Published in final edited form as:

Immunol Rev. 2019 January ; 287(1): 145–161. doi:10.1111/imr.12728.

Common Variable Immune Deficiency: Dissection of the Variable

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Summary

Starting about 60 years ago, a number of reports appeared that outlined the severe clinical course of a few adult subjects with profound hypogammaglobulinemia. Puzzled by the lack of family history and adult onset of symptoms in most, the name “acquired” hypogammaglobulinemia was given, but later altered to the current name common variable immune deficiency (CVID). Pathology reports remarked on the loss of lymph node architecture and paucity of plasma cells in lymphoid tissues in these subjects. While characterized by reduced serum IgG and IgA and often IgM, and thus classified amongst the B cell defects, an increasing number of cellular defects in these patients have been recognized over time. In the early years, severe respiratory tract infections commonly led to a shortened life span, but the wide spread availability of immune globulin concentrates for the last 25 years has improved survival. However, chronic non-infectious inflammatory and autoimmune conditions have now emerged as challenging clinical problems; these require further immunologic understanding and additional therapeutic measures. Recent study of this phenotypic syndrome have provided an increasingly fertile ground for the identification of autosomal recessive and now more commonly, autosomal dominant gene defects which lead to the loss of B cell development in this syndrome.

Keywords

Common variable immune deficiency; B cell Development; Plasma Cells; Noninfectious Complications; Autoimmunity; Genetic defects; Immune Dysregulation; Enteropathy; Immune Globulin; Antibody; Genetics

Introduction

In 1954, one year after the first publication of agammaglobulinemia in a male child¹, Janeway and Gitlin reported nine additional male children with similar findings and suggested sex-linked inheritance for this immune defect². However, the following year, the first report that agammaglobulinemia was not a disease restricted to either males or children appeared when Sanford et al. described a 39 year old agammaglobulinemic woman, who had what we now recognize as common variable immune deficiency (CVID). She had all of the most frequent complications of this disorder, with chronic bronchitis, episodes of bacterial pneumonia, *Haemophilus influenzae* meningitis, chronic diarrhea, and malabsorption³. In

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the following few years, others recognized similar cases, and commented on the development of severe bronchiectasis leading to respiratory failure, the commonest cause of death⁴⁻⁷. Autopsy reports in these cases showed lymph nodes with poorly-defined cortices, no follicle formation and absence of plasma cells in lymph nodes and bone marrow⁷. While it was suggested that plasma cells development was somehow impaired, the significance of this was unclear, as the origin of gamma globulin was not yet established⁶⁻⁸. Some evidence pointed to lack of plasma cell as production of gamma globulin as patients with low serum immunoglobulins did not respond with plasmacytosis in lymph nodes after vaccine antigen stimulation. These observations suggested a connection between loss of these cells and hypogammaglobulinemia⁹, but at this time the cellular origin of gammaglobulin was still under discussion. Seltzer et al. reported that although a hypogammaglobulinemic patient could not be successfully immunized, he still had a positive histoplasmin skin test⁴. This positive test led the authors to propose a lack of correlation between “delayed tissue hypersensitivity and humoral immunity”, which was a novel concept at that time. The formal division of cellular and humoral immunity was not demonstrated until a decade later¹⁰.

In contrast to young patients with agammaglobulinemia or hypogammaglobulinemia, young adults and older subjects were often diagnosed with “acquired hypogammaglobulinemia”. Later efforts to organize the emerging constellation of immune deficiency diseases into a framework by the World Health Organization led to the first consensus statement from a panel of experts. The syndrome of patients with “late onset” immunoglobulin failure was initially identified as variable immune deficiency (common, largely unclassified)¹¹. Later this name was condensed to “common variable immunodeficiency” (CVI, later known as, CVID) to separate this syndrome from other defects with a more uniform clinical description and a more obvious Mendelian inheritance. Recently the International Union of Immunological Societies Expert Primary Immunodeficiency Committee has redefined this condition as more of a syndrome, using the term “common variable immunodeficiency disorders”¹², thus retaining the CVID acronym, but emphasizing the intrinsic clinical and genetic heterogeneity.

Current Definitions:

Due to the clinical and immunologic heterogeneity, CVID has been variably defined over the years, but according to current consensus, identification should be first based on laboratory criteria: the immune globulin levels must be lower than the age-adjusted-reference range, and for IgG, this is generally less than 400mg/dl for adults. Serum IgA (usually) and or IgM must also be low, and vaccine responses to T dependent and independent antigens should validate loss of B cell function¹²⁻¹⁴. In all cases, other reasons for hypogammaglobulinemia must be carefully excluded, including immune globulin loss, medications, viral infections, known immune defects or other medical reasons for hypogammaglobulinemia. In some respects, the generic term “CVID” is a convenient diagnostic label that can be used to launch appropriate treatment, but it is sometimes, especially for unusual cases, more useful to consider it as a temporary designation, until additional clinical and genetic information emerges. For this reason, CVID definitions have often excluded patients younger than age 4, as in these cases, other genetic causes may indeed be more likely¹². Although most CVID patients have low to normal numbers of circulating cells with B-cell phenotype, this masks a

central failure in the differentiation of B-cells into functional immunoglobulin-secreting plasma cells. In fact CVID leads to greatly reduced numbers of isotype switched CD27⁺ memory B-cells¹⁵, a characteristic that can now be identified by sub-population phenotyping in diagnostic panels^{16,17}. Clinical conditions common in CVID, such as infections, autoimmunity, granulomatous infiltrations and lymphoid hyperplasia, have also been included in some current definitions, but due to the heterogeneity of presentation, this has not been easily justified. Gene sequencing is commercially available for many of the known gene defects and are included in primary antibody deficiency panels. While not required for the diagnosis of CVID, molecular dissection can be critically important for treatment optimization and accurate genetic counseling.

Demographics:

As one of the most common symptomatic primary immunodeficiency, CVID is estimated to affect between 1:25,000 and 1:50,000, with the majority of patients being diagnosed between the ages of 20 and 45; males and females are affected equally. In several series, males tend to be diagnosed earlier^{18,19}. Racial differences are likely and most estimates are based on Caucasian populations; CVID may be less common in patients with African-American ancestry²⁰. Due to this well-known heterogeneity, patient cohort and large-scale registry studies have been used over time with benefit, as these develop a more robust picture of disease^{18–24}. While the diagnosis is most typically made in adult life, about 20% of patients are less than 21 years of age at diagnosis, and adult patients often give a history of clinical events suggestive of an immune disorder at an early age^{18,20,22}. However, in a study of 141 pediatric patients (<21 years of age) evaluated for primary immune deficiency, only 4 were found to have CVID, suggesting that for some patients, B cell dysfunction may have evolved over time²⁵. In large data collections, most parameters examined in children with pediatric-onset CVID appear quite similar overall to subjects diagnosed in adult life, but some differences were noted. Pediatric-onset CVID patients had more frequent episodes of otitis media, developmental delay, and failure-to-thrive as compared to patients with adult-onset CVID. Adult CVID patients were more frequently diagnosed with bronchitis, arthritis, depression, and fatigue; they also had somewhat more frequent diagnoses of autoimmunity, lymphoma and other malignancies²⁶. In all series, patients in their 5th or later decades have also been reported. The causes of B cell failure in older adults are unclear, but the most of the genetic defects described below, can also be found in these subjects. In all series, it is apparent that a delay in diagnosis of 6–7 years, after the onset of characteristic symptoms is common in adults, perhaps due to the apparent later onset and phenotypically heterogeneous nature of this disease.

Clinical Spectrum:

The clinical spectrum of CVID is broad but consists of two main phenotypes, predominately recurrent infections that are identified in most subjects, but also autoimmune and/or inflammatory features which may be evident at presentation or after, in approximately 25–50% of patients. The study of these additional features has been essential. As described in many reports, these inflammatory complications together can be medically challenging, leading to substantial morbidity and/or mortality when compared to patients with infections

only²²¹⁸. The kinds of infections that develop in CVID and the variety of autoimmune and/or inflammatory complications which occur, are outlined in the following sections.

Infections:

The most common infections, often appearing as the initial symptoms of an immune defect, are upper respiratory tract infections, including pneumonia, chronic bronchitis, and sinusitis. In a Finnish study of 95 patients, sinopulmonary infections were the most common pre-diagnostic sign or symptom; 66% of patients had suffered from recurrent pneumonia, 60% with recurrent maxillary sinusitis, and 45% with recurrent bronchitis²⁴. In the early years, recurrent lung infections leading to bronchiectasis and respiratory failure emerged as the main cause of death in CVID. In one series of 250 patients, 240 had respiratory symptoms, with pneumonia in 147 (61%) of cases²⁷. Severe bacterial infections such as meningitis, osteomyelitis and organ abscesses are now uncommon, but still appear in all series of patients. Common organisms in CVID are *Streptococcus pneumoniae* or *Haemophilus influenzae* but mycoplasma sp. have also been noted in lungs, urinary tract and joints when appropriate tests (molecular or culture) were available^{282420,2123,29}. Viral respiratory infections are also common in CVID. After carefully following a cohort of 12 patients for a year, investigators reported 65 episodes of acute infections and noted that viruses were found in sputum in 54% of cases, mainly rhinovirus. Notably for these patients, the PCR stayed positive in some for several months³⁰. Gastrointestinal tract infections are also quite common in CVID, leading to recurrent or chronic diarrhea. The organisms in this location are likely to be bacterial, protozoal, or viral agents. Giardia, Salmonella, and Campylobacter infections are more common, but cryptosporidium, CMV and currently norovirus, present an increasing clinical challenge. One might assume that patients with CVID would have a higher prevalence of *Helicobacter pylori* infections but this does not seem to be the case, possibly because of the frequent use of antibiotics³¹.

Lung disease:

Airway disease is the most common medical problem in CVID, and is often manifest in chronic lower respiratory tract infections leading to bronchiectasis. Curiously, bronchiectasis was not in one study apparently related to serum immunoglobulin levels, suggesting that antibody reconstitution is not the only factor in the development of this complication, but may reflect presence of additional inflammatory conditions³². While Ig therapy has significantly reduced the numbers of pneumonias in CVID³³, severe bacterial infections and episodes of otitis, this therapy does not seem to ameliorate or cure chronic sinusitis²¹. High resolution CT (HRCT) scans often reveal parenchymal and interstitial pulmonary changes, including nodules, reticular changes, fibrosis and/or areas with a ground glass appearance³². For larger or persistent nodules, biopsy may be required to determine if these are scars, or lymphoid collections. Somewhat less common, but medically of greater importance, is interstitial lung disease, which on biopsy, is composed of both lymphocytic and/or granulomatous infiltrates³⁴. Commonly these tissue infiltrates are not limited to the lung, but are frequently observed in other organs such as lymph nodes, bone marrow, liver, spleen, and sometimes in the brain or kidneys. In the lungs, this pathology has been called granulomatous lymphocytic interstitial lung disease (GLILD), the presence of which is associated with a poorer outcome³⁵. Investigating lung disease in children, one study found

that bronchial changes and interstitial lung disease were phenotypically distinct; the former was associated with pneumonias and the latter was associated with autoimmunity and loss of memory B cells accompanied by expansion of non-naïve cytotoxic T cells.³⁶ Further examination of the pathology of interstitial lymphoid lung disease in subjects without granulomatous changes in tissue samples has demonstrated distinct B- and T-cell zones, but with B-cell predominance in some patients and T-cell predominance in others. Colocalization of Ki67, Bcl6, and CD23 within this ectopic lymphoid architecture has demonstrated presence of tertiary lymphoneogenesis with active centers of cellular proliferation³⁷.

Lung transplantation has been performed in a few patients with CVID for end-stage bronchiectasis, and respiratory failure, but the data are scarce. In one study, 2 of 3 patients had an improved life for 3 years but then subsequently died at 6 years²⁰; in another report a patient developed a chronic aspergillous infection, many hospitalizations, and survived for 4 years³⁸.

Autoimmunity:

Autoimmunity is a common complication in CVID, affecting at least 25% of patients. Curiously this may be the first manifestation of an immune defect in an occasional patient who has never experienced significant clinical infection^{18,22,39,40}. Antibody-mediated cytopenias predominate in such cases, most often immune mediated thrombocytopenia (ITP), less frequently, hemolytic anemia, or rarely, autoimmune neutropenia. For 311 CVID patients in the French registry, 55 patients (18%) had had an autoimmune cytopenia⁴¹. Of 990 CVID patients in the USIDNET registry, 10.2% had an autoimmune cytopenia; ITP was diagnosed in 7.4% of cases, hemolytic anemia in 4.5%, and autoimmune neutropenia in 1%⁴². These subjects were also significantly more likely to have one or more other CVID-associated non-infectious complication, including lymphoproliferation, granulomatous disease, lymphoma, hepatic disease, interstitial lung diseases, or enteropathy. In addition to these, patients presenting with autoimmunity and cytopenias frequently have both lymphadenopathy and splenomegaly.

Autoimmunity in CVID is not restricted to hematologic cells, as rheumatologic complications occur in perhaps 10% of patients, with females being somewhat more affected⁴³. In a study of 227 patients, juvenile rheumatoid arthritis, and adult rheumatoid arthritis were most frequently present, followed by juvenile spondyloarthritis and undifferentiated arthritis. Systemic lupus erythematosus was seen in only one patient in this study. Septic arthritis may also occur. Pernicious anemia, primary biliary cirrhosis, thyroiditis, sicca syndrome, systemic lupus, Sjögrens syndrome, vitiligo, alopecia have been reported in all series^{20,41}.

To further understand autoimmunity in CVID, B cell phenotypes have been extensively examined. In subjects with autoimmune cytopenias; the central observation that has emerged is that CD21(low) B cells are substantially increased^{41,40,44,45}. In addition, Boileau et al found that T cells in these subjects displayed an activated phenotype (increase in surface expression of HLA-DR and CD95) with correspondingly fewer naïve T cell numbers. As noted above, CD21(low) B cells are found in other autoimmune states such as rheumatoid

arthritis, and on activation, have been found potentially polyreactive⁴⁵. In another study, Romberg *et al* showed that germinal centers in lymph nodes from CVID patients with prominent autoimmunity display irregularly shaped hyperplastic germinal centers while germinal centers were scarce and smaller in patients without this history. Hyperplasia in these cases was accompanied by increase in the numbers of circulating follicular helper T cells, decreased regulatory T-cells and T-reg function⁴⁶. This germinal center drive appeared to correlate with fewer isotype-switched memory B cells, lower frequencies of somatic hypermutation, and curiously, increased serum endotoxin in these subjects. In some patients, single cell analyses revealed increased VH4–34-encoded antibodies with unmutated Ala-Val-Tyr and Asn-His-Ser motifs; the latter are of interest as these recognize both erythrocyte I/i self-antigens and commensal bacteria⁴⁶.

Granulomatous disease:

Granulomatous disease occurs in 8–22% of patients with common variable immunodeficiency (CVID). The tissue collections are variable, usually consist of well-formed non caseating granulomata, and can be found in any organ, although lungs and lymphoid tissues are the most frequent locations. These granulomatous changes, sometimes confused as “sarcoidosis” may be diagnosed on biopsy years prior to the recognition of hypogammaglobulinemia and in such cases, often delays the recognition of the immune defect^{47,48}. Among 436 subjects with CVID in the French Registry, 59 patients (13.5 %) were diagnosed with granulomatous disease in one or more organs. This group included 37% males and 63% females. The median age at diagnosis was 40 years but 4 patients were diagnosed before 18 years of age. Granulomatous disease was diagnosed before or at time of CVID diagnosis in 24 subjects, while in 35 patients, granulomatous disease was diagnosed later, as long as 21 years after the immune defect was recognized. In another study of 455 CVID subjects in the US, 37 patients were known to have granulomatous disease(8.1%)⁴⁷. Of these 64.8% were female, 29 were Caucasian, 5 African American, 2 Hispanic, and one was Asian. The median age of patients at time of CVID diagnosis was 29 years. Granuloma were found in many tissues, including lymph nodes, liver, skin, spleen, bone marrow, brain, retinae, small bowel, and kidney. Of these 59% had moderate to severe respiratory impairment and 54% had one or more episodes of autoimmunity, including ITP, hemolytic anemia, or both. Ten of the 35 subjects for whom current information was known, had died at a median age of 37.5 years. In both cohorts the association of granuloma, autoimmunity, granulomas, and splenomegaly was noted, as also for other reports^{49,50}. In the French series, there was a suggestion that lymphomas may be more frequent in CVID subjects with granuloma (25% vs. 15%; p 0.05).

Enteropathy:

Gastrointestinal complaints including bloating, pain and diarrhea, are common in CVID, and linked to both infectious agents as described, but other less well defined inflammatory enteropathies not clearly linked to infections are also recognized. Non-infectious enteropathy occurs in 20 to 60% of CVID patients, depending on the study, and histologically may resemble known gastrointestinal conditions such as Crohn’s disease, ulcerative colitis or celiac disease^{18,22,31}. Colitis and gastritis are the most frequent manifestations, while with long-standing gastrointestinal disease, weight loss and

malnutrition may appear. Osteoporosis, zinc, vitamin A, D, B12 and E deficiency lead to additional clinical complications. Upper endoscopy may reveal atrophic gastritis; mucosal histology in the small bowel is characterized by the loss of villi, paucity or absence of plasma cells, nodular lymphoid hyperplasia, and increased frequency of CD8+ T cell infiltrates in the intestinal lamina propria⁵¹. In some patients, anti-enterocyte antibodies have been found, suggesting an autoimmune component. When this histologic appearance is discovered, patients are not infrequently told to avoid gluten, and according to a few reports, withdrawal of gluten has appeared to offer benefit. While serologic markers are not useful in dissecting celiac disease in this form of enteropathy, genetic markers may be helpful⁵². However, for most patients, current consensus is that gluten avoidance is not a useful therapeutic and leads to further weight loss. Jørgensen *et al* compared the gene expression of small bowel intraepithelial lymphocytes in CVID to samples from celiac subjects, and found non- overlapping features using discriminating pathways analyses⁵³. In patients with long standing enteropathy, an almost graft-vs-host like histology has been reported. Mononuclear cells in these tissues may produce more IL-12 and IFN γ as compared to controls⁵⁴. Innate lymphoid cells (ILC) in these tissues have been identified and may play a role in pathogenesis⁵⁵. A relative lack of plasma cells in the mucosa is common in CVID, and is found more frequently in the colon (56%), followed by rectum (50%), ileum (42%), duodenum (42%), and to a lesser extent in the gastric mucosa (16%). Gastrointestinal plasma cell loss has been correlated to reduced numbers of circulating switched memory B cells and increased numbers of CD21(low) B cells. Seeking additional markers investigators have reported that CVID subjects show monocyte and T cell activation, with increased serum levels of sCD14⁵³. In a related study, 16S ribosomal RNA-based profiling of stool samples was used to identify a significant difference in the microbiota of the CVID subjects compared to controls; these alterations could be correlated with increased plasma levels of both LPS and sCD25⁵⁶.

Liver Disease:

In early reports of complications stemming from therapeutic management of CVID, viral hepatitis (HBV or HCV) due to infused blood or blood products were noted, but for the past two decades, these have been quite uncommon. Currently the most common liver pathology is nodular regenerative hyperplasia (NRH)^{57–60}. This pathology is characterized by displays of nodular areas with enlarged hepatocytes, organized into two-cell thick plates alternating with compressed liver cell plates, peri-sinusoidal fibrosis, and focal lymphocytic infiltrates. Studies of the infiltrating cells demonstrate predominance of IFN-gamma producing T cells⁵⁸. Approximately 10% of CVID patients show evidence of liver dysfunction; in many cases, a mildly elevated alkaline phosphatase is observed suggesting liver involvement. This has been consistently reported by numerous investigators^{57–60}. In the absence of clinical reasons for biopsy in most patients, NRH is likely more common than the current estimate of 5% of CVID subjects⁵⁸. NRH may be silent with no clinical consequences and preserved synthetic functions of the liver, but in some cases the pathology leads to cirrhosis, portal hypertension, splenomegaly, esophageal varices, ascites and jaundice. The cause of NRH, also found in cystic fibrosis, HIV infection, chronic granulomatous disease, and after solid organ transplantation is not known, and treatment is based mostly on lowering portal pressures. Transjugular Intrahepatic Portosystemic Shunts (TIPS) have used, but with

unclear success⁶¹. Liver transplantation has been performed, but the outcome has not been very encouraging overall with recurrent disease in the transplanted liver in some^{62,63}. Other liver conditions noted in some CVID patients are primary biliary cirrhosis and granulomatous disease.

Neoplastic Disease:

Individuals with CVID are susceptible to malignancy, and have an estimated 1.8- to 5-fold increased risk of developing cancers of all types⁶⁴⁻⁶⁷. Estimates for lymphoma are higher, possibly 30 times greater than in control populations and in one study, were more common in women^{20,68-71}. The most frequent malignancy is non-Hodgkin lymphoma, although other malignancies such as colorectal, breast, uterine, and neurogenic malignancies have been reported. In one contemporary report of 473 patients, 39 (8.2%) had a lymphoid malignancy while 33 others (7%), had other cancers, breast, gastric, melanoma, colon, lung, oral, skin, thyroid, vagina, ovary and esophagus¹⁸. In contrast to older, published data which suggested a higher incidence of gastric cancer^{23,72}, this study noted only three cases, potentially related to the reduced incidence of this cancer over time, likely related to greater use of antibiotics in CVID that could eliminate colonizing *H. pylori*, considered a major pathogenic cause^{73,74}. The lymphomas in CVID are usually of B cell origin, often extranodal and are not infrequently mucosal in location. Lymphomas may be EBV+ but most often are not. The pathogenesis is unclear, but may appear in a setting of lymphoid hyperplasia. When lymphomas are mucosal, they are termed as MALT lymphomas and may be quite indolent⁷⁵. Although lymphoma may precede the diagnosis of CVID, after chemotherapy it becomes unclear whether the patient had an intrinsic immune defect or if the therapy itself led to chronic hypogammaglobinemia. The increased risk of cancer in CVID could result from impaired immunity to potentially damaging pathogens (*Helicobacter pylori*, Epstein-Barr virus), chronic antigen stimulation, or to impaired tumor cell surveillance. However in several reports, cells of subjects with CVID have increased radio sensitivity, which is considered a significant risk factor for neoplasia^{76,77}.

Immunologic Abnormalities:

B cell immunity:

The hallmark of CVID is loss of B cell function. To elucidate and classify patients, phenotyping of B-cell subpopulations has been used to demonstrate a severe reduction of isotype switched memory B cells in most patients, accompanied by an expansion of CD21(low) B cells in some, especially those with autoimmune disease. While most patients have at least some circulating B cells, an occasional patient will not. Using the EUROclass system⁴⁹, investigators have compared patient groups, separated into those with nearly absent B cells (less than 1%), severely reduced isotype switched memory B cells (less than 2%), and subjects with expansion of transitional (more than 9%) or an expansion of CD21(low) B cells. CD21(low) B cells have been found in other autoimmune states and have unique characteristics, specifically an un-mutated B cell receptor, and while capable of IgM production under selected states of activation, have been found potentially polyreactive⁴⁵. In CVID these had significantly reduced calcium flux⁷⁸. The first group in this system contains all patients with severe defects of early B-cell differentiation; those with

severely reduced switched memory B cells suggesting the presence of a defective germinal center development.⁴⁹ Classifying patients into this framework has proven to be useful in gauging the functional capacities of B cells in groups of CVID patients, and has clear clinical relevance^{50,79}. In one study, females with CVID had higher levels of serum IgM, and greater numbers of isotype switched memory B cells^{20,80}, and, possibly not coincidentally, a higher incidence of B cell lymphomas.^{20,68–70} An additional B cell marker of interest in CVID is CD73, a GPI-anchored 5' nucleotidase that catalyzes the dephosphorylation of AMP into adenosine, essential in class switch recombination but deficient on naïve, IgM memory, and switched memory B cells of CVID patients⁸¹

In a subsequent study to examine the molecular characteristics of the CVID B cell receptor in 93 patients, high-throughput DNA sequencing of Ig heavy chain gene rearrangements showed abnormal VDJ rearrangement and abnormal formation of CDR3 regions. In addition, decreased diversity of the naïve CD27- B cell pool and also decreased somatic hypermutation in CD27+ cells were observed. Since patients also demonstrated clonal expansion of un-mutated B cells (pre-selection), the authors provided new evidence that the B cell defects in CVID originated in the pro-B stage of development in the bone marrow⁸².

T cell defects:

In addition to the B cell defects described above, CVID is often accompanied by substantial global T cell abnormalities, including reduced T-cell numbers, cytokine defects, and impaired in vitro lymphocyte proliferative response to mitogens and antigens. Many other T cell defects in CVID have been described, including abnormal lymphocyte trafficking, dysregulated T cell responses to chemokines⁸³, and reduced numbers of CD45RA +CCR7+CD4+T cells⁸⁴. Lymphopenia affects mostly CD4 T cells, especially naïve CD4 T cells while CD8 T cells, in these cases, become relatively expanded. For many CVID subjects, both CD4 and CD8 T cells may be activated as determined by the expression of activation markers and Ki67⁸⁵, and have a tendency to undergo apoptosis⁸⁶. Several reports have described reduced numbers of regulatory T cells, especially affecting CVID subjects with reduced switched memory B cells and expanded CD21(low) B cells and in especially in subjects with autoimmunity and lymphoproliferation^{87,88}.

The T cell repertoire in CVID subjects, as a group, is also both more clonal and less diverse. Ramesh *et al* noted that the CVID T cell receptor β chain of 44 CVID subjects had significantly less junctional diversity than 22 adult controls, fewer n-nucleotide insertions and deletions, and completely lacked a population of highly modified TCRs seen in controls. The sequences were also significantly more clonal than control DNA, and displayed unique V gene usage. These abnormalities appeared pervasive, and were also found in out-of-frame sequences, and thus would be considered independent of both germinal center selection. Both V region use and clonal expansions, were independent of any specific clinical complications⁸⁹.

For those CVID subjects with a severe reduction in naïve CD4 T cells, the diagnosis of late-onset CID (LOCID) has been suggested⁸⁴. Because “CVID” subjects with very low T cells often have opportunistic infections, some authors have suggested that these subjects should not be included in collections of patients without these features. Indeed, in this study,

consanguinity was more common, also suggesting that additional genetic defects are likely to be present⁹⁰.

While the origin of the T cell defects is likely to be intrinsic to the immune defect, an alternative hypothesis for some subjects, at least at diagnosis, might be that chronic translocation of bacterial products could also lead to the relative “exhaustion” of bacterial specific CD4 T cells. In one study, endotoxin was noted in serum in subjects not yet treated with Ig therapy and the CD4 T cells of these subjects revealed proliferative defects, along with higher expression of the programmed death 1 (PD1) receptor. Upon Ig therapy, bacterial translocation resolved and CD4T cell function was restored⁹¹.

Cytokine defects:

Cytokine defects have long been known in CVID, especially a lack of IL-2 production. These observations led to early clinical trials with this cytokine, which demonstrated some clinical and immunologic benefits^{92–95}. Other cytokine defects or alterations include increased IL-6^{96,97}, reduced interferon (IFN)- γ , increased TNF α , with low or increased IL-4^{98,97,99}. In contrast, IL-7, which has a role in the expansion of autoreactive T cell clones, was elevated in a subgroup of CVID patients¹⁰⁰. Though increased IL-7 levels were not associated with T cell lymphopenia, they were correlated with a more frequent incidence of autoimmunity¹⁰⁰.

Dendritic and innate lymphoid cells:

A number of other cellular defects have been described in CVID, including defective dendritic cells (DC). Reduced circulating monocyte derived DC (mDCs) and plasmacytoid (pDCs) have been reported by a number of different laboratories^{101,102,103}. Activation of mDCs results in deficient expression of CD86, CD40 and MHC class II, demonstrating lack of appropriate maturation markers potentially relevant to the defective induction of T cell proliferation found in this study^{104,105}. While excess monocyte production of intracellular IL-12 had previously been suggested¹⁰⁶, mDCs of CVID subjects were found to have a significantly reduced capacity to secrete IL-12 when cultured with the physiologic simulators, LPS, TNF- α , or CD40-L fusion protein¹⁰⁷. Additional interesting studies were focused on whether the defects in CVID pDC could contribute to disease pathogenesis since stimulation of ex-vivo-sorted CVID pDC demonstrated greatly impaired IFN- α responses to TLR-9 and TLR-7 ligands^{108,109}. This was suggested as a possible link between pDC defects and B cell dysfunction, since IFN- α is known to augment both TLR-induced B-cell activation and maturation¹¹⁰. In fact, in one study, exogenous IFN- α could partially rescue the defective TLR7-induced class switching in CVID B cells^{108,109}.

In a recent study a CD127(+), CD161(+) lymphoid population containing T-box transcription factor, retinoic acid-related orphan receptor (ROR) γ t, IFN- γ , IL-17A, and IL-22, were found expanded in the peripheral blood of patients with CVID with inflammatory conditions. In these, a mean of 3.7% of PBMCs were in this category. With the phenotype identified, these cells had the hallmarks of type 3 innate lymphoid cells (ILC3), and an inflammatory potential. The same cells were also found in gastrointestinal and lung biopsy tissues of CVID suggesting a role in these mucosal inflammation⁵⁵. A

second study identified a similar ILC3 expansion, but also showed a relative loss of ILC2 cells, especially for those subjects with enteropathy¹¹¹.

Morbidity and Mortality:

Using a large data set of 2,134 CVID patients compiled by the ESID Registry from 28 medical centers, risk of overall morbidity and mortality has been examined. In this cohort 119 (7.4%) of patients were deceased. Older age at onset of symptoms, older age at diagnosis, and diagnostic delay were all associated with an increased risk of death ($P < .001$). While lymphoma or solid tumor was associated with an increased risk of death, no other clinical complications were found associated¹⁹. This is in contrast to a previous study using a curated ESID data for a CVID cohort, in which subjects with non-infections complications had a clearly reduced survival²². This study was also validated in a single center study in the US in which demographic and immunologic markers associated with complications and poorer survival were investigated in another large cohort¹⁸. Here, the median age at death was 44 years for females and 42 years for males, both significantly different from age-matched population controls. The overall mortality in the US cohort over a 4-decade interval was 19.6%. Notably both the ESID and US data show that significant improvement in mortality has occurred over time, as compared to data collected by Healy *et al* before the introduction of intravenous immunoglobulin replacement; in this early study, there was only a 29% survival of hypogammaglobinemia patients over a 12 year period¹¹². The US data is similar to that of the curated ESID CVID cohort, with a 15% mortality over a similarly extended period²² but worse than the results of another study (6%) (Quinti *et al*,²¹) for a significantly younger CVID cohort, but also followed for 11 only years. As for the curated ESID cohort, the risk of death in the US series was nearly 11 times higher for CVID patients with one or more of the non-infectious complications, compared to subjects who had infections only (HR=10.96; $p < 0.0001$). This observation was confirmed by Kaplan-Meier analysis with 95% long term survival for CVID patients with infections only versus 42% for patients with any other complication. Specific complications that were associated with an increased risk of death included gastrointestinal disease (HR 2.78; $p = 0.0004$), liver disease/hepatitis (HR 2.48; $p = 0.0003$), lymphoma (HR 2.44; $p = 0.001$), chronic lung disease (HR 2.06; $p = 0.001$), or malabsorption (HR 2.06; $p = 0.022$). Conversely, autoimmunity, cancers other than lymphoma, history of splenectomy, presence of granulomatous disease, or the development of bronchiectasis alone, were not significantly associated with reduced survival. In terms of immunologic parameters that might serve as biomarkers to predict poorer outcomes, lower baseline serum IgG level (HR=0.998; $p = 0.0079$), fewer peripheral blood B cells (HR=0.933; $p = 0.0004$), and an increased serum IgM levels (HR=1.005; $p = 0.0021$) were all associated with increased mortality in this study¹⁸. Separately, mortality in CVID subjects with granulomatous disease has been examined. In one study, there was a median survival of 13.7 years in CVID patients with granulomatous/lymphoid interstitial infiltrates, as compared to 28.8 years in those without this complication³⁴. Finally in contrast to both the US and ESID studies, CVID mortality in Iran showed quite different characteristics. In a study of this population, CVID mortality was 0.42 per 100,000, but with the highest rate for children of ages 5 to 14. In these cases, the highest mortality was noted in subjects with infections, while the second highest mortality was found for subjects with

polyclonal lymphocytic infiltrations¹¹³. These authors pointed out the need for earlier recognition and treatment of the immune defect.

Genetic Defects leading to the CVID phenotype

Because of the late onset of clinical symptoms and striking heterogeneity, for most of its history, CVID has been assumed to be a polygenic syndrome. However, the possibility that the immune defect may have unifying features, despite its clinical and demographic heterogeneity, was suggested by a genome wide association study of 363 patients from 4 centers, genotyped for 610,000 single nucleotide polymorphisms. These studies demonstrated a strong association with both the MHC region and disintegrin and metalloproteinase (ADAM) genes (P combined = 1.96×10^{-7}). In addition, copy number variation analyses defined 16 disease-associated deletions and duplications. Furthermore, the 1,000 most significant SNPs were strongly predictive of the CVID phenotype by using an algorithm with positive and negative predictive values of 1.0 and 0.957, respectively¹¹⁴.

In a number of studies in the past two decades, linkage studies, whole exome and whole genome analyses have revealed monogenic causes that lead to the CVID phenotype. The first of these were autosomal recessive genes, but an increasing number of autosomal dominant genes with variable penetrance have now been documented. While overall, these may underlie the syndrome in perhaps 10% of subjects, in families and selected patient groups, a monogenic cause has been assigned to as many as 30% of subjects^{115–117}. As one might suspect, the genes identified reflect the complex requirements of B cell antigen signaling, activation, survival, migration, and maturation to the plasma cell stage. As it is now apparent, defects in many receptors, activators and co-stimulators, can lead to either moderate or profound B cell impairment, and ultimately, hypogammaglobulinemia. In these cases, the diagnosis of CVID has often been applied. An additional emerging theme in the study of human B-cell defects is that mutations in genes involved in immune regulation in general, are also likely to lead to the initial clinical phenotype of antibody deficiency, with hypogammaglobulinemia being an early and cardinal feature. The genetic defects identified in subjects with the CVID phenotype, are outlined on Table 1. The main genes linked to this syndrome, are discussed below.

ICOS Deficiency:

Autosomal recessive mutations in the gene encoding the inducible T-cell costimulator (*ICOS*), a T-cell surface receptor, was one of the first genetic causes of CVID to be identified¹¹⁸. ICOS, a member of the CD28 and CTLA4 (cytotoxic T-lymphocyte associated protein 4) family of proteins is required for interaction with its cognate receptor on antigen presenting cells (B7) and is required for germinal center formation and terminal B-cell differentiation. Activated CD3(+)CD4(+) T lymphocytes in one kindred with a frameshift deletion, demonstrated a complete absence of ICOS expression and a reduction in circulating T follicular helper cells¹¹⁹. Patients with homozygous and compound heterozygous mutations have been reported and have a variable age of onset. The severity of this rare immune defect is quite diverse, and may include inflammatory bowel disease, abnormal liver enzymes, enteropathy and/or opportunistic infections.

BAFF receptor deficiency:

Maturation of splenic B-cells is regulated by interactions with B-cell activating factor of the tumor necrosis family (BAFF), acting on its receptor (BAFF-R) as well as activation of BCR by self-antigen. These allow differentiation of transitional and mature B-cells, expression of Bcl-2 family members and downregulation of pro-apoptotic factors. Autosomal recessive mutations in BAFF-R were first identified in two siblings, leading to adult onset hypogammaglobulinemia¹²⁰. More common polymorphisms in BAFF-R (especially the P21R variant) in CVID, which have modifying effects on either BAFF-R assembly or ligand binding may impair B-cell maturation¹²¹.

TACI deficiency:

In addition to binding the BAFF-R, BAFF also binds to the B-cell receptor transmembrane activator and CAML (Calcium-modulating cyclophilin ligand) interactor (TACI), a product of the gene *TNFRSF13B*. TACI is expressed on mature B-cells, especially marginal zone B-cells, CD27⁺ memory B-cells, and plasma cells, and binds both APRIL and BAFF only when presented in an oligomeric or membrane-bound form. TACI mutations are found in 8–10% of CVID patients, usually in the heterozygous state, suggesting either dominant-negative effect or haploinsufficiency^{122,123}. *TNFRSF13B* haploinsufficiency or null alleles, result in decreased TACI expression on memory B-cells and impaired antibody secretion, suggesting that during later stages of B-cell development, TACI supports class-switch recombination, plasma cell differentiation and antibody secretion. Clinically, patients are found to have hypogammaglobulinemia with impaired antibody responses, however, a common feature is a propensity to autoimmune manifestations and lymphoid hyperplasia potentially due to lack of normal mechanisms of that are required for establishing tolerance^{124–127}. However, while TACI mutations are significantly associated with both immune deficiency and autoimmunity in CVID^{124,125} some of the same mutations are found in healthy controls and phenotypically “normal” relatives – although in these, lack of TACI-directed upregulation of activation induced cytidine deaminase (AID) could still be demonstrated.¹²⁸

B-Cell Costimulatory Molecule Deficiencies:

B-cell development and differentiation depends on signal transduction through the BCR and co-receptors. Autosomal recessive defects in these surface receptor, although quite rare, have been reported in subjects with the CVID phenotype. Of these, CD19 a cell-surface expressed throughout B-cell development until the plasma cell stage, forms a complex with CD21, CD81 in the membrane of mature B-cells. Autosomal recessive mutations in these genes, and also in CD20, lead to defective B-cell activation and hypogammaglobulinemia^{129–132}. Autosomal recessive mutations in an additional B-cell receptor, CD27, a marker of human memory B-cells, have also been described in patients with the CVID phenotype¹³³.

TWEAK Deficiency:

TNF-like weak inducer of apoptosis (TWEAK) has also been described as having a role in BAFF signaling and B-cell survival (TNFSF12). An autosomal dominant mutation in *TWEAK* has been identified in one CVID pedigree, associated here with recurrent

infections, reduced IgM and IgA with impaired antibody responses. The mutation appeared to affect B-cell survival by interacting with BAFF to form ineffective BAFF complexes¹³⁴.

IKAROS Deficiency:

Curiously, while Ikaros proteins are lymphoid-restricted zinc finger transcription factors considered as master regulators of lymphocyte differentiation, autosomal dominant mutations in the IKZF1 gene have been found in subjects diagnosed with CVID^{135,136}. As for the other autosomal dominant mutations discussed below, not all carriers are clinically immune deficient. Patients identified had moderate to profound hypogammaglobulinemia, / loss of antibody production and often, increased CD8+ T cells with reversed CD4:CD8 ratios. Two subjects in the first CVID cohort had had B-cell acute lymphoblastic leukemia (ALL). In 7 other subjects more recently identified, who had mutations affecting amino acid N159 in the DNA binding domain, T cells were mostly naive, and while bacterial and viral infections were also noted, *Pneumocystis jirovecii* was found in all¹³⁶.

Interferon Regulatory Factor-2 Binding Protein 2 (IRF2BP2):

A heterozygous missense mutation was found in a father and his two children who were diagnosed with CVID. *In vitro* studies showed that stimulation of the proband's lymphocytes demonstrated impaired formation of B-cell plasmablasts¹³⁷.

Major Histocompatibility (MHC) genes and MSH5:

For many years it has been noted that there may be subjects with IgA deficiency or CVID in the same family; furthermore, selective IgA deficiency may in rare cases, evolve into CVID. These genetic studies suggested a common pathogenic basis for these common antibody defects; further analyses suggested a possible linkage to the MHC region, in particular, associated haplotypes HLA (HLA) A1-B8-DR3 and B14-DR1^{138,139}. Several single nucleotide polymorphisms in the gene encoding MSH5, a DNA mismatch repair protein with likely involvement in class switch recognition, was reported to occur more frequently in CVID and IgA deficiency in a combined study of U.S. and Swedish patients¹⁴⁰. However, these polymorphisms are also found in healthy individuals, thus its role in CVID is unclear.

Deficiency in genes linked to immune regulation:

Lipopolysaccharide-responsive beige-like anchor protein (LRBA):

An emerging theme in the study of human B-cell defects is that defects in genes controlling immune regulation may present with the clinical phenotype of antibody deficiency, with hypogammaglobulinemia being an early and cardinal feature. These syndromes also commonly include autoimmunity, enteropathy, splenomegaly, generalized lymphoid hyperplasia and in some cases, opportunistic infections and granulomatous tissue infiltrations. The first mutations of this sort to be recognized in CVID were in the gene encoding lipopolysaccharide-responsive beige-like anchor protein (LRBA), in 4 consanguineous families with members with childhood-onset humoral immune deficiency and features of autoimmunity¹⁴¹. *In vitro*, the patients' lymphocytes had disturbed B cell development, defective B cell activation, poor plasmablast formation, and hypogammaglobulinemia. LRBA, is a lipopolysaccharide (LPS) inducible cytosolic protein

localized in the vesicles and endoplasmic reticulum of almost all cell types. Its function is linked to LRBA as it appears to protect Cytotoxic T lymphocyte antigen-4 (CTLA-4) from lysosomal degradation, and therefore helps maintain intracellular pools of this protein, for rapid mobilization to the cell surface for inhibitory function. Mutations leading to loss or greatly reduced LRBA protein expression are linked to a severe clinical phenotype with immune deficiency leading to recurrent infections, autoimmunity, and almost autoimmune/lymphoproliferative (ALPS)-like features in some patients, and severe inflammatory bowel disease in others¹⁴². The loss of LRBA results in reduced autophagy as shown by the abnormal accumulation of organelles in B cells. LRBA deficiency leads to Treg cell depletion, decreased expression of the Treg cell markers FOXP3, CD25, Helios, and CTLA4, expanded memory T cells and marked expansion of T follicular helper with contraction of T follicular regulatory cells¹⁴³. While most patients with childhood onset disease, have homozygous recessive mutations, compound heterozygous mutations have been identified in adults who have carried the CVID diagnosis for years¹¹⁵.

Cytotoxic T lymphocyte antigen-4 (CTLA4):

Similar to defects of LRBA, but with more variable penetrance, are heterozygous autosomal dominant mutations in CTLA4, another member of the ICOS/B7 (CD80) family. CTLA-4 is an essential effector component of T_{reg} cells and required for T cell suppressive function¹⁴⁴. CTLA-4 appears to function by removal of the ligands CD80 and CD86 from antigen presenting cells, leading to loss of antigen presenting capacity normally engendered by activation through the stimulatory receptor CD28. Haploinsufficiency of CTLA4 leads to both impaired ligand binding and an immune dysregulation syndrome characterized by autoimmunity, lymphoid hyperplasia, and in many cases, hypogammaglobulinemia, autoimmune cytopenias, enteropathy and granulomatous infiltrative lung disease^{145–147}. As an autosomal defect with variable penetrance, an estimated 67% of relatives with the same mutations were clinically affected¹⁴⁸. In selected cases, the loss of CTLA-4 can be treated with a CTLA4 fusion drug, abatacept¹⁴⁹.

Phosphoinositide 3-kinase (PI3K):

Other syndromes linked to immune regulation leading to antibody deficiency as a prominent feature, are due to autosomal dominant mutations in PI3K, which contains a catalytic subunit of 110 kDa (PIK3CD) and a 85 kDa regulatory subunit (p85) (PIK3R1). Heterozygous mutations in the 110 kDa component (*PIK3CD*, often E1021K), were first noted in a Taiwanese boy with an immune deficiency¹⁵⁰, and were subsequently described in a number of patients with a CVID-like or hyper-IgM phenotype^{151,152}. These patients also had a deficiency of naive T lymphocytes with increased highly differentiated effector T cells. Patients had recurrent respiratory infections and reactivation of persistent viruses in some cases. While the penetrance varies widely, in a large cohort study of 55 patients, recurrent sinopulmonary infections were frequently found, with lymphoproliferation in 75%, herpesvirus infections in 49%, autoinflammatory disease in 34%, neurodevelopmental delay in 19% and lymphoma in 13%¹⁵³. A related but clinically different syndrome result from mutations in the p85 subunit. While autosomal recessive mutations in p85 lead to agammaglobulinemia, dominant heterozygous mutations in this component can lead to

immune defects similar to the 110 kDa defects, with loss of B-cells and hypogammaglobulinemia¹⁵⁴.

Nuclear factor Kappa-B (NF- κ B):

In addition to the above, mutations in transcription factors of the NF- κ B family are now being described in increasing numbers of subjects with "CVID"; in fact, defects in the *NFKB1* subunit appear to be the most common genetic defect in CVID subjects of Caucasian background^{115,155}. These also lead to a quite variable form of autosomal dominant antibody deficiency, with respiratory infections, unusual infections, autoimmunity and lymphoproliferative disease^{155,156,156}. First reported in a large Dutch family with 6 subjects with CVID in 3 generations, the family was re-investigated and additional members were found to have moderate to severe hypogammaglobulinemia or IgA deficiency^{157,158}. Subsequently in this and two other families, different heterozygous mutations in the *NFKB1* gene were identified¹⁵⁹. As for other autosomal dominant defects described above, not all subjects with mutations in the same family were affected, demonstrating the variable penetrance of defects in these genes.

In addition to the *NFKB1* gene, autosomal dominant, heterozygous mutations in *NFKB2* may also lead to early onset hypogammaglobulinemia with recurrent infections. Autoimmunity, alopecia in some, but more commonly, endocrine abnormalities adrenocorticotrophic hormone (ACTH) insufficiency or other pituitary hormone deficiencies were found¹⁶⁰. The first to be described were in the C-terminal region of *NFKB2*, leading to disruption of p100 phosphorylation, inhibition of processing into the p52 active form, and prevention of nuclear translocation. Additional nonsense gain-of-function mutations have been identified in other patients, resulting in constitutive NF- κ B2 activation; these patients had a complex immune disorder with hypogammaglobulinemia, lymphopenia and more severe T cell defects¹⁶¹.

Hypogammaglobulinemia with syndromic features:

Finally, varying degrees of hypogammaglobulinemia with loss of antibody, are also noted in a number of disease with additional organ, metabolic or developmental defects. (Table 1) These are sometimes listed in tabulations of genes that may lead to a form of hypogammaglobulinemia suggestive of the CVID phenotype, including Phosphatase and Tensin Homologue, PTEN¹⁶², Mannosyl-oligosaccharide glucosidase deficiency (MOGS)¹⁶³, (TRNA Nucleotidyl Transferase) TRNT1¹⁶⁴, Tetratricopeptide Repeat Domain 37 (TTC37)¹⁶⁵, and ATPase H⁺ Transporting Accessory Protein 1 (ATP6AP1) deficiency¹⁶⁶ and Phospholipase C, Gamma-2 (PLCG2)¹⁶⁷.

Treatment

The standard of care in CVID treatment is replacement immune globulin (Ig) given at frequent intervals for life, via the intravenous (IV) or subcutaneous (SC) route¹⁶⁸. Ig greatly reduces the number of bacterial infections¹⁶⁹ and data collected over the past 30 years demonstrates that this increases life expectancy. Antibiotics are also needed for acute treatment, and many cases, are used on a chronic basis as prophylaxis. However, Ig does not

appear to protect against or treat the non-infectious inflammatory complications such as functional and structural lung disease, autoimmunity, granulomatous disease, or the development of cancer or lymphoma as discussed above^{18,22}. The autoimmune and inflammatory complications are commonly difficult to treat. While autoimmune cytopenias such as immune thrombocytopenia and hemolytic anemia, may respond to high dose immunoglobulin and/or steroids, added therapy such as rituximab has been widely used, and often provides long term benefit¹⁷⁰. In one retrospective multicenter study, rituximab was highly effective in 33 patients with CVID-associated immune cytopenias, leading to an initial response rate of 80 % and a sustained response rate of 50%, after a mean follow up of 39 ± 30 months following the first administration. Other more recent options for cytopenias include thrombopoietin-receptor agonists, which have also shown benefit¹⁷¹. However, in some cases splenectomy has already been performed, usually for treatment of cytopenias, but also for an increasingly large spleen and/or concern for lymphoma. While rituximab has largely supplanted splenectomy for resolution of cytopenias in many patients, it has often been performed before the diagnosis of CVID. However, review of large data sets has shown that a previous splenectomy did not increase mortality in CVID as long as adequate immunoglobulin replacement therapy was used^{18,164}. Therefore this treatment is likely to protect against post-splenectomy infections^{18,172}.

The management of inflammatory bowel disease in CVID is similar as for immunocompetent patients, including antibiotics, such as metronidazole or tinidazole or ciprofloxacin, 5-aminosalicylic acid and/or non-absorbed oral steroids such as budesonide, but these therapies seem less successful in CVID. Low-dose corticosteroids such as prednisone can be used in low doses of 10 mg/day; however, higher doses can lead to a significant risk of infections. Immunomodulators, such as azathioprine or 6-mercaptopurine, can be used and do not appear to affect standard T- and B-cell function tests¹⁷³. Biologics such as infliximab and ustekinumab (anti IL-12 and IL-23) or more recently, vedolizumab have been used in few cases with some benefit in severe enteropathy¹⁷⁴.

For patients with granulomatous disease, a number of therapeutic options have been used with variable success. In the French cohort, of 55 patients with lymph node, lungs, liver, skin, bone marrow and /or central nervous system involvement, 32 patients received various treatments. Corticosteroids were the most frequently used drug; other therapies included cyclophosphamide, hydroxychloroquine, rituximab and methotrexate but with limited success. Azathioprine, cyclosporine, mycophenolate mofetil, sirolimus, infliximab and thalidomide, which led to partial or no response⁴⁸. Mullighan reported granuloma in 20 of 90 patients with CVID (22%); 8 of these had an unusual TNF-alpha allele (TNF +488A)⁹⁹, but TNF-alpha production or levels were not examined. However, as previous work suggested that some CVID patients had elevated serum levels of TNF-alpha¹⁷⁵, TNF-alpha inhibitors (infliximab or etanercept) have been used in subjects with CVID with granuloma, with benefit in some cases¹⁷⁶⁻¹⁷⁸; however, no controlled trials have been performed. More recently, taking into account the lymphoid infiltrations that accompany the granulomatous involvement, the use of combination therapy with rituximab along with either azathioprine, 6MP or mycophenolate mofetil, has become more commonly accepted measures, especially in those with granulomatous lung disease¹⁷⁹.

The discovery that mutations in regulatory genes can lead to both B cell dysfunction and the clinical complications characteristic of CVID, has led to important insights into more directed therapy. As noted above, the use of CTLA4 fusion protein, abatacept, to correct for loss of CTLA4, is a striking example¹⁴⁹. In addition, chloroquine long known a lysosomal inhibitor, was noted to protect against loss of CTLA-4 in LRBA-deficient cells, thus its use could have a therapeutic role in this disease¹⁸⁰. This drug has been used for many decades for rheumatologic illnesses with a known safety record. For patients with mutations in *PIK3CD* or *PIK3R1*, hyperactivation of PI3K leads to unrestrained immune activation by generation of PI(3,4,5)P3 signals and activation of protein kinase B (PKB), also known as AKT. The result is activation of downstream pathways including the mammalian target of rapamycin (mTOR) kinase. With this in mind the logical drug, rapamycin has been used to retrain this pathway. Even more specific, is the p110δ-specific inhibitor, Idelalisib, already in used in chronic lymphocytic leukemia¹⁸⁰.

With the evolving understanding that the CVID syndrome with the additional cellular defects lead to poorer survival for some, hematopoietic stem cell transplant (HSCT) has been performed. While data on the long-term effects for subjects with clearly defined CVID are still limited, a recent multi-center study reported improved outcome for some, but poor outcome for many. In this study 25 CVID patients aged 8 to 50 years, often with immune dysregulation had an overall survival of 48%, and 83% for those with lymphoma. The major causes of death were treatment-refractory graft-versus-host disease, poor immune reconstitution and infectious complications. For the surviving and reconstituted subjects, Immunoglobulin substitution was stopped in 50%; for 92% of the surviving patients, the condition for which HSCT has been performed, resolved¹⁸¹.

Conclusions:

Most likely a surprise to internists six decades ago, adults with hypogammaglobulinemia similar pediatric immune defects, were starting to be identified. While eventually called common variable immune deficiency, and classified amongst the B cell defects, an increasing number of cellular defects have been recognized over time. In the early years, severe respiratory tract infections led to greatly shortened survival, but the wide spread availability of immune globulin concentrates has diminished early mortality. However, with longer life span, the chronic non-infectious inflammatory and autoimmune conditions of the cVID syndrome have now emerged as the most challenging clinical problems. These require further immunologic understanding and development of new therapeutic measures. Recent genetic studies of the CVID syndrome have shown that these B cell defects are a fertile ground for the identification of autosomal recessive and now more commonly, autosomal dominant gene defects which lead to loss of B cell development and in some cases, the immune dysregulation characteristic of this syndrome.

Acknowledgments:

This work was supported by the National Institutes of Health, AI-061093, AI-086037, AI-48693, and the David S Gottesman Immunology Chair, of the Icahn School of medicine at Mount Sinai.

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Table 1

Gene defects that may lead to the CVID Phenotype

Defect	Gene	Inheritance	Laboratory	Clinical
BAFF receptor deficiency	TNFRSF13C (BAFF-R)	AR	Low IgG and IgM.	Variable clinical expression
TWEAK deficiency	TWEAK (TNFSF12)	AD	Low IgM and A, lack of anti-pneumococcal antibody	Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia
ICOS	ICOS	AR	Low IgG and IgA and/or IgM	
TAC1 deficiency	TNFRSF13B (TAC1)	AD or AR	Low IgG and IgA and/or IgM	Variable clinical expression
CD19 deficiency	CD19	AR	Low IgG and IgA and/or IgM	Recurrent infections, may have glomerulonephritis
CD81 deficiency	CD81	AR	Low IgG, low or normal IgA and IgM	Recurrent infections, may have glomerulonephritis
CD20 deficiency	CD20	AR	Low IgG, normal or elevated IgM and IgA	Recurrent infections
CD21 deficiency	CD21	AR	Low IgG, impaired anti-pneumococcal response	Recurrent infections
CD27	CD27	AR	Hypogammaglobulinemia	Recurrent infections
PIK3CD mutation (GOF)	PIK3CD GOF	AD	All isotypes decreased	Severe bacterial infections; decreased or absent pro-B cells, EBV
NFKB1 deficiency	NFKB1	AD	Normal or low IgG, IgA, IgM, low or normal B cells, low memory B cells	Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia and autoimmune thyroiditis
NFKB2 deficiency	NFKB2	AD	Low serum IgG, A and M; low B cell numbers	Recurrent sinopulmonary infections, alopecia and endocrinopathies
IKZF1	IKZF1	AD	Low IgG and IgA and/or IgM	Recurrent infections, ALL
IL-21	IL21	AR	Impaired B-cell differentiation	Inflammatory bowel disease
IL2IR	IL2IR	AR	Low IgG, defective class-switched B cells and defective antibody responses	Recurrent infections, liver disease
LRBA	LRBA	AR	Hypogammaglobulinemia, low IgG and IgA	Chronic interstitial lung disease; autoimmunity; inflammatory bowel disease; endocrinopathy in some;
CTLA4	CTLA4	AD	Hypogammaglobulinemia, low IgG and IgA; sometimes IgM	Autoimmunity
PIK3CD	PIK3CD	AD, AR	Hypogammaglobulinemia, increased IgM	Recurrent infections, lymphoproliferation; autoimmunity, B-cell lymphoma
PIK3R1	PIK3R1	AD; AR	Hypogammaglobulinemia, increased IgM	recurrent infections, lymphoproliferation; B-cell lymphoma; neurodevelopmental delay
IRF2BP2	IRF2BP2	AD	Hypogammaglobulinemia	Recurrent infections, colitis

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Defect	Gene	Inheritance	Laboratory	Clinical
Mannosyl-oligosaccharide glucosidase deficiency	MOGS (GCS1)	AR	Hypogammaglobulinemia	Bacterial and viral infections, severe neurologic disease, global developmental delay, hypotonia, seizures, dysmorphic features
PTEN	PTEN	AD	Low IgG and IgA; poor antibody production	recurrent infections; Cowden's syndrome, macrocephaly,
TRNT1 deficiency	TRNT1	AR	B-cell lymphopenia; panhypogammaglobulinemia	congenital sideroblastic anemia, deafness, developmental delay
TTC37 deficiency	TTC37	AR	Hypogammaglobulinemia; specific antibody deficiency	Recurrent bacterial and viral infections, Abnormal hair findings; trichorrhexis nodosa
ATP6API deficiency	ATP6API	AD	Hypogammaglobulinemia,	Hepatopathy, neurocognitive abnormalities
PLCG2	PLCG2	AD	Reduced IgG, IgA; low CD19+ B cells; antibody defects	Cold urticarial; skin lesions, nonspecific interstitial pneumonitis