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Common Variable Immunodeficiency: a crossroads between infections, inflammation and autoimmunity

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Abstract

Common Variable Immunodeficiency is a collection of diseases characterized by primary hypogammaglobulinemia. The causes of CVID are extremely heterogeneous and may affect virtually every pathway linked to B cell development and function. Clinical manifestations of CVID include recurrent bacterial infections, but autoimmune, gastrointestinal, lymphoproliferative, granulomatous, and malignant disorders have also been frequently reported as associated conditions. We aimed to focus on the state of the art of the relationship between infections, inflammation and autoimmunity in CVID.

Introduction

Common Variable Immunodeficiency is a heterogeneous collection of diseases characterized by a primary antibody defect (hypogammaglobulinemia). CVID is defined as a diagnosis of exclusion; according to the current diagnostic criteria, CVID is considered probable in a patient who has a marked decrease in IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes, IgG, IgM or IgA and fulfills all of the following criteria: 1) onset of immunodeficiency after the age of 2 years; 2) absent isohemagglutinins and/or poor response to vaccines; 3) exclusion of defined causes of hypogammaglobulinemia, such as drugs, infections, malignancy, genetic diseases, protein loss, or hyper-catabolism (1, http://www.esid.org/clinical-diagnostic-criteria-for-pid-73-0).

Although CVID constitutes the most common cause of clinically expressed primary immunodeficiency, it is still a rare disease. In 2011, the European Society for Immunodeficiencies (ESID) estimated the prevalence of CVID as ranging from 0.073 to 0.977 living patients per 100,000 inhabitants (2). A further analysis performed on a relatively homogeneous population in Iran showed that CVID is the most frequent form of primary immune deficiency (PID) , affecting about 20% of PID patients (3).

Unlike other PID conditions, CVID usually manifests between the second and fourth decades of life. Chapel et al. established the onset of symptoms at a mean age of 26.3 years (median age of 24 years) (4). CVID represents a clinical and immunological syndrome that merges various diseases with different genetic roots. Clinical manifestations range from recurrent infections of the respiratory tract that affect from 70% to 80% of patients and often appear late in life, to autoimmune diseases, inflammatory diseases, and malignancies, especially lymphoproliferative disorders (5).

In this review of the literature, we aim to provide an overview of current knowledge about the relationships between infections, inflammation and autoimmunity in CVID.

Search strategy and selection criteria

We selected references through a PubMed search of English language papers published over the last ten years by using this research string: [common variable immunodeficiency OR CVID OR (autoimmunity AND primary immunodeficiency) OR (primary immunodeficiency and infections)]. We did not use the MeSH catalog in order to improve the sensitivity of the research.

We eventually found 1,539 articles fulfilling the search strategy criteria. Abstracts were reviewed and when relevant findings were reported, the full article was retrieved and reviewed. Further articles that could have been relevant for discussion, including those published prior to the last ten years were identified from the references cited in those articles.

CVID and autoimmunity

More than 25% of CVID patients have autoimmune complications which are poorly understood and in some cases that are difficult to manage (1, 6, 7). The pathogenesis of autoimmunity in CVID is an astonishing paradox: autoantibodies and auto-reactive B cells can be detected in patients, even if serum immunoglobulins are very low and specific response to antigens is impaired.

The most common autoimmune manifestation is cytopenia: autoimmune thrombocytopenia (ITP) is found in up to 14% of patients followed by autoimmune hemolytic anemia (AHA), which is found in up to 7% (8). Sometimes ITP and AHA coexist in Evans Syndrome. In CVID patients, cytopenia is definitely associated with an increased frequency of splenomegaly, however, hypersplenism is unable to entirely explain this association and the physiopathological link remains unclear (6). In order to minimize the risk of severe infections, splenectomy should be avoided in CVID patients, even in the presence of cytopenia, however this recommendation is not universally accepted. A large survey of splenectomized CVID patients is under way in order to clarify this question (5). It is important to underline that in up to 60% of CVID patients the diagnosis of cytopenia precedes the detection of hypogammaglobulinemia (9). Therefore, screening for serum antibody levels in patients affected by autoimmune or idiopathic cytopenia is recommended.

Other autoimmune manifestations of CVID include idiopathic neutropenia, vitiligo, pernicious anemia, anti-phospholipid syndrome, presence of anti-IgA antibodies, rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, Sjogren s syndrome, psoriasis, thyroiditis, uveitis, and vasculitis (5,8,10).

CVID and inflammation

Besides autoimmunity, CVID is commonly associated with many dysregulations of the immune system, leading to lymphoproliferation as well as to inflammatory diseases.

The inflammatory phenotype in CVID is expressed in the form of granulomatous diseases that can be either organ specific or systemic. Typically, granuloma formation is characterized by lymphocyte infiltration followed by fibrosis and eventually granuloma formation (11). For reasons that are currently unclear, granulomatous progression is further associated with autoimmunity in CVID (12). The organs which are most commonly affected by granuloma are the lungs, the liver, and the gastrointestinal tract.

Lung involvement is the main cause of death in CVID patients (8), and its prevalence increases up to 46.4% during follow-up (10). Chronic lung disease (CLD) is partly caused by recurrent, unchecked infections that result in the development of bronchiectasis in a percentage of patients that varies from 4 to 76%, depending on the cohort (5). However, at least half of the patients develop CLD in the absence of bronchiectasis (8). These patients commonly show polyclonal lymphoid infiltration of the lung, and biopsies can reveal features of reactive lymphoid hyperplasia or granulomatous inflammation (13). In a subset of patients, granulomas can also be accompanied by intense lymphocytic infiltration, a condition described as granulomatous lymphocytic interstitial lung disease (GLIDL) (14). Granulomas are found in the lungs of more than 50% of subjects with systemic granulomatous disease (8). It is however noteworthy that this prevalence may be underestimated because many patient do not undergo lung biopsy. Some authors reported that subjects with granulomatous lung diseases with GLIDL had shorter survival (15). Indeed, when they are present in the lung, granulomas are associated with considerable tissue damage that can lead to respiratory failure and reduce life expectation.

The liver is commonly involved in CVID. Hepatitis with no evidence of viral infection was reported in 43% of patients in two unrelated cohorts (16,17), and raised blood alkaline phosphatase levels were often observed. In most cases, liver biopsy showed mild to moderate periportal lymphocyte infiltration and cholestasis. Nodular regenerative hyperplasia (NRH) of the liver has recently been described as a frequent cause of liver disease involving more than 80% of CVID patients who underwent liver biopsy. In these cases, histology consistently revealed lymphocytic portal infiltration and, less frequently, the presence of granulomas. Furthermore, patients with liver NRH are prone to develop other autoimmune diseases such as ITP, AHA, Sjogren's syndrome, thyroiditis, type 1 diabetes, vitiligo, rheumatoid arthritis, celiac-like villous atrophy, inflammatory bowel diseases, pernicious anemia, vasculitis, and psoriasis, suggesting the possibility of a common pathogenesis (14).

Gastrointestinal tract involvement is present in up to 50% of CVID patients (16). Some cases of transient or persistent diarrhea or malabsorption are due to bacterial, parasitic or viral infection (5). Gastrointestinal infections are more frequent in patients with absent IgA given their role in mucosal defense (19). However, inflammatory diseases are frequently observed. The small bowel often presents celiac-like enteropathy characterized by lymphocytic intraepithelial infiltration,

shortness of villi, and hyperplasia of crypts. Celiac-specific antibodies are usually absent, and histological abnormalities are non-responsive to gluten-free diets (5). Large bowel enteropathy is quite similar to inflammatory bowel disease, including Crohn's disease, while granulomatous disease is not frequent (10, 20). Unlike classical IBD, lamina propria lymphocytes from CVID patients with large bowel enteropathy are skewed toward the production of Th1 proinflammatory cytokines, such as interleukin-12 (IL-12) and gamma interferon (IFN-) rather than TNF-alpha, IL17, or IL23, suggesting that the pathogenesis of the lesions differs at least partially (21). CVID-associated enteropathy may be suspected on the basis of the lack of plasma cells in a GI biopsy, but because this feature is only present in about two-thirds of patients, the diagnosis cannot always be confirmed in the absence of other clinical and laboratory findings (22). Gastrointestinal nodular lymphoid hyperplasia is a common finding in CVID patients (8% of an Italian cohort) (10), however the correlation of this condition with the development of mucosa-associated lymphoma is not proven.

In some CVID patients, granulomas resulted in localized, circumscribed diseases, such as njunctivitis and uveitis (20, 23). CVID may also be associated with isolated orofacial granulomatosis (personal unpublished data). It is worthy of note that when granulomas are discovered first, the diagnosis of CVID is often delayed since the patient is considered as being affected by uncomplicated sarcoidosis (20). Therefore, in the presence of systemic granulomatous disease, screening for hypogammaglobulinemia is strongly recommended.

Genetics of CVID

CVID is mainly a sporadic disease, suggesting that this syndrome results from polygenic rather than monogenic causes. About 10% of cases show familial aggregation, often in association with selective IgA deficiency (sIgAD) in the kindred. Moreover, non-immune-deficient family members may have an increased incidence of autoimmunity (24).

Despite the elusiveness of CVID genetics, in the past ten years research has identified several rare monogenic disorders with a CVID-like phenotype. Defects have been found in the genes that encode for B cell antigen receptor associated complex (CD19, CD81, and CD21) (25 27), CD20 (28), inducible co-stimulator (ICOS) (29), and B cell activating factor receptor (BAFF-R) (30). Nevertheless, taken together, these defects account for less than 3% of patients (31). Another gene involved in the pathogenesis of CVID is the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) (32), but this should be considered a disease-modifying rather than a disease-causing gene, because TACI mutations can be found not only in CVID patients, but also in non-immune-deficient family members (33). About 10% of CVID patients are carriers of the mono-allelic TACI mutation, while 1-2% have bi-allelic mutations. The most frequent TACI mutations detected in CVID patients are C104R and A181E; these mutations even occur in healthy people with a frequency of 1%. The TACI mutation affects the binding to APRIL and BAFF, and exerts this effect even in heterozygosis, most likely through haplo-insufficiency. Although the exact mechanism is still not known, the TACI mutation seems to be involved in a defect of class-switch recombination, loss of plasma-cells and consequent

hypogammaglobulinemia (34). Several TACI knockout, transgenic, and knock-in mouse models have been generated. Some of them develop lymphoproliferative disorders, splenomegaly, and severe SLE-like autoimmune disorders with premature death due to renal failure (34, 35). These data from animal models suggest that in addition to its role in B cell activation, TACI plays an inhibitory role in lymphocyte homeostasis. In fact, even CVID patients with mutations in TACI have an increased incidence of autoimmune cytopenia and splenomegaly (33). In the European cohort, heterozygosity for C104R was found to be associated with autoimmunity and lymphoproliferation (32).

Association between immunological defects and clinical manifestations

Most CVID patients have altered B cell subsets, which reflect impaired B cell differentiation (36). These alterations have been utilized in the attempt to classify different forms of CVID according to the B cell immunophenotype, and to correlate different subtypes with clinical manifestations (37 40).

The reduction of CD27+IgD-IgM- switched memory B cells (SMB) is a marker for the majority of CVID patients, although it is non-specific since a low number of SMB are also found in other primary immunodeficiencies (34). SMB develop in the germinal centers of lymph-nodes in a T-dependent manner, and their reduction may depend on functional defects in either B or T helper cells. Clinically, a severe reduction in SMB is associated with a higher risk of granulomatous disease and splenomegaly (39), suggesting that a most profound lack of B cell maturation is likely to be associated with the abnormal cellular or cytokine environment that supports granuloma formation (20).

CD38++IgM++ transitional B cells (TR) are the most immature form of physiologically detectable B cells in peripheral blood. Some CVID patients have an increased number of TR that could be ascribed to a block in the early differentiation of mature B cells. These patients CD21lowCD38low B cells (CD21lo) are an unusual B cell subset characterized by low CD21 expression (complement receptor 2). Expansion of CD21lo has been found in patients with SLE (40) and CVID (41), and in viremic HIV patients (43). CD21lo express a polyclonal and unmutated BCR repertoire and, although they are not normally reactive *in vitro*, they are able to produce higher amounts of IgM than na ve B cells under certain conditions of stimulation (7). Expansion of CD21lo in CVID patients has been clearly associated with a higher incidence of splenomegaly (39) and more recently with autoimmune cytopenia (7).

T cell abnormalities in CVID have been investigated to a lesser extent. Giovannetti et al. found a subgroup of CVID patients characterized by marked depletion of CD4+ na ve T cells (below 15% of CD4+ T cells), massive T cell activation, proliferation, apoptosis, disruption of CD4+ and CD8+ TCR repertoires, reduction of CD31+ recent thymic emigrants CD4+ T cells, and an expansion of CD21lo. Clinically, these patients are characterized by severe immunodeficiency generally associated with splenomegaly and granulomatous disease (44).

Over the last decade many studies have underlined that regulatory T cells (Treg), a specific subset of CD4+CD25+CD127- T cells expressing FoxP3, play a crucial role in the suppression of autoimmune responses. Genetic defects impairing their

function cause IPEX (immunodysregulation, polyendocrinopathy, and enteropathy, X-Linked, MIM ID #304790), a rare monogenic disease with multisystemic autoimmunity. Moreover, decreases in the number or function of Treg have been detected in several autoimmune diseases, such as SLE, multiple sclerosis, and rheumatoid arthritis, as well as in CVID (45). CVID patients had significantly fewer Treg than controls, and a low frequency of Treg is clinically associated with splenomegaly (46,47), granulomatous disease (48), and autoimmune cytopenia (49). The suppressive function of Treg from CVID subjects with autoimmune disease is significantly attenuated compared to CVID subjects with no autoimmune disease and to healthy controls, and the expression of several proteins associated with Treg function (FoxP3, Granzyme A, XCL1, pSTAT5, and GITR) is decreased in the same patients (50). The reduction of Treg is more pronounced in CVID patients with a severe decrease in SMB and expansion of CD21lo (type Ia according to the Freiburg classification) (49). These patients also display a B cell intrinsic activation defect, associated with significantly reduced Ca2+ signals in primary B cells (51). These data suggest that CVID type Ia patients represent a strongly homogeneous group that is immunologically characterized by a pronounced reduction of SMB, expansion of CD21low B cells, low Treg, and impaired BCR-induced calcium signaling. Clinically, these patients display a more severe course, with a higher incidence of autoimmune dysregulation, inflammation, and lymphoproliferation.

Finally, in the last few years some reports have underlined a clinical and immunological overlap between CVID and autoimmune lymphoproliferative disease (ALPS). ALPS is a disorder of lymphocyte apoptosis characterized by autoimmunity associated with persistent, non-infectious, non-malignant lymphoproliferation. ALPS patients have a reduced percentage of CD27+ B cells, suggesting a defect in B cell differentiation, as is found in CVID (52). Moreover, some ALPS patients develop hypogammaglobulinemia during the course of their disease (53). These findings suggest that CVID and ALPS share similar pathogenic mechanisms. It could be assumed that defective lymphocyte activation in CVID patients impairs full recruitment of apoptotic pathways that are strictly dependent on cell activation, such as Fas-induced cell death, activation-induced cell death, and perforin-induced cell death. This might favor the development of lymphoproliferation and autoimmune disorders (54).

Infections, inflammation and autoimmunity in CVID

The relationship between infections, autoimmunity and inflammation is an intriguing field of research. In this regard, primary immunodeficiency could help us to elucidate the contact points of these diseases.

It has been suggested that Granulomatous manifestations of CVID are an atypical presentation of sarcoidosis on the genetic background of immunodeficiency; otherwise the immunodeficiency could lead to a dysregulated immune response to an unknown infectious agent resulting in diffuse granulomatous reactions (55). The granulomas in CVID are usually of a non-caseating nature, although caseating granulomas have also been reported (55), thus suggesting the likelihood of an infectious aetiology as the original trigger. A case of CVID with

granulomas following an acute Toxoplasma gondii infection has been reported (56). The human herpes virus 8 (HHV8) has been observed in the lungs of some CVID patients with GLIDL (57). However, a systematic association of granulomatous CVID with particular infections has never been reported. Overall, neither the pathogenesis of sarcoidosis nor that of CVID is well understood and the supposed relationship between immunodeficiency, infection and formation of granulomas remains vague (58).

Recent studies have reported the involvement of cytomegalovirus (CMV) infection in the pathogenesis of chronic inflammation in CVID. The prevalence of CMV infection ranges from 60% to 90% worldwide. After the primary infection, virus latency and persistence is facilitated by several viral proteins that interfere with adaptive and innate immunity, with an widespread pro-inflammatory effect (63). Despite some alterations in T cell phenotype and function, CVID patients have a robust CD8+ T cell response to CMV (64). Patients with evidence of CMV exposure show a higher prevalence of inflammatory diseases compared with non-exposed subjects. Moreover, CMV-specific CD8+ T cells are elevated in patients with inflammatory CVID, and show evidence of increased proliferation *in vivo* and response of antigen *in vitro.*

Lastly, CMV antigens can be detected in inflamed organs and tissues. Taken together, these findings strongly support the hypothesis that the combination of CMV replication, and a peculiar, excessive CMV-specific CD8+ T cell response directly results in the inflammatory disease (11).

CMV-specific CD8+ T cells show a high expression on the cell surface of activation markers HLA-DR and CD57, while they do not express granzyme B or Programmed Death-1 (PD-1), a member of extended CD28/CTLA-4 family of T cell regulators that negatively regulates immune responses (65). This phenotype is consistent with impaired cytotoxic potential and a reduced propensity for programmed cell death, which could explain the remarkable accumulation of CD8+ T cells that are commonly present in CMV infected patients. In fact, CVID patients with CMV infection show a significant increase in CD8+CD27-CD28- late effector cells. The expansion of this lymphocyte population is also a hallmark of CVID patients with inflammatory diseases. These mechanisms could even provide an explanation for the inversion of the CD4/CD8 ratio, a well-known feature of a subset of CVID patients associated with autoimmunity and inflammation (66).

CMV-specific CD8+ T cells have a pattern of cytokine production skewed toward the concomitant production of both IFN-gamma and TNF-alpha. Treatment of CVID patients with anti-TNF-alpha therapy (infliximab) reduces inflammatory disease (67), and the inhibition of CMV replication with antiviral drugs (ganciclovir) has a comparable effect (64). These findings provide a rationale for antiviral and anti-TNF-alpha therapy in CVID patients with inflammatory disease.

As is well known for SLE, the prototype of systemic autoimmune disease is widely associated with infectious diseases. Moreover, recent findings on SLE immunopathogenesis have shown a close association between autoimmune manifestations and subtle immune system defects. Such defects though not being critical enough to allow overwhelming infections to develop, seem to provide the ideal background for chronic inflammatory responses typical of SLE (60). Although no single pathogen (except for a putative role for Epstein-Barr virus and parvovirus B19 (61,62)) has yet been associated with SLE immunopathogenesis, recent data seem to point towards the fact that chronic inflammation in SLE could arise from chronic immune system activation towards unknown infections (60).

The association of CVID and SLE is infrequent and their relationship appears complex. Almost all the case reports describe the onset of SLE preceding the onset of CVID. When hypogammaglobulinemia appears, some patients experience an improvement in SLE symptoms, however, some autoantibodies (including ANA, anti-DNA, and anticardiolipin) can persist even in a context of reduced serum immunoglobulins. It could be assumed that hypogammaglobulinemia is caused by the drugs (i.e. corticosteroids or immunosuppressants) used to treat SLE. Nevertheless, discontinuation of therapy does not reverse hypogammaglobulinemia (7). Two patients who developed CVID after SLE also carried the very infrequent Mannose-binding lectin (MBL) haplotype 4Q-57Glu. One of them, who had low levels of circulating MBL, presented a severe phenotype with frequent lower respiratory tract infections and development of bronchiectasis, thus suggesting that the coexistence of alterations of the innate and acquired immune system could be associated with a greater susceptibility to infectious and autoimmune diseases (59).

Take home message

- In patients affected by CVID, autoantibodies and auto-reactive B cells can be detected even if serum immunoglobulins are very low and specific response to antigens is impaired.

- Patients affected by autoimmune cytopenia or SLE can later develop CVID.

- In the presence of autoimmune cytopenia or systemic autoimmune and inflammatory diseases, screening for hypogammaglobulinemia is strongly recommended.

- Screening for autoimmune and chronic inflammatory diseases is mandatory in patients with an established diagnosis of CVID.

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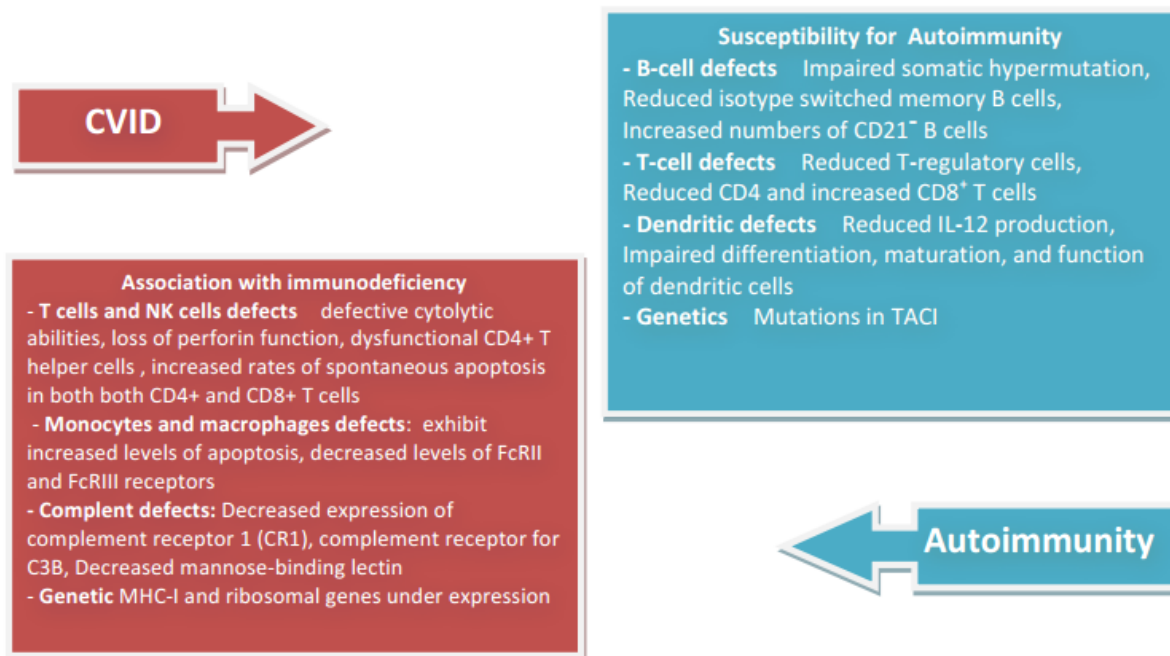
Figure 1. In this figure are represented the most important relationships between CVID and autoimmunity. More detail are provided in the text.