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Clinical and laboratory aspects of common variable immunodeficiency

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ABSTRACT

Common variable immunodeficiency (CVID) is an immunological disorder characterized by defective antibody production, recurrent infections, most notably of the respiratory tract, autoimmune phenomena and cancer. Some CVID patients may also present disturbances of the cellular immune response such as a decrease in the number and proportion of different lymphocyte populations, diminished lymphoproliferative response to mitogens and antigens, altered production of cytokines, and deficient expression of cell-surface molecules. Most Brazilian CVID patients included in this study show a decrease in T and B lymphocyte counts in the peripheral blood. Furthermore, their lymphocytes are more susceptible to apoptosis following activation than normal individuals, and they have a decrease in the expression of activation molecules like CD25, CD69, CD40L and CD70. Moreover, they show a decreased synthesis of IL-4 and IL-5 in comparison with normal individuals. The increase in susceptibility to apoptosis following activation, may also be responsible for the decrease in the expression of activation molecules and CD40L, decrease in Th2 cytokines synthesis, and in the number of T and B circulating cells. In this study we discuss some of these immunological disturbances correlating them to the patients' clinical features and comparing our patients' findings to the literature.

Key words: immunodeficiency, humans, antibody, cytokines, clinical features.

INTRODUCTION

Common Variable Immunodeficiency (CVID) is one of the most frequent primary immunodeficiencies diagnosed in humans, its incidence will vary from 1 to 10,000 to 1 to 2,000,000 people depending on the study (Tiller and Liddle 2000, Cunningham-Rundles 2001, Kainulainen et al. 2001, Sneller 2001). Interestingly, the disease is very rare among Asians; the incidence in Japan is estimated at 1 in every 2 million inhabitants. The first case of CVID was described in 1953 by Janeway and colleagues (Janeway et al. 1953). They described a 39-year-old female with bronchiectasis, recurrent pulmonary infections, sinusitis, otitis and one episode of meningitis due to *Haemophilus influenzae*. Although an electrophoresis of serum proteins was not performed hypogammaglobulinemia was the presumed diagnosis due to the lack of isohemagglutinins in the serum and the remission of the recurrent infection

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after the institution of gammaglobulin replacement. Other cases were described soon after, in 1955 Rosecan and colleagues reported two male patients with hypogammaglobulinemia and splenomegaly; and Wall and Sasla described two adult patients with hypogammaglobulinemia and recurrent bacterial infections (Wall and Sasla 1955). In 1961, Wollheim described several women with recurrent infections associated with hypogammaglobulinemia in two regions in Sweden, at the time he suggested a hereditary nature to the disease (Wollheim 1961). In 1967, Kirkpatrick and Schimke described patients with ''familiar'' hypogammaglobulinemia and very low levels of IgM (Kirkpatrick and Schimke 1967). In 1968 Kamin and colleagues observed that T cells from some patients with ''familiar'' hypogammaglobulinemia proliferated poorly when stimulated *in vitro* with phytohemagglutinin (PHA), suggesting for the first time that besides the low levels of antibodies other immunological disorder could be associated with the disease, and even be responsible for the defective humoral response (Kamin et al. 1968). In 1971, Cooper and collaborators described patients with hypogammaglobulinemia and normal levels of B lymphocytes carrying surface immunoglobulins in the peripheral blood (Cooper et al. 1971). Furthermore, these individuals displayed normal germinal center formation after antigenic stimulation. The authors suggested then that the disease could be caused by a defect in the terminal differentiation of B lymphocytes into plasma cells. They were also the first to suggest that the variable nature of the patients described in the literature was an integral part of the characteristics of the disease thus implying the designation of variable hypogammaglobulinemia. The distinction of first using the name ''Common variable Immunodeficiency'' in a widely published journal, however, belongs to Douglas and Geha, independently (Douglas et al. 1974, Geha et al. 1974).

Today, it is known that the disease may be caused by multiple gene defects, many of which have been described and will be discussed bellow. The clinical spectrum of CVID is broad, and it may present at any age, from childhood through late adult life. Most of the patients have a history of recurrent respiratory tract infections, but it may include autoimmune phenomena, bowel infections and granulomatous disease. CVID patients also have an increased incidence of malignancies. Clinical and laboratory criteria have been established for the diagnosis of CVID by the Pan-American Group on Immunodeficiencies (PAGID), the European Society for Immunodeficiencies (ESID) and the Clinical Immunology Committee of the International Union of Immmunological Societies (IUIS). These criteria may be found on each society's home page, http://www.clinimmsoc.org/pagid/, http://www.esid.org/, http://www.iuisonline.org/, respectively. It is important to note that the diagnosis of CVID, specially during the first years of life can only be made after other immunodeficiencies such as hyper-IgM syndrome (Kaneko et al. 2000, D'Addio et al. 2001, Durandy 2001), X-linked agammaglobulinemia (Van der Hilst et al. 2002) and X-linked lymphoproliferative syndrome (Aghamohammadi et al. 2003, Elenitoba-Johnson and Jaffe 1997, Fontan Casariego 2001, Morra et al. 2001, Soresina et al. 2002) have been excluded. In adult patients, it is important to rule out lymphomas and Good's syndrome, most notably when hypogammaglobulinemia is diagnosed in females above the age of 40 (Gompels et al. 2003, Belmonte et al. 1989, Akai et al. 1996). In our service, patients have been diagnosed with CVID when they present clinically relevant immunodeficiency signs and symptoms and serum IgG and IgA levels two standard deviations bellow the average for their age, if serum levels were normal before the age of two. Additional criteria include low or absent isohemagglutinins, poor antibody response to vaccines and when other causes for hypogammaglobulinemia were ruled out. Patients with a reduction in IgG levels (two standard deviations bellow de average for the age group) but not in IgA levels that fulfill the other conditions are considered with CVID whenever they present clinical

symptoms and signs compatible with this immunodeficiency (see above).

CVID patients generally have a normal number of T and B lymphocytes in the peripheral blood; these are more often than not equipped with their surface antigen receptors and are capable of recognizing antigen in a first encounter. However, B cells from these patients become incapable of differentiating in plasma cells *in vivo* (Cunningham-Rundles and Bodian 1999, Stevens et al. 1980), resulting in hypogammaglobulinemia. This defect on B cell maturation results in susceptibility to recurrent infections of the respiratory tract mostly by *Haemophilus influenza* or *Streptococcus pneumoniae*, otitis, sinusitis and intestinal infections by *Giardia lamblia*, *Campylobacter jejuni* and or *Candida albicans*. The frequent pulmonary infections may lead to bronchiectasis and chronic obstructive pulmonary disease (Kainulainen et al. 2001, Sneller 2001, Cunningham-Rundles and Bodian 1999, Abonia and Castells 2002, Hausser et al. 1883, Martinez Garcia et al. 2001).

Diseases with similar characteristics have also been shown to appear spontaneously in animals such as the horse, the llama and even dogs (Flaminio et al. 2002, Davis et al. 2000, Lobetti 2000, Day et al. 1997). Hypogammaglobulinemia with decreased B cell memory, hallmarks of CVID, was induced in transgenic mice through the inactivation of a specific gene, the X-Box protein 1, or XBP-1 (Reimold et al. 2001). Although the animal models, both spontaneous and induced, are important and their study may yield significant information regarding human disease, due to the variable nature of this immunodeficiency and the multiple genes that may cause, studies in humans are pivotal to the understanding of this complex disease, to a better definition of patient subsets and consequent better management of these individuals.

All data shown here were obtained from protocols approved by the Internal Review Board at the Biomedical Sciences Institute and ''Hospital das Clínicas'', University of São Paulo.

B LYMPHOCYTES IN CVID

Patients with CVID may have normal or decreased levels of B cells in the periphery (Caballero et al. 1984, Farrant 1991, Farrant et al. 1989, 1985, 1994). In some of the patients with normal levels of B cells these will have a mature phenotype bearing surface immunoglobulins, others will only possess cells with an immature phenotype characterized by an enlarged volume, restricted usage of V_H families and decreased mutating capacity at the hypervariable regions of the immunoglobulin genes (Braun et al. 1992a, b, 1991).

Schwartz and colleagues identified a group of patients with a distinctive defect on the transduction signals necessary for differentiation into plasma cells. Using Sendai virus loaded on vesicles containing plasma membrane (PM) from normal B cells, they observed a group of patients with a deficit in phosphorilation of certain tyrosine kinases in which the transplant of PM reconstituted the phosphorilation capacity. Nevertheless, in an other group this procedure was inefficient, suggesting a primordial defect (Schwartz et al. 1999), which we have been investigating and seems traced to a chaperone involved in immunoglobulin RNA processing (Baracho GV et al., manuscript in preparation).

Affinity maturation is the result of cumulative point mutation on the hypervariable region of immunoglobulin genes (Figure 1A and 1B), resulting from antigenic stimulation and proper co-stimulation of B cells. This process culminates with the emergence of memory B cells and terminally differentiated plasma cells. Frequency of hypermutation in patients with CVID may be normal or slightly decreased, as described above. Nevertheless, a group of patients may present with a severe deficit in the affinity maturation process. Through the analysis of intronic sequences from the J_{H4}-J_{H5} flanking regions of the V_H-J_{H4} junction on $CD19^+IgM^-IgD^-$ memory B cells and aided by the analysis of the mRNA transcript for the $V_{3\text{-}23}$-$C\gamma$ region, some patients were suggested to have a reduction of 40 to 75% of the normal hypermutation rate for this region thus im-

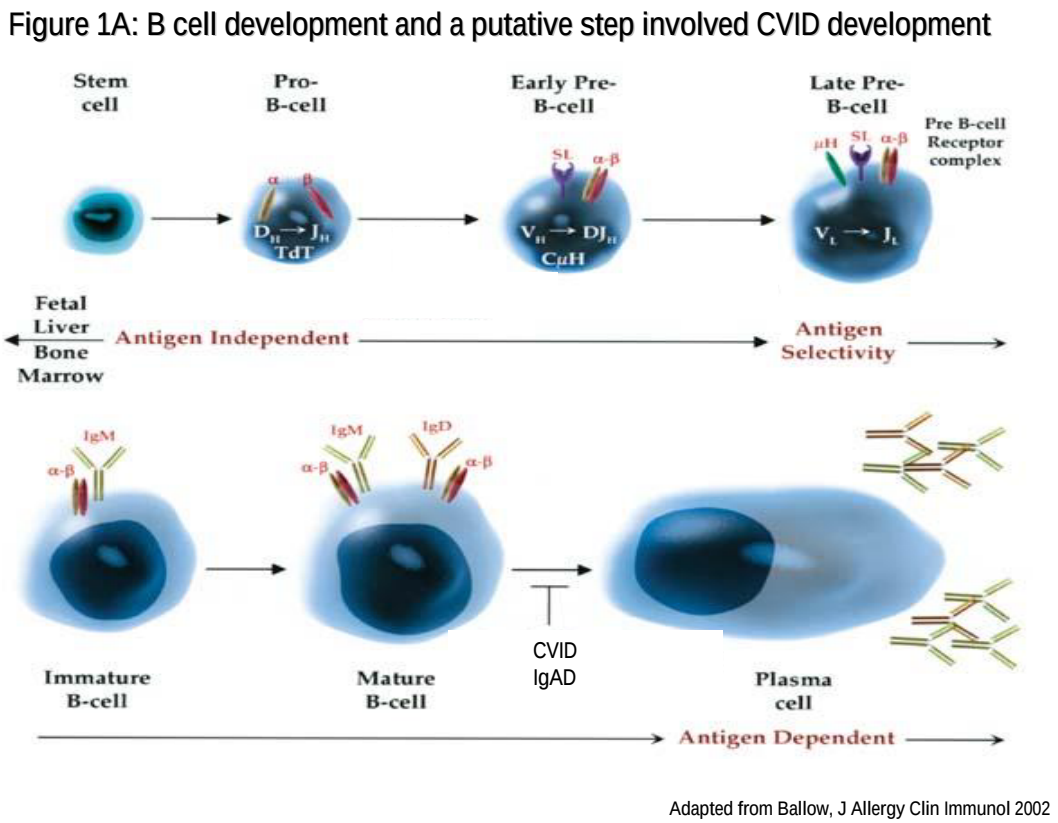

Fig. 1A – Steps involved in the development of B cells and their maturation. The differentiation into antibody forming cells may be compromised in CVID patients. The figure shows the immunoglobulin gene rearrangements involved in the process and the steps necessary for antibody production and secretion, highlighting the changes that are antigen-independent and consequently autonomous from T cell interaction, and those that are T cell dependent and may be affected in CVID patients.

pairing B cell differentiation, antibody synthesis and memory development. The functional analysis of T cells from these patients confirmed that the defect was restricted to B lymphocytes (Levy et al. 1998), which was confirmed independently (Bonhomme et al. 2000).

The putative defect on B cell activation was studied by Nonoyma and colleagues in 22 patients with CVID by *in vitro* stimulation of patients' B cells in the presence of combinations of anti-CD40, IL-4, IL-10 and in the presence or absence of CDw32L cells. Four groups of patients were identified regarding B cell response to these multiple stimuli; a group incapable of producing IgM, IgA or IgG, a group that synthesized IgM an IgG but not IgA, a third group that produced IgM and low levels of IgA and IgG, and a forth group that produced minute amounts of IgM. The subsequent analysis of IgG subclasses in the patients that synthesized this antibody isotype revealed that IgG_4 was most affected followed by IgG_2, whereas the synthesis of IgG_3 and IgG_1 was normal. Similarly, in the patients capable of producing IgA, the secretion of IgA_2 was more affected that that of IgA_1. These finding suggest an hierarchy in the synthesis of isotypes and subclasses that seem to correspond to the location of the heavy chain gene in the human genome on chromosome 14 (Nonoyama et al. 1993). The same phenomena was confirmed by other studies but using bacterial polysaccharides and cytokines as the stimulants for antibody produc-

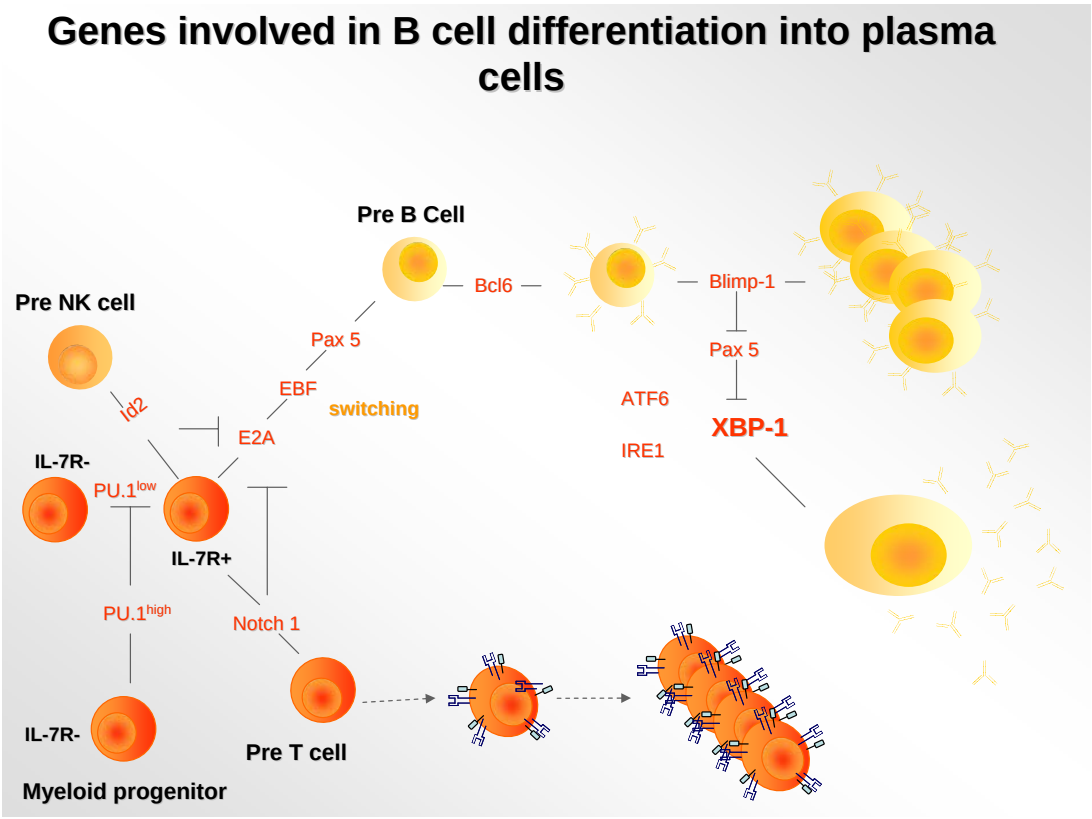

Fig. 1B – Genes expressed in the maturation of B cells from the myeloid precursor to plasma cells. All genes that must be expressed at each step of T cell differentiation are denoted. The sequential expression of these genes is necessary and the order in which they are expressed is represented from left to right in the figure. IL-7R represents the surface expression of the interleukin-7 receptor.

tion (Eisenstein et al. 1994, Eisenstein and Strober 1995, Punnonen et al. 1997).

Histologically, lymphoid tissues from most CVID patients have normal B cell differentiation areas, suggesting that these cells are capable of recognizing antigen on a primary encounter and reinforcing the notion that the defect is associated with terminal stages in the differentiation cascade. The analysis of mucosal B lymphocytes on the small intestine of patients revealed that 65% of the individuals studied did not have IgA_1 or IgA_2 positive cells and 41% did not present IgG_2 either. In contrast only 18% were negative for IgM (Herbst et al. 1994), further supporting the notion of a B cell maturation deficit in these patients.

The analysis of activation markers for B cells showed a decreased expression of B7-2 (CD86) and also 4-1BB. Since the activation of these cells with mitogen plus engagement of CD40 did not restore the expression of either CD86 or 4-1BB, it seems that, at least for the patients analyzed in this study a defect on B-T cooperation is also present and may explain some clinical features seen in these patients that are more commonly associated with T cell defects (Denz et al. 2000).

T LYMPHOCYTES IN CVID

Up to 50% of the patients with CVID will also present defects in the cellular immunity compartment (Kondratenko et al. 1997), and thus in these patients part of the impaired immunoglobulin synthesis may be due to the inefficient help provided by T cell, the presence of regulatory cells or suppressor

cells (Braun et al. 1991), the latter was associated in the past with the inversion in the CD4:CD8 ratio observed in the peripheral blood of some patients (see bellow). Kamin and collaborators were the first to identify a deficit in the proliferative response of T lymphocytes to PHA in patients with ''familiar hypogammaglobulinemia'', which was later named CVID (Kamin et al. 1968). Therefore, many authors have suggested that this disease is a combined immunodeficiency (Sneller 2001, Duarte et al. 1990). Among the patients that we follow 56% of them (40/71) present a decrease in the CD4/CD8 ratio (< 1.0), due to increased CD8+ lymphocytes, diminished CD4+ lymphocytes or both. Furthermore, from 34 patients who were submitted to delayed type hypersensitivity skin test, 21 were non-responsive.

There are many reports, either as series of patients or as isolated case reports that support the notion that some patients with CVID have a cellular defect associated with the hypogammaglobulinemia. These studies, describe infections that are commonly associated with T cell deficits and vary from severe infection with viruses such as the cytomegalovirus (CMV), or herpes zoster (CMV) (Kainulainen et al. 1999, Linde et al 1988, Mullighan et al. 1996, Tarr et al. 2001, Witte et al. 2000), and also include infection with intracellular parasites like the *Toxoplasma gondii* or *Strongyloides stercorallis* (Duarte et al. 1990, Naspitz et al. 1987, Mushiake et al. 1993, Bonilla et al. 1997).

The TCR/CD3 complex is fundamental for the antigen recognition and activation of T cell. It is associated with two families of tyrosine kinases Src and Syk. Src family kinases will phosphorylate the Immune Receptor Tyrosine Associated Motif (ITAM), for instance on the cytoplasmatic domain of the CD3/ξ chain. Following this phosphorylation, the enzyme ZAP-70 is recruited and further phosphorylate the ξ and ε CD3 chains. Although the analysis of the nucleotide sequence of the ITAMs on the CD3/ξ or on the ZAP-70 enzyme did not show any differences when compared to normal individuals, a defect in the interaction of ZAP-70 with p23ξ leading to defective activation of T cells through the TRC was described (Boncristiano et al. 2000). In contrast, Majolini and colleagues were unable to reproduce these results, although, they recognized a defect in the phosphorylation cascade that follows antigen recognition by the TCR in CVID patients (Majolini et al. 1997).

Farrington and colleagues reported a decreased expression of CD40L mRNA on activated T cells from patients as compared to controls, although the study did not specify the clinical status of the patients which could potentially interfere with the expression of this molecule, the authors proposed that this marker should be used to classify the patients based on the presence or absence of a T lymphocyte defect (Farrington et al. 1994).

Cytokines play an essential role on antibody synthesis and the regulation of the immune response in general. Reports on the importance of cytokines for the development of CVID have been presented briefly above and will be discussed in depth here.

North and collaborators and Cambronero and collaborators observed that IL-12 synthesis *in vitro* by LPS-stimulated monocytes from the peripheral blood was increased in CVID patients. In turn, this could be responsible for the increase in the frequency of IFN-γ producing T cells, as defined by intracellular staining for this cytokine. The authors suggest that this changes would represent a shift to a polarized Th1 response in these patients which would account for the decreased antibody production and some of the granulomatous features of the disease in some individuals affected (North et al. 1996, Cambronero et al. 2000). Although interesting as a concept and even useful to classify yet another subtype of CVID patients, it is important to note that some other studies have failed to show the same increase in IFN-γ producing T cells, some have reported normal levels of this cytokines, while others have reported diminished levels (Matricardi et al. 1984, Paganelli et al. 1988, Pastorelli et al. 1989a).

IL-10 is another cytokine whose importance in CVID has been underlined. Lymphocytes from CVID patients have been reported to secrete

less IL-10 when activated than normal lymphocytes (Aukrust et al. 2000, Holm et al. 2003). In contrast, monocyte-derived IL-10 has been implicated in the diminished production of IL-2 by some patients and as a contributor to the proliferative deficit observed in a subset of individuals with CVID (Zhou et al. 1998). Interestingly, the effect of IL-10 on IL-2 synthesis by T lymphocytes from CVID patients and its effect on antibody synthesis *in vitro* was only observed in the presence of IL-4 and anti-CD40 antibody but not in the absence of IL-4 (Punnonen et al. 1997). It is noteworthy that defects on IL-2 production have also been described independently from the interaction with other cytokines (Fischer et al. 1993, Nonoyama et al. 1994).

Changes in the number and function of CD8+ T lymphocytes have been described in CVID patients for a long time. Enhanced numbers of these cells, followed or not by a decrease on CD4+ T cells, leading to an inversion of the CD4+/CD8+ are characteristic of a subset of CVID patients with severe compromise of the cellular immunity (Jaffe et al. 1993a, b). Changes in the expression of CD40L and other activation molecules expressed in the surface of T cells have also been reported, in association to changes in cytokine synthesis (North et al. 1998), as described above, or independently (Errante PR et al. manuscript in preparation).

The antigen-specific T cell response has also been reported as deficient in some patients with CVID. The generation of memory cells to several antigens seems compromised, for example, memory cells for purified protein derivative (PPD), tetanus toxoid (TT), *keyhole limpet hemocyanin* (KLH) and a peptide derive from the *env* gene on HIV have all being reported as lacking in exposed individuals with CVID (Kondratenko et al. 1997, Funauchi et al. 1995, Stagg et al. 1993, 1994). In addition, mRNA for IL-12 (Farrington et al. 1994), IL-2, IL-4 (Pastorelli et al. 1989a, b, 1990), IFN-γ (Paganelli et al. 1988), IL-5 and IFN-γ (Sneller and Strober 1990a, b) has also been reported as decreased in response to specific antigenic stimulation in PBMCs from CVID patients.

CLINICAL CHARACTERISTICS OF THE PATIENTS WITH CVID

Immunodeficiency in CVID patients is often unapparent during the first years of life. Although patients less than three years old have been diagnosed correctly with CVID, diagnosis during early childhood is not the norm and the disease is most commonly diagnosed in teenagers (Cunningham-Rundles and Bodian 1999, Abonia and Castells 2002, Piqueras et al. 2003), with the peak in diagnosis occurring between the ages of 13 and 30 years old (Tiller and Liddle 2000, Cunningham-Rundles and Bodian 1999, Aghamohammadi et al. 2002, Pfluger et al. 2000, Strober and Chua 2000). Interestingly, immunodeficiency symptoms may not be manifested until much later, and many cases of diagnosis after 65 years of age are described, including a case with the primary diagnosis made in a 88-year-old patient (Hawkins et al. 2003). Because most physicians are unaware of this condition it is often misdiagnosed, frequently confused with AIDS (Kaczmarski et al. 1994), severe asthma or autoimmune diseases (Fontan Casariego 2001, Rusconi et al. 2003, Kart et al. 2003, Heeney et al. 2003, De Vera and Yu 2003, Byrne et al. 2003).

CVID has no gender preference, although women tend to manifest the disease later in life, after the diagnosis the survival rate is similar for both sexes (Cunningham-Rundles 2001, Cunningham-Rundles and Bodian 1999, Martinez Garcia et al. 2001, Pfluger et al. 2000, Strober and Chua 2000, Gottesman et al. 1999, Manson et al. 2000).

Between 1980 and 2003, our group followed at the Division of Clinical Immunology and Allergy of University of São Paulo Medical School, a reference service for adult patients, 71 patients with CVID. Patients followed during this period had a similar distribution of gender (38 males and 33 females), in agreement with the medical literature cited above. The follow-up period for our patients varied from 2 months to 23 years (mean number of years of follow-up = 4.5). The age range of patients currently under our care is between 15 and 78 years. Most

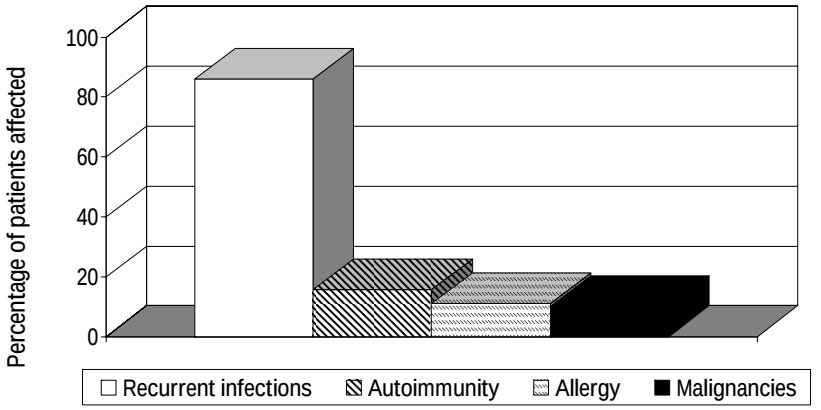

Fig. 2 – Clinical Manifestations of a Brazilian Cohort of CVID patients (n=71) is shown in percentages. The percentage of patients with CVID that manifest specific clinical signs of the disease. Recurrent infections of any nature are the most common feature of CVID, followed by autoimmunity, allergy and malignancies.

of the patients are Caucasians (50-70%), some are mixed race (20-19.8%) and one patient is African-American (1.5%). The mean age at onset of symptoms for this group was 20 years and 11 months and the mean age at the time of diagnosis was 30 years and 11 months, thus averaging 10 years and 11 months between the beginning of the symptoms and the final diagnosis. During this period 11 patients died (15%).

Figure 2 represents graphically the main clinical manifestations observed in our patients during the 23 years of follow up. As expected, the most frequent circumstance associated with CVID was recurrent infections, observed in 55 patients (86%). Autoimmunity was observed in 15% of the patients (11/71) and malignancies in 8% (6/71).

Pneumococcus and *Haemophilus influenza* are the most common bacteria responsible for the respiratory tract infection observed in patients with CVID according to large series of patients reported (Cunningham-Rundles and Bodian 1999, Abonia and Castells 2002). *Campylobacter spp.*, rotavirus and *Giardia lamblia* are the most frequent culprits of gastrointestinal infections (Zullo et al. 1999, Lai Ping So and Mayer 1997, Estrada Perez et al. 1991). On Table I we summarize our experience with the patients we have been following. Upper airway infections (otitis, sinusitis and/or tonsillitis) were seen in 51 patients (72%), while pneumonias were present in 93% of them. At the time of CVID diagnosis thirty-nine patients had already developed bronchiectasis. This is probably due to the repeated infections with a long time course observed in these patients and the lack of adequate care before the diagnosis of immunodeficiency was established. Diarrhea was also a very common finding among CVID patients (46/71-65%). The diarrhea was often infectious. Interestingly, whereas most cases were caused by *Giardia* (23/46-50%) as described in the literature, we also had many cases of strongyloidiasis (6 patients – 13%) and *E. coli* infection (6 patients – 13%). In 16 patients the etiology of the diarrhea was unknown.

Six patients in our cohort presented a history of furunculosis before immunoglobulin replacement therapy was instituted. Interestingly, six patients have had repeated urinary tract infections, which are not a usual feature in patients with CVID. Bacterial or viral meningitis was observed in two patients. Sepsis was seen in 13 patients and unfortunately, it was the immediate cause of death of all but one of them.

TABLE I

Most common infectious diseases in a cohort of Brazilian patients with CVID.

	Number of patients	%
Recurrent tonsillitis, sinusitis, otitis	51	72
Pneumonia	66	93
Infectious diarrhea		
Giardiasis	23	32
Strongyloidiasis	6	8
E. coli	6	8
Non-identified agent	16	22
Bacterial skin infections	6	8
Urinary infections	10	14
Meningitis	3	4
Sepsis	13	18
Arthritis	4	6
Opportunistic infections		
Candidiasis	4	6
Herpes I/II	2	3
Herpes Zoster	4	6
HPV	1	1.5
Toxoplasmosis		
Ocular	1	1.5
Neurotoxoplasmosis	1	1.5
CMV -	1	1.5
Cryptococcosis	1	1.5
Tuberculosis	5	7
Other		
Schistosomiasis	1	1.5
Paracoccidioidomycosis	1	1.5

Opportunistic infections like herpes zoster, genital HPV, tuberculosis, candidiasis, toxoplasmosis, cryptococcosis and CMV were observed in 13 patients – 18% – (in some patients the episodes were repetitive and there were more than one type of opportunistic infection). Five patients reported tuberculosis (7%) prior to the diagnosis of CVID, but disease was only confirmed in one of the patients and it is possible that severe pneumonia was confused for tuberculosis because of the difficulties in treating an immunodeficient patient with conventional antibiotic therapy. Fungal infections by *Cryptococcus neoformans* and protozoan infections by *Pneumocystis carinni*, *Toxoplasma gondii* e *Cryptosporidium spp* (Tzipori 1988, Esolen et al. 1992, Macura et al. 2003), have been occasionally described in these patients. Viral infections are also common and Herpes, Epstein-Barr and CMV are among the most frequently reported (Cunningham-Rundles and Bodian 1999, Webster 2001). Another virus reported as chronically affecting CVID patients is the parvovirus B19, leading to aplastic anemia (Chuhjo et

al. 1999).

Approximately a third of the patients with CVID will develop some autoimmune phenomena, including hemolytic anemia, purpura, autoimmune hepatitis, thyroiditis, diabetes, dermatomiositis and Graves disease, among others (Heeney et al. 2003, Andon Saavedra et al. 1996, Cunningham-Rundles 2002, Lee et al. 1993). In our series of patients autoimmune disease was observed in 11 individuals (15,5%). Contrary to what is described in the literature, most of them males (n=8). Furthermore, the autoimmune disorder that is described most often among the CVID patients is Idiopathic Thrombocytopenic Purpura, which was not observed among our patients.

Two patients have more than one autoimmune disease, one female patient has hemolytic anemia and Sjögren Syndrome and one male patient has atrophic gastritis and pernicious anemia. Among the autoimmune disorders found were: hemolytic anemia (15.4% of the conditions), pernicious anemia (7.7%), atrophic gastritis (15.4%), celiac disease (7.7%), autoimmune hepatitis (7.7%), vitiligo (23.1%), psoriasis (7.7%), Sjögren syndrome (7.7%) and rheumatic fever (7.7%). Rheumatic fever was diagnosed in a 38 years old male patient. The results are summarized on Table II.

TABLE II

Most common autoimmune diseases in a cohort of Brazilian patients with CVID.

	Total	%
vitiligo	3	23.1
Hemolytic anemia	2	15.4
Pernicious anemia	1	7.7
Atrophic gastritis	2	15.4
Celiac disease	1	7.7
Hepatitis	1	7.7
Sjögren syndrome	1	7.7
Rheumatic fever	1	7.7
Psoriasis	1	7.7
Total	13**	

*One female patient had both hemolytic anemia and Sjögren Syndrome and one male patient had atrophic gastritis and pernicious anemia. **13 autoimmune conditions seen in 11 patients.

CVID patients may develop benign or neoplastic lymphoproliferative diseases. Among the benign manifestations, esplenomegaly, generalized lymphadenopathy and nodular lymphoid hyperplasia are the most common. Unfortunately, the incidence of lymphoma in these individuals is 300 higher than in the general public, some related to Epstein-Barr or retroviral infection (Gompels et al. 2003).

Besides the hematological malignancies, patients with CVID also have a propensity to develop gastric cancer, with an incidence 50 times higher than in the normal population. Part of the problem may be cased by genetic defects associated with CVID (Zullo et al. 1999, Alonso Falcon et al. 1999). However, a higher incidence of achlorhydria (Vorechovsky et al. 1991), suggest that environmental factors also play a role in the development of gastric cancer in these patients. Infection with *Helicobacter pylorii* may be one of them, although the prophylactic treatment of this infection did not seem to alter the course of gastric atrophy in this patients, suggesting that other factors, such as secreted immunoglobulins in the gastric mucosa may also play a role in preventing the development of pre-malignant lesions (Misbah et al. 1992). Among our patients, seven developed malignant tumors of six different types (Table III). One of the female patients had the CVID diagnosis made after resection of an adrenal tumor. The other diseases found were Non-Hodgkin lymphoma, T cell lymphoma, gastric cancer, basal cell carcinoma and melanoma. Non-Hodgkin lymphoma was the cause of death in one patient. Only one patient of our cohort had both autoimmunity (autoimmune hemolytic anemia) and malignancy (melanoma). Interestingly, this patient is one of the patients that evolved from IgA deficiency to CVID.

Hereditary factors play a role in most primary immunodeficiencies and CVID is not an exception.

TABLE III
Neoplasias developed in a cohort of Brazilian patients with CVID.

	Total (n=71)	%
Non-Hodgkin lymphoma	1	1.5
T cell lymphoma	2	3
Gastric adenocarcinoma	1	1.5
Basal cell carcinoma	1	1.5
Melanoma	1	1.5
Adrenal tumor	1	1.5
Total	7 (10%)	

However, because of the polymorphic nature of this disease it has been hard to assign a specific pattern of transmission of disease, although the association with IgA deficiency has been better characterized in this aspect. Nevertheless, there are many reports of individuals who develop CVID and no specific hereditary association is found (Webster 2001). Specific genetic defects will be discussed bellow. In the cohort we are currently following, immunodeficiency diseases have been diagnosed in the families of nine patients. Six relatives with IgA deficiency were found, low IgG levels (2 persons) and CVID (5 persons). One of the female patients had a daughter with IgA deficiency, a son with transitory hypogammaglobulinemia and a cousin with CVID. Another female patient had a son with low IgG levels and a niece with IgA deficiency. A third female patient, who has Sjögren syndrome beside CVID, has two children (a son and a daughter) with IgA deficiency and SLE. These patients' families also reported cases of autoimmunity and cancer. Autoimmunity was seen in the families of 7 patients (inflammatory bowel disease; thyroiditis; diabetes; SLE and scleroderma).

The median follow-up time for these patients was 4.5 years (range 1 month – 28.3 years, some of them were being treated elsewhere before). We observed 11 deaths (15.5%), four females and seven males. This difference was not statistically significant. The main death causes were: sepsis, in 7 patients with bronchiectasis, one patient with lymphoma, one patient with malabsorption syndrome and one patient with neurocryptococcosis; and probable *P. carinii* infection in one patient with acute respiratory insufficiency.

Treatment of CVID

The basis for the treatment of patients with CVID is the timely replacement of serum gammaglobulins. Initially, replacement was performed by the subcutaneous or intramuscular injection of pooled gammaglobulin from blood donors. For the past twenty years, the availability of gammaglobulins for intravenous injection (IVIG) has greatly improved the outcome of these patients. Ordinarily, IVIG is used once or twice a month with an attack dose of IVIG at 600 mg/kg of body weight and follow up injections aiming at keeping the blood levels of immunoglobulins above 400 mg/dL. Although other immune deficits associated with CVID, e.g. immunoglobulins are absent in blood fluids like the saliva and gastric juice, the increase in serum antibody has proven effective in preventing pulmonary infections, sepsis and meningitis (Cunningham-Rundles 2001, Cunningham-Rundles and Bodian 1999). It is noteworthy that the administration of large doses of immunoglobulins intravenously has very well reported immunomodulatory effects that are frequently used in the treatment of autoimmune diseases. These immunomodulatory properties may contribute to the overall effect IVIG has on CVID patients. It was shown that it may cause an increase in the expression of IL-2 by CD4+ and more importantly $CD4^{+}28^{-}$. It can also increase the expression of TNF-α in these same cells (Sewell et al. 1999, 1998).

Adjuvant therapy has been tried in CVID in an attempt to improve the results obtained with IVIG, especially in view of the poor effect IVIG has on preventing cancer in these patients. Recombinant IL-2, pure or polymerized with poly-ethylene-glycol, is the most commonly use adjuvant therapy (Cunningham-Rundles et al. 1995, 2001, Rump et al. 1997). Although the results on preventing malignancies are unclear, the addition of IL-2 decreases the incidence

of severe disease and it increases the overall level of serum IgG, which may be due to direct stimulation of the patient's own B cells to secrete antibodies. Less conventional therapies such as cimetidine, which was thought to enhance IgA secretion, bacterial products and vitamins have been tried sporadically (Litzman et al. 1996a, Segal et al. 1989, Saxon et al. 1993, Della Bella et al. 1997).

In our group, patients diagnosed before 1994 (10-15.6%) were treated with plasma or intramuscular (IM) immunoglobulin. Following the availability of IVIG at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, starting in 1995 all patients have received IVIG as described above. Three patients from the cohort we describe here died before IVIG treatment was established. Two patients were diagnosed elsewhere and received IM immunoglobulin irregularly up to the time (1.5 and 10 y) they were referred to our service.

It is clear that the establishment of immunological criteria that allow the early detection of CVID and consequently the implementation of therapy will contribute to prolonging the life of patients with this disease and enhance their quality of life. Large series of studies as described above and our own experience with the 71 cases described here show that the patients with earlier diagnosis and treatment survive longer and with less sequellae than those who are diagnosed later, especially if a diagnosis is made after pulmonary complications have been established.

GENETIC DEFFECTS ASSOCIATED WITH CVID AND THE RELATIONSHIP WITH TOTAL IgA DEFICIENCY (IgAD)

The characterization of specific genetic defects leading to failures in the immune response that characterize CVID is pivotal for the understanding of the different subsets of patients with this disease and to comprehend the differential evolution of each patients. Furthermore, as these defects are identified and correlated with specific symptoms one can better understand the effector and regulatory mechanism of the human immune system.

The inducible co-stimulatory protein (ICOS) is a member of the CD28/CTLA-4 family and is expressed specifically by T lymphocytes, interacting with its ligand B7H on the surface of B cells and macrophages. This interaction will increase the expression of CD40L and the proliferation of T lymphocytes. ICOS also possess antiapoptotic properties and induces the secretion of many cytokines that act on B cells (Grimbacher et al. 2003a, Sporici and Perrin 2001). Recently, Grimbacher and colleagues have described an autossomic recessive disorder in 4 patients with CVID out of 32 studied. These patients came from two families with a possible common ancestor (Grimbacher et al. 2003b). The patients had a homozygous partial deletion of the ICOS gene. Laboratory analysis of these individuals revealed, besides hypogammaglobulinemia, B cell lymphopenia, normal T cell response to PHA, PWM, mAb-anti-CD3 and TT with proliferation and synthesis of TNF-α, IFN-γ, IL-2, IL-4, IL-10 and IL-13. Interestingly, B cells from these individuals stimulated in the presence of T CD4+, IL-2 and SAC were capable of secreting all isotypes of antibodies *in vitro*. It is noteworthy that the IgG subclasses were not studied. We were unable to detect this or any mutation in the ICOS gene in any of the 38 patients studied, out of the 56 we currently follow.

A few patients with IgAD may develop CVID over time. Furthermore, the frequency of relatives from CVID patients with low levels of IgA is much higher than what expected in the general population (Carvalho Neves Forte et al. 2000, Cham et al. 2002). This has led to the hypothesis that IgAD and some cases of CVID represent two different poles of a spectrum of antibody deficiency (Ashman et al. 1992, Litzman et al. 1996b). Although the precise molecular defect that causes IgAD is still unrecognized, in many patients with CVID or IgAD association with specific regions inside the MHC loci have been described.

An association with the MHC III region on chromosome 6 has been described by many authors. A high frequency of null alleles for the C4a component of the Complement systems was observed in

patients with IgAD. In a study including CVID and IgAD patients it was observed that 12 out of 19 patients with CVID (63%, $p < 0,01$) and nine out of sixteen patients with IgAD (56%, $p > 0,01$) showed rare alleles for C2 and or a deletion of the genes that encodes 21-OHase A. In another study, nine out of eleven patients with a deletion of C4a also carried HLA-A1, -B8, -C4AQ0, -C4B1, -BFS e -DR3 haplotypes, all previously associated with IgAD and or CVID (Schaffer et al. 1989, Schroeder et al. 1998, Schroeder 2000). The putative gene for IgAD was then named IGAD1. A genome-wide genetic linkage analysis to study IGAD1 in a large number of IgAD/CVID patients implicated the HLA-DQ/DR as a major susceptibility locus (Kralovicova et al. 2003).

Other studies have suggested that certain genes in the MHC III region are on linkage disequilibrium with alleles from the MHC I and or II (De La Concha et al. 1999), registering an association with the HLA-DR3, -B8, -A1 haplotypes. In these regions the susceptibility types for CVID and IgA would be related to the HLA-D821/D823 e HLA-B8 haplotypes, localized at the *G1/AIF1* and HLA-B regions, respectively (Schroeder et al. 1998, Schroeder 2000). Another studied suggested that the association with CVID and IgAD was in the loss of specific genes on the region 6p21.3 (Vorechovsky et al. 2000, 2001).

The findings described above suggest that a common defect for all patients with CVID is unlikely, nevertheless groups of patients with similar defects can be found and thus they must be typed and studied accordingly.

CONCLUDING REMARKS

CVID is a complex disease very likely caused by multiple different gene defects resulting in similar but not identical clinical signs. Besides the devastating effect that it has on its carriers and the consequent medical quagmire it represents, CVID offers us the opportunity to understand the functioning of the immune system and thus grant us with unique tools to learn how to modulate it, not only to improve the quality of life of patients with CVID but also patients with other immune-mediated diseases.

CVID is the most frequent primary immunodeficiency followed by clinical immunologists and it should be recognized by the physicians as soon as possible in order to avoid the complications determined by the delay in the diagnosis and consequently a better life quality.

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RESUMO

A imunodeficiência comum variável (CVID) é uma doença caracterizada por hipogamaglobulinemia, infecções recorrentes, especialmente das vias aéreas, enfermidades auto-imunes e neoplasias. Alguns pacientes com CVID possuem diversos distúrbios do sistema imune como alterações no número e proporção de diferentes populações leucocitárias; resposta proliferativa linfocitária diminuída para antígenos e mitógenos; produção alterada de citocinas e alteração na expressão de moléculas de superfície. Neste trabalho, são discutidas várias destas alterações imunológicas procurando correlacioná-las aos achados clínicos dos pacientes e incorporar aos dados da literatura os nossos próprios achados.

Palavras-chave: imunodeficiência, humanos, anticorpos, citocinas, dados clínicos.

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