



The many faces of the clinical picture of common variable immune deficiency

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Purpose of review

To summarize the recent advancements in common variable immune deficiency (CVID), specifically CVID genetics, clinical discoveries and treatment implications.

Recent findings

Large genomic studies have implicated new genes in the pathogenesis of CVID, and basic science studies have contributed to our knowledge of potential mechanisms. Cohort studies have further defined the immunologic parameters and clinical presentation of CVID, as well as the factors that contribute to morbidity and mortality in this disease. Immunoglobulin remains the mainstay of treatment, although there may be a role for immunosuppression and other therapies.

Summary

CVID is a genotypically and phenotypically heterogeneous primary immune deficiency, the genetic and clinical characteristics of which are under active investigation. Further, discovery may yield important new treatment protocols that can continue to reduce the morbidity and mortality from this disease.

Keywords

autoimmunity, genetics, immune deficiency, immunoglobulin therapy

INTRODUCTION

Common variable immune deficiency (CVID) is a primary immune deficiency characterized by reduced serum levels of IgG, IgA and/or IgM (at least two standard deviations below the mean for age) with reduced or absent isohemagglutinins and/or poor response to vaccines in a patient of more than 2 years of age in whom other causes of immune deficiency have been ruled out [1,2]. CVID is associated with an increased number of infections, most often bacterial respiratory tract infections. However, inflammatory complications occur in varying proportions and include autoimmunity, chronic lung disease, bronchiectasis, gastrointestinal disease with or without malabsorption, systemic or localized granulomatous disease, liver disease, splenomegaly, lymphadenopathy with or without lymphoma and other malignancies [3,4^{••},5]. Although the diagnosis is most typically made around 30 years of age, about 28% of patients are less than 21 years of age at diagnosis, and many others give a history of clinical events suggestive of an immune disorder before this age [3,4^{••},5]. However, in a recent study [6] of 141 pediatric patients (<21 years of age) evaluated for primary immune deficiency, only four were found to have CVID, suggesting that for many

patients B-cell dysfunction has evolved over time. A delay in CVID diagnosis of 6–7 years is common, perhaps due to the later onset and phenotypically heterogeneous nature of the disease [3,5,7].

CVID is a clinically important immune defect, due to both its prevalence of 1:25 000–1:50 000, and also because of the large numbers of medical encounters that may be needed to treat its associated complications [1,3,4^{••},5,7]. Here we review the recent advances in CVID, specifically the genetic defects associated with this syndrome, as well as clinical features and treatment implications.

GENETICS

One year after the report of Bruton's X-linked agammaglobulinemia, CVID was first described in 1953 in a woman of 35 years of age [8]. However, the

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KEY POINTS

- CVID is a genotypically and phenotypically heterogeneous primary immune deficiency.
- Large genomic studies have implicated new genes in the pathogenesis of CVID.
- Cohort studies have further defined the immunologic parameters, clinical presentation and morbidity and mortality in CVID.

fundamental genetic, environmental, or other causes of CVID remain still poorly understood despite extensive investigation [9]. CVID has been linked in a handful of cases to autosomal recessive genetic mutations, including inducible costimulatory [10], CD19 [11,12], B-cell activating factor (BAFF) receptor [13], CD20 [14], CD21 [15] and CD81 [16]. Both heterozygous and homozygous mutations in the gene for the B-cell receptor transmembrane activator and calcium-modulating cyclophilin ligand interactor (*TACI*) are found in 8–10% of patients [17–19]. However, although *TACI* mutations are significantly associated with both immune deficiency and autoimmunity in CVID [20,21], some of the same mutations are found in healthy controls and phenotypically ‘normal’ relatives – although some of these are IgA deficient – suggesting that these may be disease-associated polymorphisms [22]. Perhaps in concert with this, a recent study [23] of *TACI*-deficient mice showed that *TACI* promotes sustained BLIMP-1 expression by B cells responding to antigen, which limits B-cell clonal expansion and facilitates differentiation of long-lived antibody-secreting cells. These observations suggest a potential mechanistic explanation for some of the complications seen in CVID, namely lymphoproliferation, and hypogammaglobulinemia with impaired plasma cell generation. To further support this claim, a recent

report [24] of a Greek cohort of immune deficient patients, 16 of whom had CVID, found *TNGRSF13B/TACI* mutations in CVID subjects, IgG4 deficient patients and healthy relatives. The details and results of many of these genetic studies [25,26,27] were recently reviewed in detail. Recently, two other complex syndromes leading to hypogammaglobulinemia have been described. In one, mutations in *CD27* in two brothers led to impaired immune globulin production and EBV viremia, suggesting a combined immune deficiency phenotype [28]. In the other, mutations in phospholipase *Cγ(2)*, a signaling molecule expressed in B cells, natural killer cells and mast cells, were associated with hypogammaglobulinemia, cold urticaria, autoimmunity and in some cases, granulomatous disease [29]. The addition of these syndromes to the causes of reduced serum immune globulins suggests that other genetic diseases overlapping with the CVID syndrome are likely to emerge.

To approach CVID using genome-wide association studies (GWAS), single nucleotide polymorphism (SNP) arrays have been performed for high-throughput genotyping of genomic DNA [30]. For this study [30], samples were collected from CVID subjects followed at three medical centers in the United States and one in the United Kingdom. This study investigated 610 000 SNPs of 363 CVID subjects as compared with 3031 controls. A strong association with the MHC region was revealed, and associations with the disintegrin and metalloproteinases 28 (*ADAM28*), *ADAM7*, *ADAMDEC1* and stanniocalcin-1 (*STC1*) were suggested (Table 1).

To further elucidate potential genotype-phenotype correlations, the CVID subjects in this study were classified by clinical phenotypes, including cancers, lymphoma, lymphadenopathy, nodular regenerative hyperplasia of the liver, lymphoid interstitial pneumonitis, bronchiectasis, biopsy-proved granuloma, gastrointestinal enteropathy, malabsorption, splenectomy, cytopenias and

Table 1. Most significant associated regions based on genotype association

Gene	Count SNP top 1000	Distance from exon	P-value	SNP	A1
MHC	110	0	8.62×10^{-10}	rs3117426	T
ADAM28, ADAM7, ADAMDEC1, STC1	4	0	6.24×10^{-6}	rs4872262	A
SDK1	5	0	4.7×10^{-5}	rs895710	T
FIJ32784, UBXN10	7	0	9.09×10^{-5}	rs7514144	C
FGGY	2	2458	1.52×10^{-4}	rs11207520	G
FIJ16124	2	784	5.2×10^{-4}	rs1194849	G

SNP, single nucleotide polymorphism. Adapted from [30].

organ-specific autoimmunity. They were also classified by immunologic and demographic parameters, including low IgM (<50mg/dL), low IgA (<10mg/dL), low B-cell numbers (CD19⁺ cells <1%) and young age at symptom onset (<10 years) [30^{••}]. SNP analysis revealed genes associated with particular phenotypes, including mitogen-activated protein kinase 7-interacting protein 3 (*MAP3K7IP3*) significantly associated with low IgA. *PFTK1*, *HAVCR1* and *KIAA0834* were significantly associated with lymphoma and *CACNA1C* (calcium channel, voltage-dependent, L-type, alpha 1C subunit) was significantly associated with gastrointestinal enteropathy [30^{••}].

In the same study [30^{••}], investigation of copy number variations (CNVs) in this cohort found several genes significantly associated with CVID. Eighty-four CNV deletions and 98 duplications were identified in one or more patients but were not found in any of the control subjects. Five deletions and 11 duplications were significantly increased in CVID cases compared with controls; 15 regions were unique to CVID cases. A significant number of subjects had duplications in *ORC4L*, essential for initiation of DNA replication in immune cells and previously associated with B-cell lymphoproliferative disorders [31]. Overall, CNV analysis revealed that deletions were significantly enriched in the CVID cases, and all but five of the 182 CNVs exclusive to the CVID cohort were intraexonic. These observations suggest that a degree of genomic instability may prevail in CVID, not clinically irrelevant, as radio sensitivity has been noted in several previous studies [32–34]. More recently, Offer *et al.* [35] surveyed candidate DNA metabolism genes and found that other markers in several mismatch repair proteins were associated with IgAD/CVID. Resequencing found four rare, nonsynonymous alleles associated with IgAD/CVID: two in MutL homolog 1 (*MLH1*), one in *RAD50*, a protein involved in DNA double-strand break repair, and one in Nijmegen breakage syndrome 1, nibrin (*NBS1*). A premature *RAD50* stop codon identified in one conferred an increased sensitivity to ionizing radiation [35].

LABORATORY FEATURES

As CVID is so heterogeneous, many groups have attempted to classify these subjects into clinically relevant groups, based on laboratory parameters. Many classifications in recent years have naturally focused on the B-cell phenotypes, as dissected by flow cytometry. The majority of patients have reduced numbers of serum isotype switched memory B cells (IgD[−] IgM[−] CD27⁺), and defective somatic hypermutation [36–38]. In addition, these

studies [37,39,40] have shown that patients with the most severe clinical disease had the lowest proportion of isotype switched memory B cells. Confirming the loss of B-cell differentiation, bone marrow examination confirmed loss of plasma cells [36–38]. To further define the mechanism of the potential B-cell defect, 35 CVID patients followed at the same medical center were divided into those with isotype-switched memory B cells less than 0.55% of peripheral blood lymphocytes (group 1) and those with isotype-switched memory B cells greater than 0.55% (group 2). TLR7 or TLR9 activated B cells from group two patients had increased mature Cγ1 and Cγ2 heavy-chain mRNA transcripts in comparison to those from group 1. Furthermore, TLR stimulated plasmacytoid dendritic cells for all subjects had impaired IFN-α production, but TLR7 or TLR9 stimulation in the presence of IFN-α normalized isotype-switched B cells enhanced activation-induced cytidine deaminase mRNA, and significantly improved IgG production for group 2 only. This indicates that the loss of IFN-α could be an important contributor to the B-cell defect in these subjects [41^{••}].

Other methods have re-examined some of the known cellular defects of CVID to attempt further dissections. A recent study [42] examined T-cell receptor excision circles (TRECs) and kappa-deleting recombination circles (KRECs) in CVID patients. Interestingly, both TREC⁺ lymphocytes and KREC concentrations were found to be lower in CVID patients than in controls. Another study [43] noted shorter telomeres in both B and the T cells from a subset of CVID subjects.

CLINICAL IMPLICATIONS

Due to the clinical heterogeneity of CVID, patient cohort studies are necessary to determine a more robust clinical picture of this disease [3,5,44–46]. A report [47] of all types of immunodeficiency in Chinese children, the first of its kind from China, described 27 cases of CVID in a cohort of 195 children. There were twice as many men as women in this group with a median age at diagnosis of 10.5 years and a median delay in diagnosis of 5 years. Four of these patients with CVID developed lymphoma and two later died.

We have outlined the demographic, clinical and immunologic data for the largest published cohort of CVID patients (*n* = 473) followed at one medical center over four decades [4^{••}]. The median age at diagnosis was significantly earlier for men (30 years) than for women (33.5 years, *P* = 0.0004) in this group. Nearly one-third of subjects were under age 21 at diagnosis. Women were found to have

significantly higher serum IgM levels at diagnosis and greater numbers of isotype switched memory B cells than men. Ninety-for percent of patients had a history of significant infections. Of the group, 68% also had noninfectious complications: hematologic or organ-specific autoimmunity 28.6%, chronic lung disease 28.5%, bronchiectasis 11.2%, gastrointestinal inflammatory disease 15.4%, malabsorption 5.9%, granulomatous disease 9.7%, liver disease/hepatitis 9.1%, lymphoma 8.2%, or other cancers 7.0% (Table 2).

As described above, the CVID phenotype can range from mild infections only to severe associated complications. A French study [48[■]] recently collected specimens from CVID kindreds to examine the effect of parental consanguinity on this disease. Twenty-four patients out of 436 had consanguineous parents (cCVID group). Although age at diagnosis was similar to those without consanguinity (ncCVID group), the cCVID group had a higher incidence of splenomegaly, granulomatous disease and bronchiectasis. The cCVID group also had a higher incidence of opportunistic infections and lower naive CD4⁺ T-cell numbers. This group concluded that patients in the cCVID group should be considered for a diagnosis of late-onset combined immune deficiency (LOCID) as opposed to CVID [48[■]]. A previous examination of some of the same patients in a different study [49] found that of 313 patients diagnosed with CVID, 28 patients (8.9%) actually met criteria for LOCID, defined by the occurrence of and opportunistic infection of CD4⁺ T-cell count of less than 200.

Although many primary immune deficiencies manifest with significant, life-threatening infections in infancy, the first clinical presentation of CVID may occur at any age, and may be any of the infectious or noninfectious complications described above. A recent Japanese case report described a 5-year-old child who presented with severe complications of influenza virus including acute respiratory distress syndrome and nephrotic syndrome. The child was found to have IgA and IgG2 deficiency and diagnosed with systemic lupus erythematosus, which over the next 5 years progressed to low serum total IgG and an eventual diagnosis of CVID [50]. The pathogenesis of this type of gradual decrease in IgG levels eventually leading to a clear cut diagnosis of CVID is not well understood, but it is possible that CVID in children is phenotypically different from the adult disease. A recent study [51] investigating lung disease in children with CVID found that airway disease and interstitial lung disease were phenotypically distinct, the former significantly associated with pneumonias and the latter associated with autoimmunity, severe memory B-cell reduction, and expansion of nonnaive cytotoxic T cells. This suggests a different treatment strategy may also be necessary for children with CVID.

MORBIDITY AND MORTALITY

The large CVID cohort ($n=473$) described above was further investigated for the demographic and immunologic markers associated with complications and poorer survival [4[■]]. In general, the

Table 2. Selected complications from a large cohort ($n=473$) of common variable immune deficiency patients followed at one medical center over four decades

Associated condition	Number ($n=473$)	Percentage of cohort (%)
Infections only (no complications)	151	31.9
Chronic lung disease (functional/structural)	135	28.5
Bronchiectasis	53	11.2
Autoimmunity	134	28.6
Immune thrombocytopenic purpura (ITP)	67	14.2
Autoimmune hemolytic anemia (AIHA)	33	7
Gastrointestinal disease	73	15.4
Malabsorption	28	5.9
Inflammatory Bowel Disease (Crohn's disease, ulcerative colitis, ulcerative proctitis)	20	4.2
Liver disease/hepatitis	43	9.1
Granulomatous disease	46	9.7
Lymphoma	39	8.2
Cancer	33	7
Splenectomy	39	8.2

Adapted from [4[■]].

median age at death was 44 years for women and 42 years for men, both significantly different from age-matched population controls (Fig. 1). By Cox Proportional Hazards modeling, the risk of death was nearly 11 times higher for CVID patients with one or more of the noninfectious complications, than for subjects who had infections only (hazard ratio = 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 (Fig. 2). Specific complications associated with an increased risk of death included gastrointestinal disease (hazard ratio = 2.78; $P = 0.0004$), liver disease/hepatitis (hazard ratio = 2.48; $P = 0.0003$), lymphoma (hazard ratio = 2.44; $P = 0.001$), chronic lung disease (hazard ratio = 2.06; $P = 0.001$) or malabsorption (hazard ratio = 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 may be used as biomarkers to predict poorer outcomes, lower baseline serum IgG level (hazard ratio = 0.998; $P = 0.0079$), fewer peripheral blood B cells (hazard ratio = 0.933; $P = 0.0004$) and an increased serum IgM level (hazard ratio = 1.005; $P = 0.0021$) were all associated with increased mortality [4^{¶¶}].

TREATMENT

The standard of care in CVID treatment is replacement immune globulin given at frequent intervals

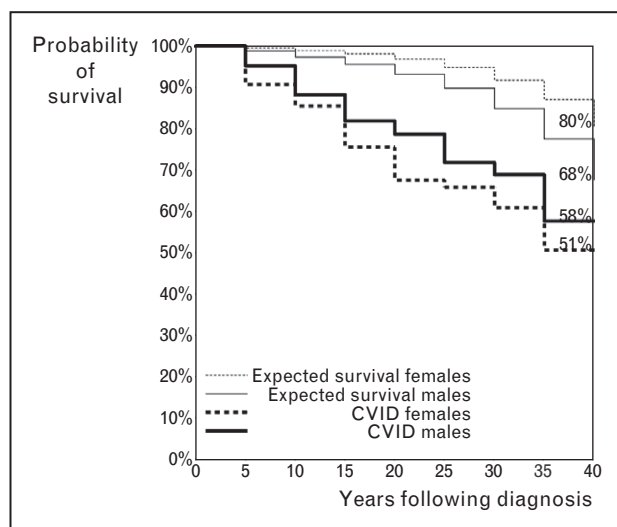


FIGURE 1. Kaplan–Meier survival curves for common variable immune deficiency patients versus population controls. Adapted from [4^{¶¶}].

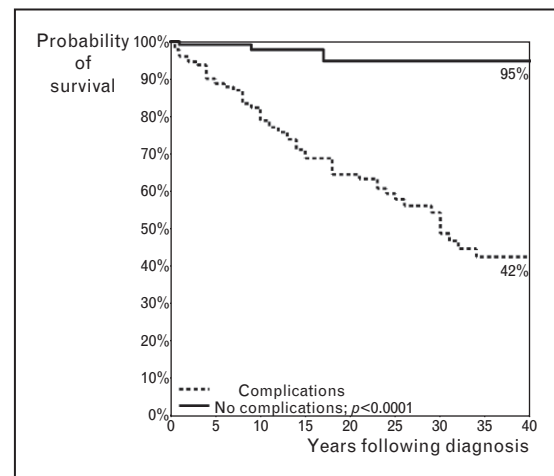


FIGURE 2. Kaplan–Meier survival curves for common variable immune deficiency patients with infections only versus those with any other complication. Adapted from [4^{¶¶}].

for life [52], via the intravenous (i.v.) or subcutaneous route. Immune globulin greatly reduces the number of bacterial infections [53] and likely enhances survival [3,4^{¶¶}]. Indeed, a recent review [54] of subcutaneous immune globulin therapy found that in patients with primary immune deficiency (not only CVID) the incidence of infections, excluding ‘serious bacterial infections’ was inversely related to the steady-state IgG level [54]. However, immune globulin does not appear to protect against or treat the noninfectious inflammatory complications such as functional and structural lung disease, autoimmunity, granulomatous disease or the development of cancer or lymphoma which are found in varying percentages of patients in different series [3,4^{¶¶},5].

The process by which CVID patients develop certain complications is poorly understood. A recent review [55] summarized the possible mechanisms for the increased incidence of viral infections and malignancies found in primary immune deficiencies including CVID. Immunoglobulin therapy has not been shown to impact the incidence of malignancy in this disease. The autoimmune complications develop in certain patients more frequently, as described above, and can also be varied and potentially difficult to treat. Autoimmunity may arise from retained B-cell autoimmune potential, lack of somatic hypermutation, loss of proliferative potential, or delayed apoptosis, and/or abnormal T-cell function [56]. Treatment may involve high dose immunoglobulin and/or steroids or other immune suppressants. For autoimmune cytopenias, rituximab can provide substantial benefit in a number of cases [57].

CONCLUSION

CVID is a genotypically and phenotypically heterogeneous primary immune deficiency, the genetic and clinical characteristics of which are under active investigation. Here we summarize the recent advancements in CVID, specifically in the areas of CVID genetics, clinical discoveries and treatment implications. GWAS studies of SNPs and CNVs in CVID have implicated new genes that can be further investigated for their role in CVID pathogenesis. Basic science studies have increased our knowledge of potential cellular mechanisms in CVID. Large cohort studies have further defined the immunologic parameters and clinical presentation of CVID, as well as the factors that contribute to morbidity and mortality in this disease. Immunoglobulin remains the mainstay of treatment, although there may be a role for immunosuppression and other therapies in the future. Further research is needed to continue to develop new therapies and continue to reduce the morbidity and mortality from this disease.

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Conflicts of interest

E.S.R. reports no conflicts of interest. C.C.R. reports previous research grants from Baxter Healthcare and Octapharma and participation in Medical Advisory Boards of Baxter Healthcare and Grifols.

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