IMMUNOLOGY

Common Variable Immunodeficiency: Experience in Puerto Rico

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Common variable immunodeficiency (CVI) is a primary immunodeficiency characterized by hypogammaglobulinemia and an increased susceptibility to infections. The degree and the type of deficiency of serum immunoglobulins, as well as, the clinical course vary from patient to patient, hence the term "variable". The aim of this report is to describe the clinical characteristics and the response to gammaglobulin therapy of a group of patients with CVI followed at the University Hospital of the Puerto Rico Medical Center. To our knowledge, no data on primary immunodeficiencies in Puerto Rico has been reported in the literature. The study group exhibits specific characteristics as compared to other reported series.

Key words: Common variable immunodeficiency; Hypogammaglobulinemia, Immunoglobulin therapy.

The primary immunodeficiency diseases are a diverse group of disorders, mostly of genetic origin, in which one or several components of the immune system are altered (1). The net result is failure to mount an appropriate and effective immune response against pathogens, thus leading to infections. Approximately one hundred different types of these conditions have been described, and the overall prevalence of all types in Europe is estimated to be as high as 1:500, while the other 1:500 remain undiagnosed (2,3).

Common variable immunodeficiency (CVI) accounts for over 50% of the primary immunodeficiencies cases encountered clinically. The term variable denotes the fact that the immunoglobulin levels are not uniformly decreased and that the clinical manifestations are diverse. Its onset may occur at any age, but frequently it is diagnosed after puberty.

Besides infections (usually in the sinuses and the respiratory tract), CVI is associated with several autoimmune conditions, such as rheumatoid arthritis, idiopathic thrombocytopenia, hemolytic anemia, neutropenia and pernicious anemia. Gastrointestinal manifestations include a myriad of conditions, mostly malabsorption syndromes and infectious diarrhea. The mechanism(s) explaining this type of immunodeficiency remains unknown. Defects in transcriptional activation of switch regions, excessive CD8 T cells interferon gamma production, suboptimal T-B cell interactions through the CD40 ligand and transcription factor deficiencies have been suggested, among other etiologies (4).

The aim of this report is to describe the clinical characteristics and the response to therapy with intravenous gammaglobulin of a group of patients with CVI followed at the University Hospital at the Puerto Rico Medical Center.

Methods

The study group comprised patients referred by primary physicians and subspecialists for evaluation of suspected immunological compromise to the Immunology Clinic of the University Hospital. Of the total population of patients with CVI identified at the clinic, a group of twenty patients was entered in the study and followed over a three-year period. Those patients under 2 years of age and with an underlying cause for hypogammaglobulinemia were excluded.

All patients underwent a complete history and physical examination using a standard format at the initial visit. Baseline laboratory tests were performed through a uniform protocol, including complete blood count, liver and renal function tests. In addition, patients had an immunological evaluation consisting of: quantitative immunoglobulin levels (two separate samples), lymphocyte profile (T,

B, CD4, CD8 and natural killer cells), CH50, PCR-HIV and HCV, ANA and antibody profiles, as indicated.

Protocol. After the screening for CVI, informed consent was obtained for data gathering and prior to initiation of IV gammaglobulin therapy. Participating patients received

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IV gammaglobulin therapy every four weeks using 400mg/kg, as the standard dose. Pre-infusion immunoglobulin levels were taken at 3, 6, 12, 18, 24, 30 and 36 months of treatment.

Gammagard (Baxter) Solvent/Detergent Treated Human gammaglobulin preparation was administered to all patients, except in one case in which the same preparation was used but was not solvent/detergent treated. All patients received pre-medication with steroids.

Statistical analysis. Continuous variables that were normally distributed were expressed as mean standard deviations (±SD). The one sample T test was used to determine differences between the normal values of immunological parameters and the values of the patient group. The repeated measures analysis of variance was applied to express the differences in improvement in the trough IgG level within the measured intervals.

Results

As shown in Figures 1 and 2, the majority of the patients were females (60%) and most of the patients were diagnosed between the age ranges of 15 to 25 years. A family history of immunodeficiencies was present in only five cases.

Table 1 describes the major presenting symptoms. As seen, infections were the most common manifestation of the disease. Allergies and bronchial asthma were common, followed by autoimmune conditions. Only one patient in the study group had IgA deficiency prior to the diagnosis of CVI.

As shown in Table 2, sinusitis was the most frequent infectious presentation. Within the study period of three years, various clinical conditions were identified in the patient group, including autoimmune entities and *H. pylori* infestation.

Figure 1. Gender distribution of patients in the study

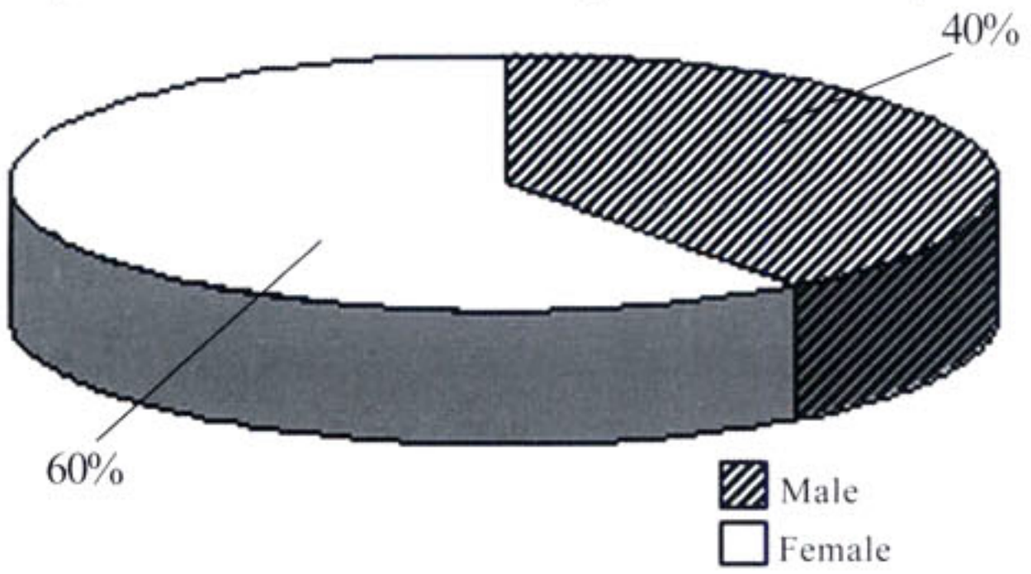

Figure 2. Age distribution (in years) of patients in the study

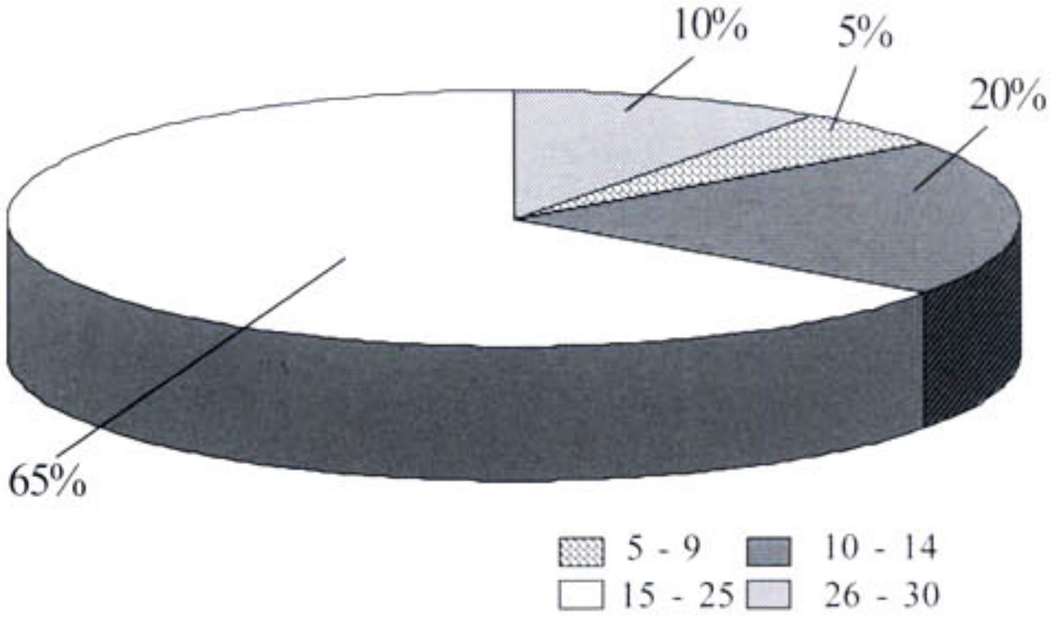

Table 1. Presenting Symptoms of Patients with CVI

Symptoms – Diagnoses	# of cases
• Infections	20
• Allergies	13
• Bronchial asthma	10
• Malabsorption syndromes	9
• ITP	5
• Aseptic arthritis	3
• Hypothyroidism	2
• Bronchiectasis	2
• Rheumatoid arthritis	2
• Crohn's disease	1
• IgA deficiency	1

Table 2. Infections in CVI Patients

Type of infection	# of cases
• Sinusitis	.20
• Otitis	15
• Bronchopneumonia	14
• Infectious diarrhea	9

One interesting aspect of the population studied was the prevalence of antibodies directed against different cells and tissues, with the predominance of anti-platelet antibodies (Table 4). All of the three major immunoglobulins: IgG, IgA and IgM were decreased in these patients to a variable degree. As illustrated in Figure 3, the baseline IgG levels were significantly low, not exceeding a mean value of 64.7 mg./dL.

Figure 3. Baseline immunoglobulin G levels of study group

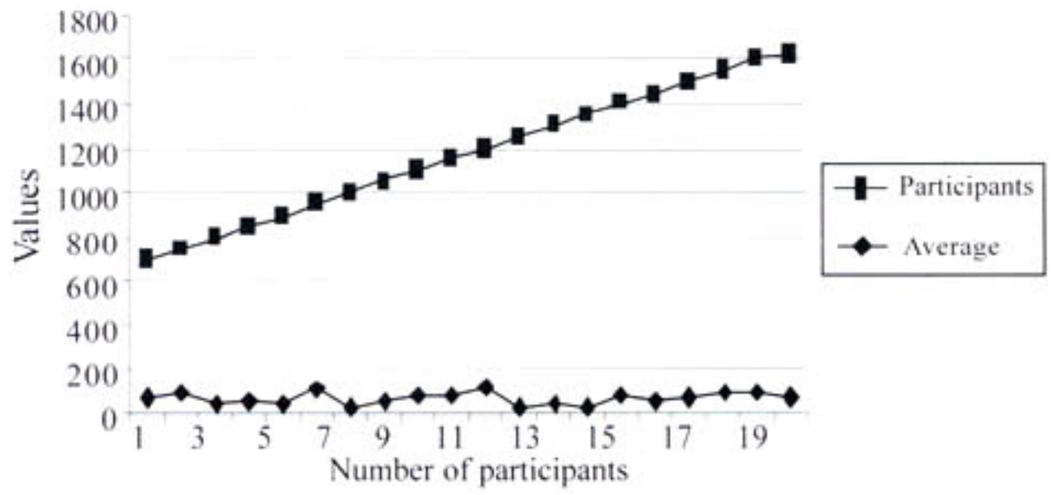

Figure 4. Immunoglobulin G Pre-infusion Levels Within the Time Frame of the Study

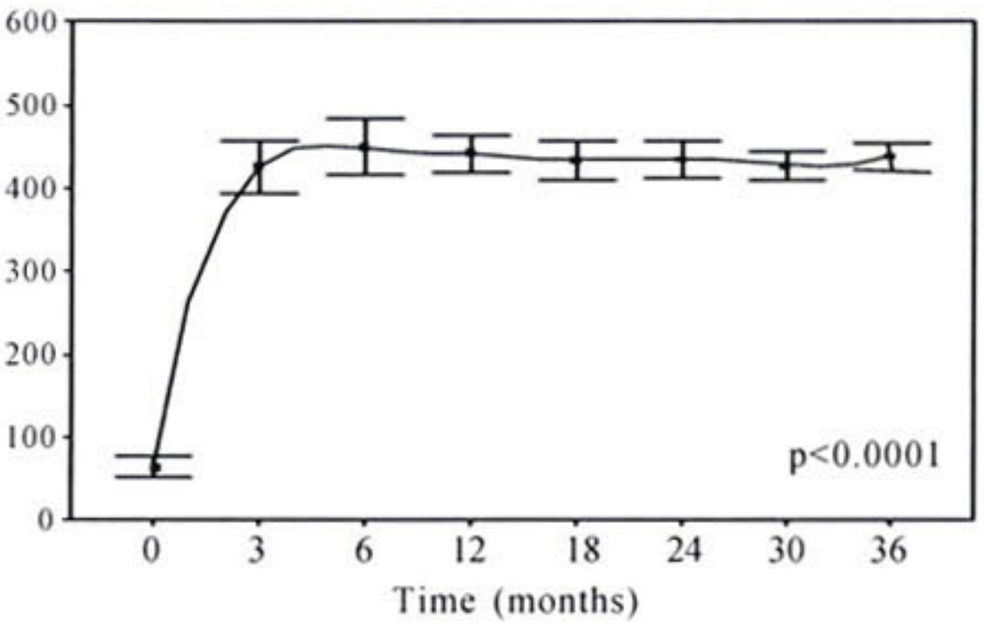

Table 5 describes the results of the lymphocyte analysis in the study group. All patients had T, B, CD4, CD8 and NK cells within the normal ranges for the given parameter. The IgG pre-infusion levels at the intervals measured did not show statistically significant variations within the time frame of the study (baseline to three years), as presented in Figure 4. After one year of IV gammaglobulin therapy, there was a significant reduction in episodes of pneumonia, as compared to baseline. Patients tolerated the therapeutic regimen reasonably well, as there were no major complications reported. Table 6 describes the minor side effects seen, headache being the most frequent.

In the patient identified with chronic active hepatitis by HCV, this condition was related to the IV gammaglobulin recall that occurred in 1994, and was the only one who received the non-solvent/detergent treated product.

Table 3. Medical Conditions Identified in CVI Patients Throughout Study Period

Condition	# of cases
• ITP	2
• Alopecia totalis	1
• Autoimmune hemolytic anemia	1
• Pernicious anemia	1
• Neutropenia	1
• *H. pylori*	4

Table 4. Autoantibody Profile in CVI Patients

Antibod	# cases
• ANA	5
• Antiplatelet	7
• Anti-parietal cell	1
• Anti-thyroid	2
• Anti-intrinsic factor	1

Table 5. Baseline Immunologic Parameters in Patients Studied

Item	Baseline value % (mean ± SD)	Normal ranges (%)	P value
T cells	70.8	60 – 80	n. s.
CD4	43.7	34 – 58	n. s.
CD8	29.1	20 – 36	n. s.
B lymphocyte	11.3	6 – 19	n. s.
Natural killer	10.7	7 – 31	n. s

Table 6. Side Effects Reported by Patients After IV Ig Therapy

Finding	# of Patients
Headache	18
Body aches	15
Nausea – vomiting	7
Fever	4
Chronic active hepatitis (HCV)	1

Discussion

The group of patients presented in this study shows particular characteristics, as compared to other published series. A predominance of female to male patients was observed in contrast to the series reported by Cunningham-Rundles, which had an equal gender representation (5). As reported in other series, infection was the most frequent presentation in the study group. However, the predominance of respiratory conditions, allergies and bronchial asthma observed in the study group has not been consistently reported in other patient groups. This factor may be related to the overall high prevalence of asthma in Puerto Rico (6).

Another peculiar aspect of the group studied was the significantly high frequency of autoimmune manifestations (47%), as compared to a reported frequency of 26% in other reported series (7). It is interesting to note that autoimmune phenomena in patients with CVI have been associated to granuloma formation in other reported series, yet that relationship was not seen in the patients studied by us (8). Immune thrombocytopenic purpura was the most common autoimmune manifestation observed in the group of patients studied, whereas autoimmune hemolytic anemia has been the most frequently reported one by other authors. Gastrointestinal tract involvement was found in 51% of the studied patients, compared to 17% in other reported groups (9).

Although the just mentioned differences might indicate peculiarities of CVI in Puerto Rico, it must be remembered that our study group was small. No attempt was made in

this study to identify subsets of CVI patients in terms of defective T cell function, as no proliferative in vitro studies, cytokine analysis or apoptosis indexes were assessed. However, none of our patients had lymphopenia.

It has been previously described in the medical literature that more than half of CVI patients present abnormalities of T cell activation and a deficient secretion of interferon gamma and interleukins 2, 4, 5 and 10 (10,11). All our patients had B cell positive agammaglobulinemia and absence of underlying conditions to explain the low antibody production, so the diagnosis of CVI was uniformly established.

Further study of T cell function is advisable in this group of patients to determine if it is related in anyway to the high frequency of autoimmune conditions observed. An extension of the study population is in order to assess if the tendencies observed in the group of patients studied holds. An ongoing surveillance study is in effect as lower serum IgG levels at the time of diagnosis have been associated to an earlier mortality.

Resumen

La inmunodeficiencia común variable es una de las inmunodeficiencias primarias más comunes. El propósito de este estudio ha sido el analizar las características clínicas y la respuesta a la terapia con inmunoglobulina intravenosa de un grupo de pacientes a los que se hizo el diagnóstico de inmunodeficiencia común variable en el Hospital Universitario del Centro Médico de Puerto Rico. Los datos obtenidos se compararon con varias series de pacientes informados en otros lugares. No tenemos conocimiento de que este tema haya sido presentado ni informado en la literatura médica de nuestro país anteriormente. En el grupo de pacientes estudiados, se observaron diversas presentaciones clínicas entre las que se incluyen: desórdenes alérgicos, fenómenos de autoinmunidad y procesos infecciosos. En general, los pacientes estudiados mostraron características clínicas similares a las observadas en otras series informadas en la literatura médica revisada, a excepción de una mayor incidencia de alergias y la presencia de autoanticuerpos. Estos hallazgos ameritan ser corroborados mediante el examen futuro de una muestra de pacientes más signiticativa.

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