytometer analyses were performed for all patients (new or old). In all cases where the history suggested that another family member might also have an immunodeficiency, that individual was also tested by us or by a family physician to determine whether the quantitative immunoglobulin levels were in the normal range. In many cases this was also done on serum of the parents, siblings, and/or

children of our patient in the absence of a suggestive clinical history.

Further patient assessment was done by obtaining complete blood counts, chemistries, electrolytes, and other tests to define specific diseases (thyroid hormones, thyroid autoantibodies, thyroid stimulating factor, antinuclear antibody, rheumatoid factor, sedimentation rate, C-reactive protein, vitamin B-12, Schilling test, vitamin A, carotene, folic acid, and xylose tolerance test). Chest and sinus X rays, gastrointestinal X rays, electrocardiogram, complete pulmonary functions, and arterial blood gases were obtained as medically required. Other procedures, such as endoscopies and biopsies, were performed where medically necessary.

Statistical Analyses

The data for all patients were entered and collated in D-Base III (Ashton-Tate, Culver City, CA). For the statistical evaluation of immunologic tests, the initial testing results were used. Analyses of immunologic parameters were made by chi-square tests and by a test of correlation (Pearson). To determine whether the presence of a specific clinical illness (pulmonary disease, autoimmune disease, hepatitis, malabsorption, or cancer) was associated with immunologic parameters (individually or collectively), stepwise discriminative analyses were performed (25).

RESULTS

Patients Analyzed

In the group of 103 referred patients, there were 52 females and 51 males, of age range 3–71 years. Figure 1 illustrates the numbers of patients of each sex and age group at the time of the first clinic visit. The average age of these patients at the time of referral was 29 years, which shows that this patient group is predominantly an adult one. For reasons which are not understood, the average age of males at the time of referral was younger (age 24.4 years) than that of females (age 32 years). A review of the charts and histories showed that the average age at the onset of symptoms was 25 years and the age at which the diagnosis of immunodeficiency was made was age 28 years. In 1986, of the 103 patients, 79 were alive, 23 had died, and 1 could not be located.

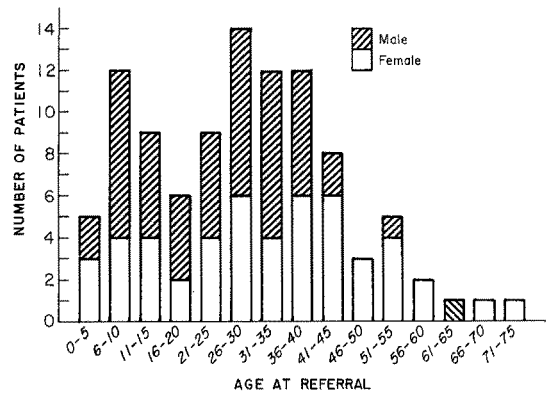

Fig. 1. The age and sex of the 103 CVI patients at the time of the first clinic visit.

Immunologic Parameters and Statistical Analyses

Serum immunoglobulins IgG and IgM varied over wide ranges and serum IgA levels were almost uniformly quite low (Fig. 2 and Table I). These serum levels were determined when patients receiving intramuscular immunoglobulin were at a

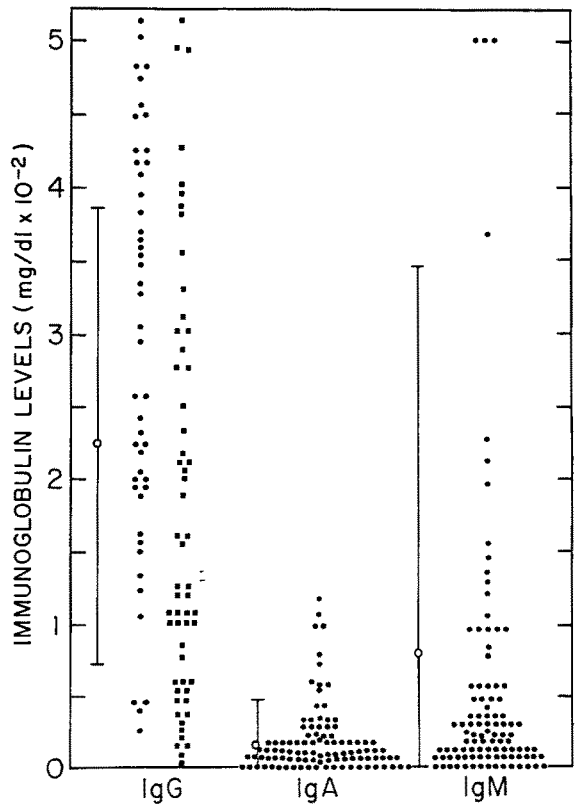

Fig. 2. Serum immunoglobulins IgG, IgA, and IgM are given for the patient group. Patients receiving intramuscular immunoglobulin replacement (●); those on no treatment (■). The mean plus or minus 1 SD for the group is shown. Normal ranges are given in Table I.

Table I. Immunologic Parameters

	Normal range[a]	Patient		Number tested
		Average	Range	
Immunoglobulins				
No immunoglobulin treatment	(mg/dl)	(mg/dl)		
IgG	800–1800	174.4	0–565	57
IgA	90–450	15.3	0–115	57
IgM	80–350	52.3	0–370	57
Intramuscular immunoglobulin treatment				
IgG	800–1800	301	25–570	46
IgA	90–450	14.0	0–126	46
IgM	80–350	40.2	0–645	46
Lymphocyte markers	(%)	(%)		
T cells	65–95	72.7	60–97	95
B cells	3–25	7.7	0–29	95
Leu3/Leu2	1.7 average	1.5	0.45–3.9	50
Lymphocyte proliferative response	(cpm)	(cpm)		
Phytohemagglutinin (PHA)	16,000–29,000	17,873	183–30,354	94
Concanavalin A (Con A)	10,000–24,000	9,739	269–32,298	92
Pokeweed mitogen (PWM)	5,000–13,000	6,742	584–29,982	92
Mixed lymphocyte culture (MLC)	5,000–12,000	8,352	824–19,230	65

[a]Taken as the range including 2 SD above and below the mean for normals, of age range 18–45 years.

trough immunoglobulin value, just prior to a treatment, and no patient was receiving intravenous immunoglobulin at the time the first test was performed. The average serum IgG value for the immunoglobulin treated group was 301 mg/dl, while that for the nontreated group was 174.4 mg/dl. Average values for serum IgA and IgM did not differ for the two groups. Despite the clearly wide range for serum immunoglobulins for the group as a whole, serum IgG and IgA levels for individuals were found to be highly associated with each other ($P = 0.008$).

T-cell abnormalities were found in numerous patients in this group. Forty-four of the 94 patients tested (47%) had subnormal lymphocyte proliferative responses to phytohemagglutinin (PHA) of 16,000 cpm or less (the mean for normal controls minus two standard deviations). Similarly, 54 of 93 patients tested (58%) had an abnormally low response to concanavalin A (Con A) of 10,000 cpm or less, and 44 (45%) had an abnormally low response to pokeweed mitogen (PWM) (5000 cpm or less). Fewer patients of the 65 patients tested (32%) had an abnormally low response on lymphocyte stimulation with allogenic cells. These results are shown graphically in Fig. 3 and are summarized in Table I. As expected, the lymphocyte function parameters were closely correlated with each other; the PHA proliferative response was correlated with the ConA response ($P = 0.0001$),

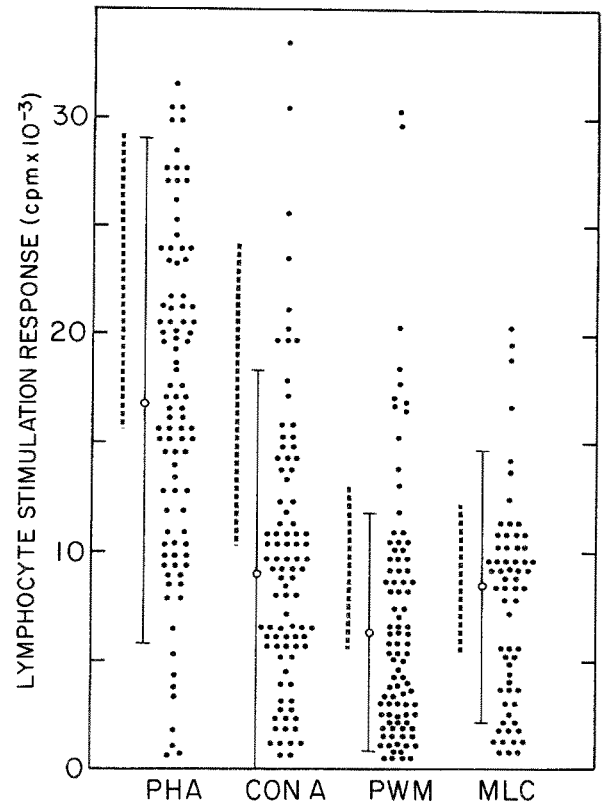

Fig. 3. The levels of lymphocyte stimulation responses to the mitogens phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen and (PWM) allogeneic cells (MLC) are given for the patient group. The mean plus or minus 1 SD for the patient group is shown. Normal ranges are given in Table I and are shown by blocked lines here.

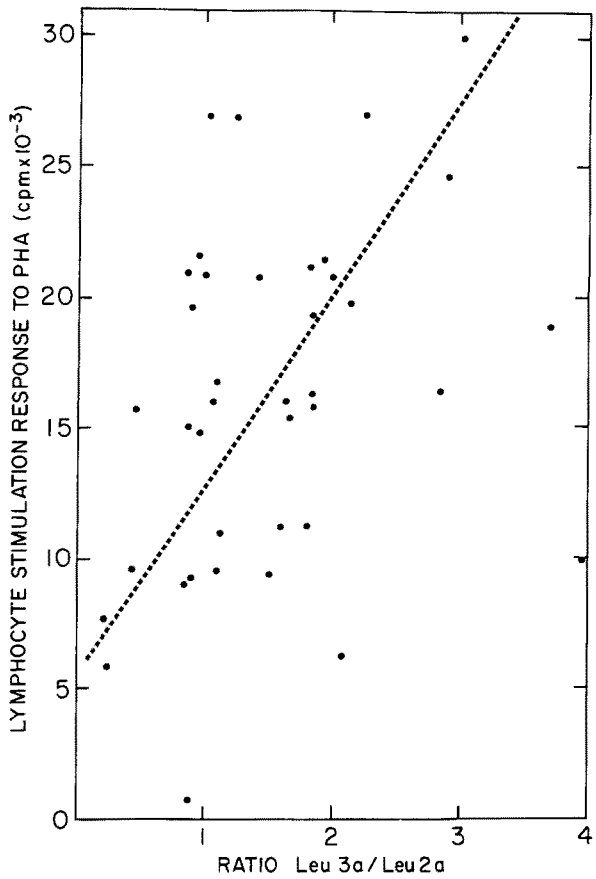

Fig. 4. The lymphocyte stimulation response to PHA (*Y* axis) and the Leu3/Leu2 ratio (*X* axis) are given for the group of patients tested by both these parameters.

PWM ($P = 0.0001$), and mixed lymphocyte culture (MLC) ($P = 0.01$)

Additionally, the Con A lymphocyte response was directly correlated with the serum level of IgG ($P = 0.01$). Interestingly, it was observed that the age at the first visit was inversely associated with lymphocyte proliferation responses to all three mitogens—PHA ($P = -0.03$), Con A ($P = -0.003$), and PWM ($P = -0.01$). Thus, the younger the patient, the better the T-cell immunity, and with age, a decline in T-cell immunity was observed.

Cell surface analysis of T and B cells and T-cell subsets are also summarized in Table I. Averaged lymphocyte surface markers for the total number of T and B cells were in the normal range, but this included 13 patients who had less than 3% B cells. T-cell subset analyses showed that the tested patients as a group had a somewhat reduced ratio of helper- to suppressor-phenotype cells (Leu3/Leu2). Relating these data to other lymphocyte parameters, the Leu3/Leu2 ratio was found to be closely related to the lymphocyte stimulation response to PHA ($r = 0.39209$, $P = 0.006$). This relationship is shown graphically in Fig. 4.

Using stepwise discrimination analyses to discover significant variables, these data were analyzed to determine if any immunologic parameter (individually or collectively) was specifically associated with the development of autoimmune disease, chronic lung disease, malabsorption, hepatitis, or cancer. No clear associations were observed.

Associated Diseases

To assess the diseases which had appeared in members of the group over the period of 13 years, analyses of all charts and records were performed. Table II summarizes the diseases recorded for these patients. Distinct categories of disease complications were observed: (i) acute or recurrent infections, (ii) autoimmunity, (iii) cancer, (iv) hepatitis, (v) malabsorption, and (vi) lung disease. The ages at which these complications developed are shown in graphic form in Fig. 5.

Infectious Disease. In the first category, all of the 103 patients had had recurrent bronchitis, sinusitis, and/or otitis. The majority had also had pneumonia at least once and chronic or recurrent conjunctivitis. By 1986, 23 (22%) had documented chronic lung disease (with or without bronchiectasis) which developed in the wake of repeated pulmonary infections, and 5 patients in this group had developed cor pulmonale. Other areas of infection included joints, bones, skin, parotids, and brain (see Table III).

Table II. Associated Diseases

Illness	Number of patients
Serious or recurrent infections	103
Autoimmunity	23
Chronic lung disease	23
Cancer	15
Hepatitis	13
Malabsorption	9
Splenectomy	7
Other problems	
Ulcerative colitis	2
Schizophrenia	2
Diabetes mellitus	2
Cerebral atrophy	2
Mucocutaneous candidiasis	1
Duodenal ulcer	1
Gastric ulcer	1
Interstitial nephritis	1
Crainial synostosis	1
Crohn's disease	1
Sarcoidosis	1

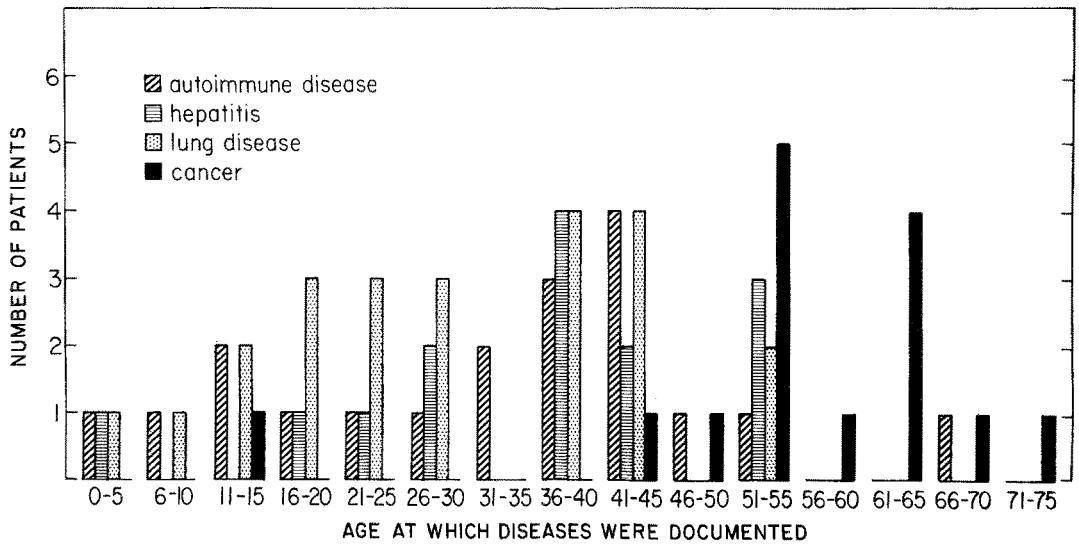

Fig. 5. The patients who developed disease complications are shown graphically to convey the number of patients at various age intervals who were found to have pulmonary disease, autoimmunity, hepatitis, or cancer.

Patients who had had sepsis during various infections were not specifically noted, so precise data on these events are lacking.

Autoimmunity. Twenty patients (20%) had developed one or more autoimmune diseases, and three other patients (of those tested) were found to have anti-IgA antibodies (Table IV). The most common autoimmune disease was idiopathic thrombocytopenia purpura followed by autoimmune hemolytic anemia and rheumatoid arthritis. In all, 23 patients had 29 instances of autoimmunity. In this group there were 16 females and 7 males, and of the 6 patients who had more than one autoimmune disease, 5 were also female. In most cases thrombocytopenia was treated with a short course of prednisone, with a good response in each. (No patients reviewed in this report received intravenous immunoglobulin for this diagnosis since these cases were seen prior to 1981.) Two patients with hemolytic anemia and one patient without lymphoma had autoimmune hemolytic anemia which was relatively refractory to prednisone treatment. A third patient with autoimmune hemolytic anemia was unresponsive to high-dose iv γ-globulin and had a splenectomy, which produced a remission.

Cancer. Another major category of disease for the hypogammaglobulinemic patient was cancer. Nine lymphomas and eight other cancers were diagnosed for 15 patients in this follow-up period (Table V). The types of cancer found in this group of patients have been reported previously in detail (11). Excluding skin cancers, 13 patients had had cancer (13%). Nine patients in the group had developed lymphoma, and three additional patients had adenocarcinomas of various organs. Two female patients who had lymphoma had also had a second

Table III. Infections

	Number of patients
Recurrent bronchitis, sinusitis, otitis	103
Conjunctivitis	90
Pneumonia	80
Hepatitis	13
Meningitis	4
History of severe herpes zoster	2
Pneumocystis carinii	2
Osteomyelitis	1
Suppurative parotitis	1
Recurrent parotitis	1
Septic arthritis	1
Pyoderma gangrenosum	1

Table IV. Autoimmunity

Number of cases	
6	Idiopathic thrombocytopenia purpura
5	Autoimmune hemolytic anemia
4	Rheumatoid arthritis
3	Juvenile rheumatoid arthritis
3	Anti-IgA antibody
2	Sicca syndrome
1	Primary biliary cirrhosis
1	Systemic lupus erythematosus
1	Alopecia totalis
1	Pernicious anemia
1	Hyperthyroid disease
29	Shared by 23 patients (16 females, 7 males)

Table V. Cancers[a]

	Number of cases
Non-Hodgkin's lymphoma	8
Waldenstrom's macroglobulinemia, progressing to lymphoma	1
Adenocarcinoma of stomach	2
Adenocarcinoma of ovary	1
Adenocarcinoma of colon	1
Squamous-cell carcinoma of vagina	1
Squamous-cell carcinoma of cervix	1
Basal-cell epithelioma	1
Squamous-cell carcinoma of skin	1
	17 cancers shared by 15 patients

[a]For more details see Ref. 11.

cancer of epithelial origin—one of the cervix and one of the vagina.

Hepatitis. Over the 13-year observation period, 13 patients (13%) had developed hepatitis (Table VI). In most instances, the cause was believed to non-A, non-B hepatitis resulting from prior plasma infusions. Two patients developed non-A, non-B hepatitis as a result of treatment with an experimental intravenous immunoglobulin; one recovered and one has chronic disease. Two patients had hepatitis B and both recovered. Four patients in the entire group recovered completely, four patients are alive with continued liver disease, three died of other problems, and two died of liver failure.

Malabsorption. Significant malabsorption was documented in nine patients, six females and three males. In these cases, weight loss and reduced serum carotene and folic acid were found, and in five cases, increased fat was detected in the stool. A small intestinal biopsy showing flattened villi was found in the four cases in which a biopsy was performed. Two patients also had nodular lymphoid hyperplasia. All patients in this group had other disease complications (autoimmune disease and/or respiratory insufficiency) and six of these patients died (Table VII). Giardiasis was diagnosed in none of these cases but treatment with metronidazole was given in all cases, with a detectable improvement in malabsorption seen in only one case.

Outcome of Splenectomy

Seven (six males, one female) patients in the group had had a splenectomy. To determine whether this procedure resulted in specific morbidity or mortality, data were collected for this group. The reasons for the splenectomy in each case and the outcome are given in Table VIII. Four patients had an uncomplicated operative procedure and three other patients had significant postoperative difficulties. Six of the seven had long-term survival but one died 12 months postsplenectomy after further complications of pulmonary lymphoid interstitial infiltrates and steroid use which resulted in a fatal pneumocystis carinii infection. (Four of the five patients now alive remain on antibiotic prophylaxis at all times for chronic respiratory tract infections.)

Immunologic Defects in Other Family Members

For approximately one-half of the 103 patients, the sera of other family members had been tested for an quantitative lack of one or more immunoglobulins. All families with more than one immunodeficient individual are shown in Fig. 6. In some

Table VI. Hepatitis

Patient			
Age[a]	Sex	Type of hepatitis	Outcome
4	M	Unknown	Chronic hepatitis, died of other problems at age 16
21	F	Non-A, non-B, from plasma?	Chronic hepatitis, died of other problems
25	M	Non-A, non-B, from plasma?	Chronic hepatitis
25	M	Hepatitis B, from plasma?	Recovered
30	F	Non-A, non-B, from plasma?	Recovered
33	M	Non-A, non-B, from plasma?	Died at age 38, liver failure
34	M	Non-A, non-B, from plasma?	Died at age 38, liver failure
34	M	Non-A, non-B, from experimental IVGG	Recovered
35	F	Unknown	Chronic, low grade
35	M	Hepatitis B, source?	Recovered
45	F	Primary biliary cirrhosis	Chronic hepatitis, died of other problems at age 61
48	M	Non-A, non-B, from plasma?	Chronic hepatitis
53	F	Non-A, non-B, from experimental IVGG	Chronic hepatitis

[a]Age (years) at which hepatitis developed.

Table VII. Malabsorption

Age (years)	Sex	Other conditions	Outcome
10	M	Chronic lung disease, bronchiectasis	Died of respiratory insufficiency and malnutrition
21	M	Mucocutaneous candidiasis, eosophageal stricture, respiratory insufficiency	Died of malnutrition and respiratory insufficiency
22	F	History of ITP, hemolytic anemia, bone marrow aplasia, ulcerative colitis, colectomy, non-A, non-B hepatitis	Died of bone marrow aplasia, malnutrition
30	F	Leukopenia, Sicca syndrome, history of hemolytic anemia, nodular lymphoid hyperplasia	Alive with malnutrition
40	M	Chronic ITP	Alive, on prednisone
43	F	Chronic restrictive lung disease	Died of respiratory insufficiency and malnutrition
43	F	Recurrent pneumonia, anemia, neutropenia	Died of respiratory insufficiency
43	F	Recurrent pneumonia, nodular lymphoid hyperplasia, jejunal lymphoma, cancer of vagina	Alive, post radiation to vagina
65	F	Hemolytic anemia, lymphoma	Died of lymphoma

families, extensive testing was performed; in others, only parents or children were tested. In general, more extensive testing was done where the clinical history suggested further affected members. Among the group of 103 patients, two families contributed 5 hypogammaglobulinemic individuals. In one family, two sisters were affected; in another, the father and two daughters were hypogammaglobulinemic. In one additional family, one male patient and his aunt (the latter not included as part of this patient group since she had not attended the clinic) had hypogammaglobulinemia. More commonly, in six additional families, one or more other family members (for a total of 11 relatives) had selective IgA deficiency. (In these cases, IgA was not detected in the serum by radioimmune assay).

Immunoglobulin Treatment

By 1986, 51 of the original patients were receiving intravenous immunoglobulin, either in their own community or at the Mount Sinai Medical Center; 10 patients had received intravenous immunoglobulin but had died prior to 1986. An additional 22 patients were receiving intramuscular treatment (10 patients on intramuscular immunoglobulin had died prior to 1986); 2 patients in 1986 were receiving plasma and 5 patients in the group were on no immunoglobulin treatment. Whether or not an individual patient was receiving intravenous immunoglobulin or not was not always based upon the severity of the immune defect, but upon physician or patient reference or insurance factors.

Mortality

Twenty-three of the originally referred group of 103 individuals had died during the follow-up period of 13 years, for an overall mortality of 22%. There were 15 females and 8 males in this group (Table IX and Fig. 7). The average age of females at the time of death was older (55.4 years) than the average age

Table VIII. Reasons for Splenectomy and Outcome

Age at splenectomy (years)	Sex	Reason	Operative complications	Outcome
14	M	Hypersplenism	None	Died of lymphoid pulmonary infiltrates 12 months later
18	F	Idiopathic thrombocytopenia purpura	None—pneumococcal sepsis 1 year later	Alive and well 4 years later
35	M	Presumed lymphoma	None	Alive and well 14 years later
36	M	Autoimmune hemolytic anemia	Draining fistula to back, closed in 2 years	Alive and well 6 years later
38	M	Presumed lymphoma	None	Alive and well 9 years later
40	M	Abcesses in spleen (*E. coli* + bacteroides)	Postoperative fever due to collection of fluid; drainage performed successfully	Alive and well 8 years later
55	M	Uncertain	Pneumococcal sepsis 2 years after splenectomy	Died at age 63 of lymphoma

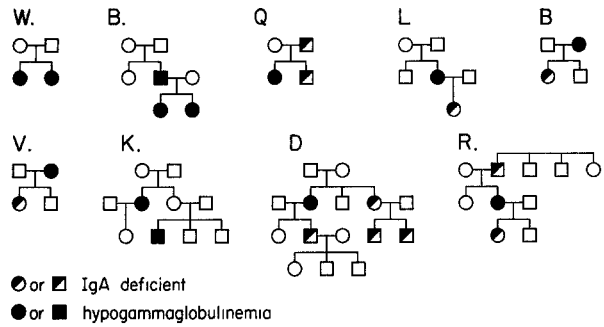

Fig. 6. Families in which other members were found to be immunodeficient are shown. The immunodeficient individuals (hypogammaglobulinemia or IgA deficiency) are indicated by shaded areas.

Fig. 7. The age and sex of the patients who died.

of males (28.8 years). The major single case of death was cancer (seven cases). Of patients over age 50 years who died, five of seven died of cancer. Under the age of 40 years, one patient of nine died of cancer. Another important cause of death was chronic pulmonary infections and resulting cor pulmonale (five patients). For reasons which are not understood, the average age for females at death was 55 years, and that for males was 29 years.

DISCUSSION

Common variable immunodeficiency is an intriguing immunodeficiency disorder because of its widely diverse form of presentation, varied clinical manifestations, and range of immunologic abnormalities. The data collected here reinforce the generally presented spectrum of illnesses which have been reported in association with hypogammaglobulinemia—chronic or recurrent bacterial infections, autoimmune disease, malabsorption, risk of hepatitis due to infusions of blood products, and cancer. Although CVI is considered a primary (congenital) immunodeficiency disease, most individuals who are diagnosed with this disorder are adult. In a previous report of 50 cases in 1976, the average age at diagnosis was 41.9 years, while the average age at onset of symptoms was a decade earlier (30.7 years) (6). In the group of patients presented here, the average age at diagnosis was 28 years, and that at onset of symptoms was 25 years. Thus, the patients with hypogammaglobulinemia studied here were younger overall than those previously reported, and the average length of time for diagnosis was 3 years. Possibly the increased awareness of this immunodeficiency disease over the decade since the appearance of the previous report has permitted earlier diagnosis.

Earlier diagnosis and institution of treatment should produce a reduced mortality rate in this disease. We observed a 22% mortality rate over a 13-year period, which was equivalent to 750 patient years or 7.3 years per patient. Hermans found a 22% mortality for an average observation period of 4.2 years per patient (6). Thus, the mortality rate for the current study was effectively reduced since the study time was longer. Nonetheless, it seems important to point out the substantial mortality rate in this disease. The high rate of death in our study was due partly to the prevalence of lymphomas (particularly in older females) and the high incidence of cancer overall (13%) (report published separately;

Table IX. Causes of Death

Age (years)	Sex	Cause of death
8	M	Cor pulmonale
11	M	Respiratory insufficiency, malnutrition
13	F	Lymphoma
15	M	Pulmonary lymphoid interstial infiltrates
21	M	Malabsorption, mucocutaneous candidiasis, esophogeal stricture, chronic lung disease
22	F	Bone marrow aplasia, malabsorption
38	F	Fatal measles infection
38	M	Chronic non-A, non-B hepatitis, pancreatitis
38	M	Chronic non-A, non-B hepatitis
41	M	Cor pulmonale, respiratory insufficiency
42	F	Suicide
43	F	Carcinoma of stomach
44	F	Recurrent pneumonia, cor pulmonale
44	F	Recurrent pneumonia, malabsorption, malnutrition
45	F	Restrictive lung disease, malabsorption
47	F	Viral meningitis → paraplegia, suicide
57	F	Recurrent pneumonia, cor pulmonale
58	F	Lymphoma, IgM macroglobulinemia
61	F	Chronic biliary cirrhosis, arteriosclerotic heart disease
65	F	Carcinoma of stomach
66	M	Lymphoma, Waldenstrom's macroglobulinemia
66	F	Lymphoma
71	F	Lymphoma

Ref. 11). Prior studies have shown that cancer developed in 6.4% of CVI patients in Great Britain (12) and in 15% of CVI patients in the United States (6). In both of the latter analyses, gastric cancer was more common than in our group, in which lymphoma was the predominant cancer. Another important cause of death was respiratory insufficiency and cor pulmonale. (In one patient who has more recently developed this complication, a cardiopulmonary transplant was successfully performed in May 1987; this patient is now doing well.)

It is interesting that the younger patients referred were more typically male and that male patients overall had an earlier death than the females observed here. It is entirely possible that the natural history of hypogammaglobulinemia in males differs from that in females and that this is also connected to the finding that females in the older age group developed lymphoma. In fact, in our group, there were fewer older males (see Fig. 1).

In the current study, the majority of autoimmune disease occurred in females. Sixteen females had 21 instances of autoimmunity, while 7 males had 8 instances of autoimmunity. Thus, of the six patients who had had two autoimmune diseases, five were females. This association has not previously been made.

We also found that T-cell function tests were closely related to age; thus, older patients appear to have more impaired cellular immunity. A decline in T-cell responses to mitogens has also been found for normal subjects, particularly individuals over age 65 years (26). The normal controls used here were of the age range 18–45 years and no attempt was made to match the ages of controls to those of the patients. Thus it remains uncertain whether this relative decline in T-cell immunity is comparable to that seen in healthy controls. We previously showed that patients who developed cancer (and were in fact older) had poorer T-cell functions (11). Whether or not there is an association between these observations is not known. Previous analyses of hypogammaglobulinemic patients have given different estimates for the percentage of individuals with T-cell dysfunction; since we now know that the age of the patient is an important factor, this discrepancy may be more easily understood.

These data reflect, for the most part, the course of this disease for a patient population treated with intramuscular immunoglobulin and, in a few cases, long-term plasma infusions. Intravenous immunoglobulin was introduced to 25 members of this group as early as 1980, but most of the 51 individuals who now receive intravenous immunoglobulin did not start this treatment until between 1982 and 1986. Thus, the illnesses experienced by the group and recorded here do not reflect whatever impact intravenous immunoglobulin may have on the clinical manifestation of this disease. In particular, one would hope that a reduction of chronic lung disease and cor pulmonale will occur and that fewer cases of non-A, non-B hepatitis (usually from plasma) will develop. In our group, two individuals developed non-A, non-B hepatitis from the use of an experimental intravenous immunoglobulin (27); however, no cases have been reported in patients treated with licensed intravenous immunoglobulins.

Data from splenectomized patients were compiled because the question of the outcome of splenectomy in hypogammaglobulinemic has been difficult to answer. In seven patients in this group, splenectomy had been, or was later, performed. Of the seven splenectomized patients, two had immediate operative complications, and another had pneumococcal sepsis 1 year later. However, six of the seven patients experienced a resolution of the problem for which splenectomy was performed and had a long-term survival. Each of these patients remains on penicillin prophylaxis (or equivalent).

Genetic associations of immunoglobulin deficiencies are clearly demonstrable in a small percentage of cases. In the group described here, six individuals had hypogammaglobulinemic relatives (5% of the group) and six others had one or more IgA-deficient family members. Thus, 11% of the hypogammaglobulinemic patients can be said to have a definite genetic immunologic disease. While this figure may underestimate the true incidence of affected family members (since not all family members were tested), it is clear that most hypogammaglobulinemic individuals do not have affected family members. We have found these data useful in discussing family planning with young adults who have hypogammaglobulinemia.

Because of the heterogeneity of the patients who have hypogammaglobulinemia, it is assumed that this disease includes a spectrum of different molecular defects affecting primarily B cells. Since other family members are not usually affected, and the disease can become manifest in the second, third, or fourth decade of life, it is also tempting to hypothesize that some individuals in this group may have received a later injury to B or T cells which renders them permanently immunoincompetent.

For example, hypogammaglobulinemia may follow acute infectious mononucleosis (28), and in one patient in our group mononucleosis was known to precede the diagnosis of hypogammaglobulinemia. Specific T-cell suppression of otherwise normal B cells (by an abnormality which is not understood) has been demonstrated in a rare patient with hypogammaglobulinemia (29); in the group described here, 50 patients had been studied for this defect and it was documented in 4 cases (30, 31). However, it is not known how such an abnormality might arise.

In summary, this report compiles the clinical and immunologic data for a large group of hypogammaglobulinemic patients observed over a period of 750 patients years, in order to provide information about the spectrum and frequency of illness and the range of immunologic abnormalities which exist in this disease.

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