EXPERT REVIEWS

Common variable immunodeficiency in adults: current diagnostic protocol and laboratory measures

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Yashwant Kumar*[1] and Alka Bhatia[2]

[1]*Department of Immunopathology, Post Graduate Institute of Medical Education & Research, Chandigarh, India*
[2]*Department of Experimental Medicine and Biotechnology, Post Graduate Institute of Medical Education & Research, Chandigarh, India*
**Author for correspondence:*
Fax: +91 172 2744401
dryashwant@ymail.com

Common variable immunodeficiency (CVID) is one of the most common symptomatic primary immune defects in adults. Unfortunately, the diagnosis of CVID is often delayed because of its variable presentations and manifestations. Sincere efforts from experts in the field of primary immunodeficiency disorders all over the world have made us wiser regarding the clinical features, associated complications and long-term outcome of the disease. However, a systematic compilation of diagnostic protocols and laboratory measures is desirable. The present review highlights in brief the immunological and molecular defects characterizing adult CVID along with a comprehensive discussion on currently followed laboratory criteria and methods used to identify these cases. The article may benefit the clinicians, immunologists, infectious disease specialists, pulmonary medicine specialists, gastroenterologists, dermatologists and other physicians who are involved in the team management of the patients with CVID.

KEYWORDS: CVID • class-switched memory B cells • flow cytometry • hypogammaglobulinemia • immunoglobulins • memory B cells

Common variable immunodeficiency (CVID) is one of the commonest symptomatic primary immunodeficiency disorders (PIDs) with a wide range of clinical manifestations, disease severity and progressive course. It is characterized by poor or absent antibody production causing significantly decreased levels of circulating immunoglobulins (IGs) and an increased susceptibility to infections. CVID is most frequently diagnosed in adults aged 20–40 years, although it may be present at any age from childhood to late adult life with another peak of onset between ages of 2 and 5 years. In most patients, symptoms, however, start after puberty. Both males and females are equally affected with slightly earlier onset of disease in males as compared with the females. The 20-year survival after diagnosis of CVID is 64% for males and 67% for females [1–4]. Since majority of PIDs occur in pediatric age group, the possibility of CVID in adults sometimes is ignored. The usual presentation in CVID is recurrent infections, but the primary symptom may be related to one or other complications like an autoimmune or an inflammatory disorder. In such a situation, the patients may visit different medical specialties like pulmonary medicine, gastroenterology, otolaryngology, rheumatology or even oncology rather than coming to a clinical immunology or a PIDs expert. Due to all these reasons, diagnosis of CVID is delayed for an average duration of 6–7 years, and only 20% of the patients are diagnosed before 20 years of age [5,6].

In the last two decades, several attempts have been made to further define this complex syndrome and improve our understanding of the disease pathogenesis. This review highlights some of the recent modifications in diagnostic criteria and protocols being followed, newer immunological and molecular defects discovered and various laboratory measures used to identify these defects. Despite several lacunae in our knowledge on disease pathogenesis, there has been significant advancement in

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management of CVID that has led to reduced morbidity and improved survival and prognosis in the diagnosed patients. Therefore, it becomes important to analyze critically the currently available diagnostic measures that may help in early recognition and timely management of the patients of CVID.

Epidemiology

CVID is one of the major groups of PIDs being second only to selective IgA deficiency, which is mostly asymptomatic [7,8]. The incidence of CVID ranges from 1:50,000 to 1:200,000 per year in the general population. The prevalence of disease is estimated to be about 1:10,000 to 1:200,000 individuals with an average prevalence of 1:30,000 [9–11]. There are geographical differences in the incidence of CVID. In Europe and Northern America, the prevalence of CVID is estimated to be approximately 1:25,000 [12]. The incidence in Japan is about 1 in every 1,000,000 inhabitants [13]. It is rare among Asians and Afro-Americans; nevertheless, it is believed that the prevalence may increase in the coming years with increase in awareness and documentation of more number of cases [2,14,15]. In majority, CVID is sporadic but familial inheritance may be seen in about 10% of cases [16–18]. Almost 80% of these patients have autosomal-dominant inheritance [3]. CVID is often present in one parent and may be accompanied by IgA deficiency in the descendants. In fact, some cases of IgA deficiency progressing to CVID have also been reported [19,20].

Table 1. Common infections seen in common variable immunodeficiency.

Manifestations	Infectious agent
Pneumonia	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catharralis* *Mycoplasma pneumonia* *Pneumocystis jiroveci*
Sinusitis, bronchitis, otitis	*S. pneumoniae* *H. influenzae* *M. catharralis*
Gastrointestinal tract infections (diarrhea, enteritis, gastritis, and so on)	*Giardia lamblia* *Salmonella spp.* *Campylobacter jejuni* *Helicobacter pylori* *Clostridium difficile* *Cryptosporidium parvum*
Central nervous system (meningitis, encephalitis, and so on)	*S. pneumoniae* *H. influenza* *Neisseria meningitidis* Enteroviruses (ECHO)
Skin (shingles, wart)	Herpes zoster Human papilloma virus
Joint infection	*Mycoplasma* spp.
Liver	Hepatitis virus
Sepsis	*S. pneumoniae*
Others (abscesses, oral thrush)	*Staphylococcus aureus* *Candida albicans*

Data taken from [3,11,80–82].

Clinical features

CVID is a heterogeneous group of disorders and known for tremendous variety of symptoms. Since the patients lack a protective antibody response to pyogenes, respiratory bacterial infections are most common especially of encapsulated (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*) or atypical (*Mycoplasma spp*.) bacteria. More than 90% of the patients develop respiratory infections in the form of pneumonia, sinusitis, bronchitis and about 70% develop otitis media and there may be multiple episodes of such infections (Table 1). These infections if untreated develop in to chronic and persistent lung damage resulting in bronchiectasis, emphysema, lung fibrosis and finally respiratory failure. In addition, some patients may present with infections of gastrointestinal tract (GIT), skin, liver, CNS or even with sepsis (Figure 1). These infections are usually controlled by antibiotics and parenteral IGs. In addition, 40–50% of the patients may also have associated complications such as autoimmune manifestations, gastrointestinal disease, granulomatous inflammation and malignancy (Table 2). The patients are also more susceptible to *in vitro* irradiation that could be a possibility for predisposition to malignancy in CVID [21]. One or more of these disorders may be present at the time of diagnosis or develop later during the course of the disease. A significant number of patients also have enlarged spleen, associated portal hypertension, lymphadenopathy and liver disease [18,22]. Based on the presence of these complications, Chapel *et al.* described five clinical phenotypes of CVID: infection only, polyclonal lymphocytic infiltration, autoimmunity, enteropathy and lymphoid malignancy. They recruited 334 patients of CVID of which 83% exhibited features of one phenotype only while 12.6% had more than one clinical phenotypes [23]. The first category patients had infections only and in the second category, the patients in addition to infections also developed other associated conditions, that is, autoimmunity, malignancy, etc. [11]. The patients of second category are more unfortunate since the noninfectious manifestations are difficult to handle as they may require immunosuppressive therapy. This was well demonstrated in a subsequent study by Resnick *et al.* in which 68% of subjects with noninfectious complications had markedly decreased survival compared with 32% subjects with infections only [24].

Differential diagnoses

CVID is a great mimic; hence, it is important to exclude a variety of clinical conditions while investigating a patient with recurrent infections. Patients with anatomic anomalies of lungs and sinuses, for example, immotile cilia syndrome, cystic fibrosis, bronchial asthma should always be investigated for immune functions. There are several conditions that can present with hypogammaglobulinemia and recurrent sinopulmonary infections (Table 3). The genetic and chromosomal abnormalities

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generally present in pediatric age group hence can be easily excluded in adults. Besides age and genetic analysis, there are several other laboratory parameters that help in identifying the disease. For example, in X-linked agammaglobulinemia, reduction in B cell numbers is much severe (<2%) and more consistent than in CVID, and Western blot will reveal absent or markedly reduced expression of Btk protein. In hyper IgM syndrome, the IgM levels are typically increased or normal and the diagnosis can be ruled out by detection of normal CD154 (CD40L) on activated T cells [25]. X-linked lymphoproliferative syndrome may be differentiated by deficiency of one or more IG subclasses and inappropriate immune response to Epstein–Barr virus. Transient hypogammaglobulinemia can be ruled out by milder infectious manifestations and normal response to vaccines [26]. Wiskott–Aldrich syndrome has classical symptoms of eczema, thrombocytopenia and bloody diarrhea by which it can be easily differentiated from CVID. Severe combined immunodeficiency presents with opportunistic fungal or viral infections and shows marked reduction in T cells and dendritic cells (DCs) with normal, reduced or increased B cells and defects in ADA, RAG1, RAG2 or Artemis genes [27]. Complement deficiency can be differentiated by their normal B and T cell numbers with functional or quantitative deficiency of complement proteins [28]. Chronic granulomatous disease can be easily distinguished by performing nitroblue tetrazolium test or by flow cytometry using dihydrorhodamine dye [29]. The leukocyte adhesion defects are characterized by lack of pus formation at the site of infection, leukocytosis and CD18 deficiency [30]. The acquired conditions are more commonly encountered in adults and mostly are revealed if appropriate clinical history is obtained followed by proper clinical examination and baseline investigations. For example, patients with drug-induced hypogammaglobulinemia will be on medications. In malignancies like lymphoma, the patient will present with lymphadenopathy, which may be accompanied with anemia, bleeding tendencies or anorexia as in case of leukemia or other B-cell tumors. Conditions like severe burns, protein losing enteropathy, malnutrition, proteinurea, etc. are self-explanatory as the protein loss is the cause of reduced IGs. Selective IgA and IgG subclass deficiency may also mimic CVID though most of the cases are usually asymptomatic. Such patients may be investigated if present with recurrent infections without other features of CVID [31]. In selective IgA deficiency, there are absent or low titers of IgA with normal IgG and IgM levels. Selective IgG subclass deficiency is characterized by low levels of one or more IgG subclasses (G1, G2, G3 and G4), and normal total IgG levels unless IgG1 is deficient.

Pathogenesis

CVID is considered to be predominantly a B cell defect leading to failure of production of IGs but several other defects including abnormal T cell response and defect in innate immunity may also accompany. Hence, CVID is basically a consequence of multiple immune defects leading to dysregulation and failure of immune response against various pathogens [32].

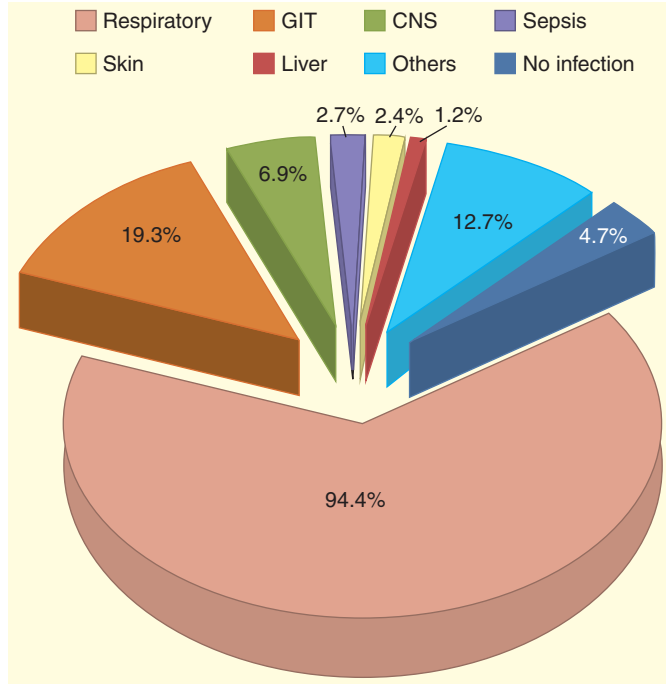

Figure 1. Incidence of various infections in common variable immunodeficiency.
GIT: Gastrointestinal tract.

Defects of innate immunity

Several defects related to innate immunity have been described in CVID (Table 4). Antigen presenting cells, for example, DCs and toll-like receptors (TLRs) are key components of innate immunity. DCs interact with naive T cells in the T-cell zone of secondary lymphoid organs and promote differentiation of T and B cells. They also play an important role in initiation of IG class switching and terminal B-cell differentiation in the absence of T cell help via signals through TLRs and the cytokines. In CVID, there is severe defect in differentiation, maturation and function of DCs with markedly reduced expression of the co-stimulatory molecules that are critical for T-cell stimulation [33]. Reduction in circulating natural killer (NK) cells has also been reported, and marked reduction in $CD3^-$ $CD28^{dim}$ subset of NK cell has been found to be specific for CVID [34]. NKT cells may also be markedly reduced in CVID patients particularly those with low isotype-switched memory B cells [35]. Moreover, there is skewing of NKT cell subsets and $CD4^+$ NKT cells circulate at higher frequency [36].

Defects of T cells

Patients of CVID show phenotypic and functional abnormalities of T cells and impaired secretion of their signaling molecules. At least in a subset of CVID patients, there may be numerical abnormalities of various T cells, that is, $CD4^+$, $CD8^+$ and $CD25^+FoxP3^+CD4^+$ regulatory T cells (Table 4).

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Table 2. Common noninfectious complications of common variable immunodeficiency.

Complications	Diagnosis	Incidence (%)
Autoimmunity	Idiopathic thrombocytopenic purpura	9.7
	Autoimmune hemolytic anemia	4.9
	Autoimmune cytopenia	3.8
	Noninfectious arthritis	2.6
	Neutropenia	2.3
	Pernicious anemia	2.6
	Thyroid disease	1.4
	Celiac disease	1.1
	Alopecia	1.0
	Diabetes mellitus, multiple sclerosis, connective tissue disorder and others	<1.0
Enteropathy	Chronic diarrhea including giardiasis	8.7
	Inflammatory bowel disease	6.4
	Malabsorption	6.0
	Nodular lymphoid hyperplasia	5.4
	Gastritis	4.1
Malignancy	B-cell non-Hodgkin's lymphoma	5.4
	Hodgkin's lymphoma	<1.0
	Carcinoma (breast, ovary, large gut, prostate)	<1.0
	Squamous cell carcinoma (skin, mouth, lung)	<1.0
	Melanoma	<1.0
	Waldenstrom's macroglobulinemia	<1.0
Granulomatous lesions	Lung, lymph node, liver, spleen, skin, intestine, and so on	9.7

Data taken from [2,14,22,24,52,83,84].

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There is activation of T cells with reduced proliferative response and lack of replenishment by new thymically derived cells. All these T-cell abnormalities are more commonly associated with autoimmune cytopenia, granulomatous disease, polyclonal lymphoproliferation and splenomegaly [37,38].

The French DEFI study group identified a subgroup of CVID patients with clinically relevant T-cell insufficiency. They coined the term 'late onset combined immunodeficiency' (LOCID) for such patients. These patients showed marked decrease in $CD4^+$ T-cell counts with a severe defect in naive $CD45RA^+CCR7^+CD4^+$ T-cell counts. LOCID was more common among consanguineous families (29 vs 8%) with a higher prevalence of splenomegaly (64 vs 31%), granuloma (43 vs 10%), gastrointestinal disease (75 vs 42%) and lymphoma (29 vs 4%) and required more intensive therapy [39].

Defects of B cells

In the bone morrow, pleuripotent stem cells give rise to Pro B cell that differentiate in to pre B cells and then immature B cells. The positively selected cells or the mature pre B cells then differentiate in to transitional B cells (T1B). Only 10–20% of T1B cells are exported from bone marrow to secondary lymphoid organs (e.g., spleen), where they transform in to BAFF-R expressing T2B cells [40]. In the lymphoid organs, the cells localize themselves in the follicular (follicular B cells) and marginal zone (marginal zone B cells) from where they reach the circulation. The follicular B cells comprise main B-cell population, and marginal zone B cells comprise about 15–20% of peripheral B cells [41]. After somatic hypermutation and affinity maturation in the germinal centers T cells-derived signals, for example, CD40L promote isotype class switching, survival of B cells and their differentiation in to memory B cells. The cytokines like IL-10, IL-21 stimulate differentiation of B cells in to plasma cells [42,43]. Memory B cells divide into two populations based on the expression of IgD on their surface. $CD19^+/27^+$ IgM^+ IgD^+ B cells are considered as non-switched memory cells, whereas those not expressing IgD are called switched memory B cells (Figure 2) [44].

In about 40–50% of CVID cases, peripheral B-cell count may be low; however, some patients may also show an increased B-cell count. In 10% of cases, B cells may be drastically reduced or completely absent [23,45]. Impaired terminal B-

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Table 3. Conditions leading to hypogammaglobulinemia and to be considered among differential diagnosis of common variable immunodeficiency.

Cause	Examples	Age of occurrence
Protein loss	Loss of immunoglobulins (protein losing enteropathy, severe diarrhea, nephrotic syndrome, severe burns, lymphangiectasia) Hypercatabolism of immunoglobulins (myotonic dystrophy)	>4 years
Malignancy	Chronic lymphocytic leukemia Lymphoma Good's syndrome (thymoma and immunodeficiency) B-cell tumors	
Drugs	Anticonvulsants (carbamazepine, valproic acid, phenytoin) Captopril Gold salts D-penicillamine Salfasalazine Glucocorticoids Fenclofenac Azathioprine Rituximab (anti-CD20) Alkylating agents (cyclophosphamide, chlorambucil) Imatinib Antimalarials	
Genetic and chromosomal abnormalities	Agammaglobulinemia (X-linked, autosomal recessive) Class switch recombination defects (CD40L, Hyper IgM syndrome) X-linked lymphoproliferative syndrome (Epstein–Barr virus-associated) Transient hypogammaglobulinemia of infancy Severe combined immunodeficiency Wiskott–Aldrich syndrome Di-George syndrome WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis) Transcobalamin II deficiency and hypogammaglobulinemia Ataxia telangiectasia DiGeorge anomaly Chromosome 18q syndrome Down syndrome Trisomy 8 Cystic fibrosis	<4 years
Infections	Congenital rubella Congenital cytomegalovirus Congenital toxoplasma gondii	
Others	Human immunodeficiency virus Epstein–Barr virus infection Complement deficiencies Leucocyte adhesion deficiency Chronic granulomatous disease Selective IgA deficiency Selective IgG subclass deficiency	Any age

Data taken from [3,81].

cell differentiation into memory B cells and plasma cells and failure of somatic hypermutation causes hypogammaglobulinemia and defective-specific antibody responses. This is due to impaired germinal center reaction in secondary lymphoid organs [3]. The defective B-cell maturation has also been suggested to be partially responsible for reduced number of T-regulatory cells (T_{reg}) [46]. This causes reduction in the number of class switched memory B cells seen in 80–90% cases [45,47]. B1 B cells ($CD27^+CD43^+$), a further subdivision of switched memory cells and important producer of natural IgM and IgA, have recently been shown to be reduced in CVID, but their significance in pathogenesis of CVID is not yet clear [48].

Most of these abnormalities have been studied in peripheral blood cells. Recently, Ochtrop *et al.* tried to define these abnormalities in bone marrow biopsy of 25 CVID patients. They found major pathological alterations in lymphoid

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Table 4. Immunological defects in common variable immunodeficiency.

Immunological defect		Ref.
Innate immunity	Altered distribution and reduced number of blood DCs	[85,86]
	Impaired maturation of myeloid derived DCs, decreased levels of co-stimulatory molecules and reduced secretion of IL-12 by DC causing defective antigen presentation and T-cell activation	[33,87,88]
	Diminished number and alteration in distribution of plasmacytoid DCs	[86]
	Defective TLR9 activation hence impaired recognition of DNA containing CpG motifs from virus and bacteria and stimulus for B cells for immunoglobulin production	[89]
	Dysfunctional TLR7 and TLR8 signaling	[90,91]
	Reduced CD1d restricted invariant NKT cells	[35,92]
T cells	Reduction of total $CD4^+$ T cell, naive $CD4^+CD45RA^+$ subset and $CD25^+FoxP3^+$ $CD4^+$ T-cell counts	[93–99]
	Increase in $CD8^+$ T cell number and inverted CD4/CD8 T cell ratio	[100]
	Oxidative stress in $CD4^+$ T cells due to persistent TNF activation and decreased levels of glutathione	[101,102]
	Impaired secretion of the cytokines IL-2, IL-4, IL-6, IL-7, IL-10 and IFN-γ along with increased levels of granzyme B	[81,98,99]
	Reduced expression of surface molecules (e.g., CD40L, L-selectin, attractin and defective T-cell receptor signaling)	[103–105]
	Reduced generation of antigen-specific memory T cells	[106]
	Increased T-cell apoptosis	[107]
B cells	Reduction in total number of peripheral B cells and impaired terminal B-cell differentiation in to memory B and plasma cells	[45,50]
	Reduction of class switched $CD27^+$ memory B cells	[45,47,108]
	Failure in somatic hypermutation leading to severe reduction in the generation of high-affinity antibodies	[109,110]
	Failure of B cells to differentiate into antibody secreting plasma cells	[111]
	Impaired upregulation of the co-stimulatory molecules CD70 and CD86 on B cells	[112,113]
	Defective B-cell receptor activation in response to T-cell stimuli	[114]

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compartment with no significant abnormality in the hematopoietic lineage. In 94% of the patients, plasma cells were either reduced or absent with partial block in B-cell development and an activated T-cell compartment comprising of $CD3^+$ infiltrates [49]. In another study by Taubenheim *et al.*, development of plasma blasts and plasma cells was disturbed after intact development of centroblast/centrocyte stage [50].

Genetic defects

In contrast to most of the PIDs that present as a single gene defect with Mandelian inheritance, CVID has largely undefined genetic roots. Both single gene mutations and polymorphisms have been found to be associated with CVID; however, their strength of association in terms of whether they are disease causing or disease modifier is controversial [14,51]. In past few years, quite a few efforts have been made in the form of genome-wide association studies (GWAS), targeted gene approach and genetic analysis in the family to unravel the disease-causing genetic defects in CVID. Though several distinct molecular defects have been identified to be associated with CVID together, they are present only in <3% of cases, an exception being transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) mutation, which may be seen in up to 10% of cases (Table 5) [3]. All these defects behave more as disease modifiers than disease-causing factors. Recently, International Union of Immunological Sciences classification has segregated ICOS, TACI, BAFF-R, CD19, CD20, CD21, CD81 and LRBA1 deficiencies as separate entities [27].

In addition to the above-mentioned genetic abnormalities, GWAS study further revealed a strong association with MHC region and showed that genetic loci present on chromosomes 4q, 6q and 16q are possibly involved in CVID etiology, and HLA region on chromosome 6p has been found to have strongest association [3,52]. Disintegrin and metalloproteinases 28 (ADAM28), ADAM7, ADAMDECI, SDK1, UBX10 and stanniocalcin-1 (STC1) are other candidate genes [52,53]. Recently, Amanzadeh *et al.* concluded that HLA-DR and DQ loci may contribute to the pathogenesis of CVID [54]. Few other polymorphisms that have also been claimed to modify the disease process include genes coding for cytokine TNF, complement activator mannose-binding lectin, regulator gene for IL-10, IL-12, interferon and cytotoxic T lymphocyte-associated protein 4 [13,55–58]

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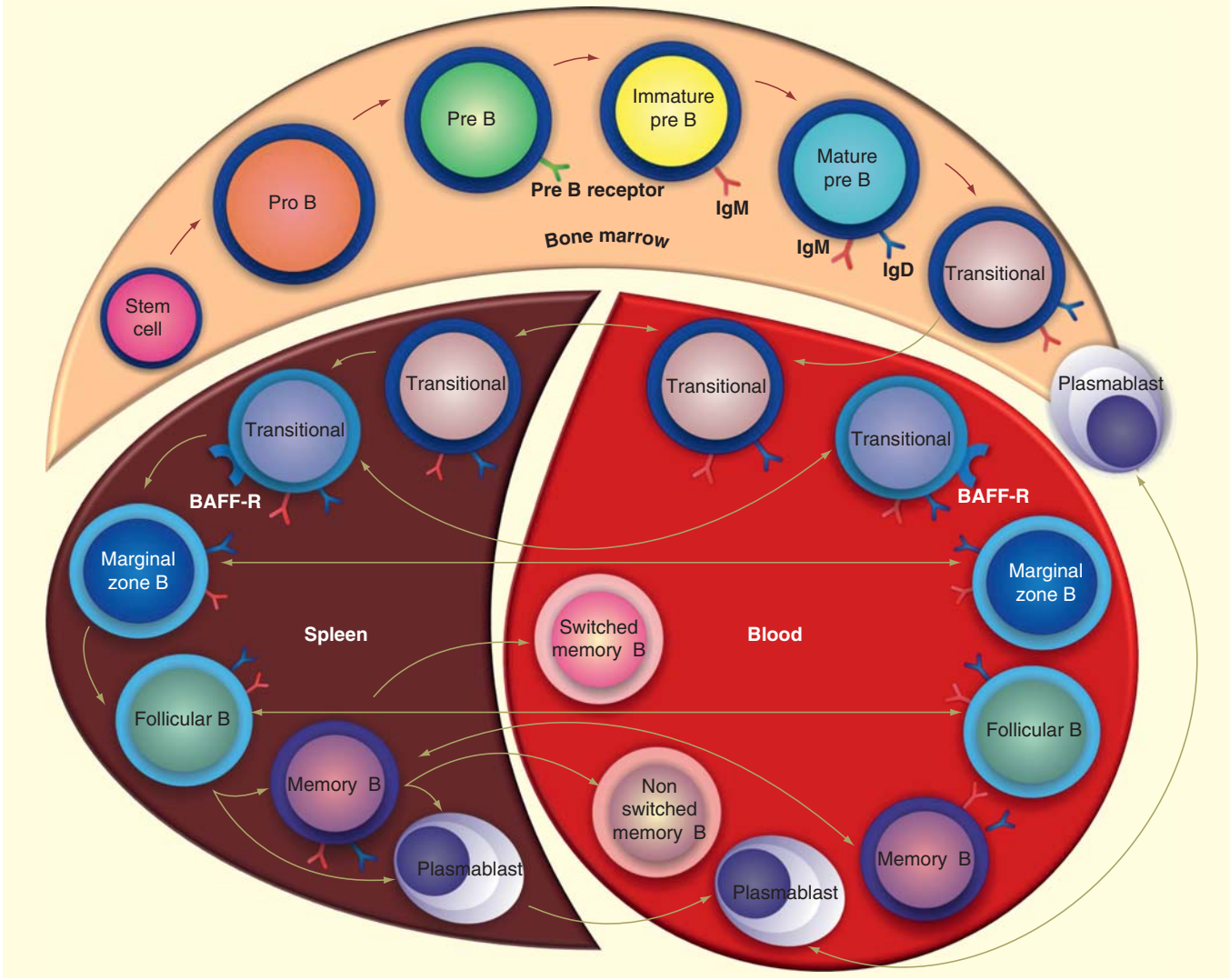

Figure 2. Central and peripheral development of B cells.

Diagnostic protocol & laboratory measures

Early diagnosis of CVID is important as it may drastically change the course of disease. It helps in patient counseling both in terms of explaining the symptoms and planning future management. Appropriate therapy in the form of antibiotics and IGs if given timely can prevent irreversible organ damage as well as disease-associated complications [59]. Although the diagnostic criteria for CVID (Box 1) were formulated by the European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency almost 15 years earlier, still a significant number of patients are either misdiagnosed or there is a delayed diagnosis [60]. In a study by De Santis *et al.*, diagnosis of CVID was delayed for a decade in about a quarter of their patients [61]. Hence to further strengthen these criteria and to avoid confusion with other conditions causing failure of antibody production and resembling CVID, for example, transient hypogammaglobulinemia of infancy, modifications in original diagnostic criteria have been proposed by Helen Chapel, Cunningham-Rundles and recently by Ameratunga *et al.* (Box 2). According to these modifications, criteria in the ABC or ABD category indicate probable CVID. These are the patients who require parenteral IGs. Patients with criteria of A, AB, AC, AD but not those of B should be labeled as possible CVID. In addition to these modifications, they also suggest that other known causes of antibody failure should be excluded first and a follow-up may be done for a period of 2 years after detection of low serum IGs to exclude the secondary antibody failure due to a lymphoid malignancy [55,62].

Clinical & laboratory workup in CVID

A high index of suspicion in all patients presenting with multiple and recurrent infections especially of respiratory and GIT with or without noninfectious complications is important to avoid delay or misdiagnosis of CVID. On encounter with such patients, evaluation should begin with detailed personal and family history followed by careful clinical examination and a systematic laboratory assessment (Box 3). Initially,

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Table 5. Monogenic defects sharing clinical phenotypes with common variable immunodeficiency.

Deficiency	Gene; chromosome	Functions	Associated clinical and laboratory features	Ref.
ICOS	ICOS; 2q33	Co-stimulatory molecule expressed on activated T cells and enables them to interact with B cells, monocytes, DCs	Hypogammaglobulinemia, reduced memory and switched memory B cells	[115,116]
TACI	TACI; 17p11.2	Cell surface receptor, role in B cell differentiation and function, isotype class switching	Hypogammaglobulinemia, autoimmunity, lymphoid hyperplasia	[117,118]
BAFFR	TNFRSF 13C; 22q13.1-q13.31	Interacts with BAFF and provides survival signal for peripheral B cell differentiation	Reduced IgG and IgM	[119]
CD19	CD19; 16p11.2	B cell co-receptor, B cell activation	? Renal involvement, hypogammaglobulinemia, reduced $CD27^+$ memory B cells	[120,121]
CD20	CD20; 11q12	Regulation of B cell activation and proliferation	Recurrent pneumonia, hypogammaglobulinemia, reduced memory B cells, impaired response to pneumococcal polysaccharides	[122]
CD21	CR2; 1q32	B cell co-receptor, B cell activation	Abnormal and short lived immune response with the generation of few memory cells	[123,124]
CD81	CD81; 11p15.5	B cell co-receptor, B cell activation	Hypogammaglobulinemia, absent $CD19^+$ B cells, reduced memory B cells, impaired specific antibody responses	[125]
LRBA1	LRBA1; 4q31.3	B cell activation, autophagy	Autoimmunity, hypogammaglobulinemia, low proliferative response	[126]
MSH5	MSH5; 6p22.1-21.3	DNA mismatch repair	Increased frequency of lymphoproliferative disorders	[127]

BAFFR: B cell-activating factor receptor; DC: Dendritic cell; ICOS: Inducible co-stimulator; LRBA1: Lipopolysaccharide responsive beige-like anchor protein 1; MSH5: MutS Homolog 5; TACI: Transmembrane activator and calcium modulating cyclophilin ligand interactor.

Box 1. European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency diagnostic criteria for common variable immunodeficiency.

Probable diagnosis

Male or female patient who has a marked decrease (at least 2 standard deviations below the mean for age) in serum IgG and IgA and fulfills all of the following criteria:

- Onset of immunodeficiency at >2 years of age
- Absent isohemagglutinins and/or poor response to vaccines
- Defined causes of hypogammaglobulinemia have been excluded

Possible diagnosis

Male or female patient who has a marked decrease (at least 2 standard deviations below the mean for age) in one of the major isotypes (IgM, IgG, and IgA) and fulfills all of the following criteria:

- Onset of immunodeficiency at >2 years of age
- Absent isohemagglutinins and/or poor response to vaccines
- Defined causes of hypogammaglobulinemia have been excluded

Data taken from [62].

patient should be investigated by baseline screening tests (Table 6). During clinical examination, all target organs, that is, lungs, GIT, ear, nose and throat, eyes, skin, liver and spleen should be carefully assessed and if required, help of laboratory and imaging measures may be taken. The initial screening before assessment of integrity of immune response helps in exclusion of more common nonimmunodeficient conditions and also in defining the patient's overall general condition. Once other causes of recurrent infections are ruled out and clinical features and baseline investigation suggest a PID, next step should include specific immunological tests followed by flow cytometric assays for disease confirmation and classification (Table 7).

Serum IGs assay

Reduction in serum IGs (IgG, IgA and IgM) is the most characteristic feature of CVID. However, the assay results depend on age, gender and ethnicity of the population and also the method used. Endpoint nephelometry is the most popular method for the assay as it can produce results in no time and has good sensitivity and specificity. The distribution of serum IGs is nonparametric; hence, 97.5% percentile is used to define

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Box 2. Proposed modifications in the diagnostic criteria for common variable immunodeficiency.

A) Major criteria (must meet all criteria)
- Onset of immunodeficiency at the age of 4 years or more
- Serum IgG levels <4.5 g/l for adults or the 2.5th percentile for age, usually with levels of serum IgA below the lower limit of normal for age but alternatively serum IgM below the lower limit of normal for age
- Exclusion of all other known causes of failure of immunoglobulin production

B) Clinical complications as a result of failure of immune system (one or more criteria)
- Recurrent, severe or unusual infections
- Bronchiectasis/chronic sinus disease/autoimmune disorders
- Poor response to antibiotics
- Bacterial infections despite prophylactic antibiotics
- Failure of vaccination and re-infection

C) Laboratory parameters (three or more criteria)
- Presence of B cells but very low numbers of circulating switched or memory B cells
- IgG3 deficiency (<0.2 g/l)
- Significant lack of antibody responses to protein antigens following immunization or exposure antigens in at least two assays
- Absent isoagglutinins (in non-AB blood group)
- Serological assays positive for autoimmunity

D) Specific histological findings (supporting but not required for diagnosis)
- Lymphoid interstitial pneumonitis
- Granulomatous inflammation
- Nodular regenerative hyperplasia of the gut
- Nodular regenerative hyperplasia of the liver
- Absent plasma cells in duodenal/gut biopsy

Data taken from [15,55,62].

Box 3. Clinical details to be obtained while cross-examination of a suspected case of common variable immunodeficiency.

Age of onset and duration of symptoms
History of similar illness in other family members or siblings
Symptoms related to infections
Recurrent fever, cough with or without expectoration, chest pain, purulent rhinitis, nasal blockage
Ear discharge or frequent conjunctivitis
Chronic or recurrent diarrhea, dysentery, gastritis, and so on
Eczema or urticaria
Skin, soft tissue or visceral abscesses
Neck rigidity with fever and unconsciousness
Symptoms related to autoimmune complications
Multiple symptoms related to various organ systems
Inflammation of bones and joints
Petechial hemorrhages or bleeding tendencies
Jaundice
Symptoms related to malignancy
Nodular growth or lump in the body
Weight loss, anorexia, fatigue and lethargy
Any drug history (e.g., antiepileptics, gold salts, D-penicillamine, steroids, and so on)

Data taken from [29,56,128–131].

IG levels in normal population. For a diagnosis of CVID serum, IGs must be below the minimum levels found in healthy population of that age (i.e., less than the levels found in 2.5% population). Required levels of IGs for CVID are: IgG <4.5 g/l (reference range 7–18 g/l for adults), absent or markedly reduced IgA (reference range 0.7–3.5 g/l for adults) and normal or below normal IgM (reference range 0.4–2.6 g/l for adults). Rarely, high IgM levels may also be seen if the patient has in addition a hyper IgM syndrome or switch defect [63]. The elevated IgM level is important from prognostic point as polyclonal lymphocytic infiltration and lymphoid malignancy has been described in such patients [23]. An isolated deficiency of IgG needs quantitative measurements for IgG subclasses and further evaluation for IgG subclass deficiency (reference range for adult IgG1 = 4.8–9.5 g/l; IgG2 = 1.1–6.9 g/l; IgG3 = 0.3–0.8 g/l; IgG4 = 0.2–1.1 g/l) [64].

Antibody response to vaccines & isoagglutinin titers

Antigen-specific antibody responses should be considered in patients who have only mild-to-moderate reduction in IGs, particularly IgG. It can further clarify the degree of immunodeficiency and sometimes helps in deciding whether or not the patient will be benefitted from IG therapy. The test, however, may not provide appropriate results in patients with markedly reduced IgG levels (<1.5 g/l) and/or B cells (<2%). Antibody response to at least two protein vaccine antigens, for example, tetanus or diphtheria toxoids and hemophilus conjugate should be assessed. Healthy individuals usually show a fourfold increase in prevaccination levels 4 weeks after immunization or at least the patient should show protective titers if less than threefold increase from baseline to label an acceptable B-cell response [55]. Vaccination responses to polysaccharide antigens are difficult to interpret due to poor reaction to different serotypes and variability of responses in healthy individuals [65]. Conjugation of these polysaccharides to protein carriers, however, has improved the vaccine efficacy as well as antibody response against them though results may still be poor in elderly [66]. Two antipneumococcal vaccines, a 23-valent pneumococcal polysaccharide vaccine (Pneumovax containing 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F serotypes) and a 13-valent conjugated vaccine (Prevnar 13 containing 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F serotypes) are currently available.

Since the ABO blood group antigens are polysaccharides, an antipolysaccharide antibody can be assessed by quantitating isoagglutinin titers. Isoagglutinins can be measured after 2 years of age, and low or absent titers in a patient without AB blood group is indicative of a poor functional IgM response. Isoagglutinin titres, however, may be normal at the time of diagnosis of CVID.

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Table 6. Suggested initial tests to be done before ordering specific tests in a suspected case of common variable immunodeficiency in whom other causes of recurrent infections have been excluded.

Type	Investigation
Immunology	Quantitative serum immunoglobulin assay for IgG, IgA, IgM and IgE Serum and urine electrophoresis for proteins Immunofixation Nitroblue tetrazolium/dihydrorhodamine flowcytometry test Antitransglutaminase antibody C-reactive protein determination Complement CH50 β2 microglobulin
Hematology	Complete blood cells count with manual differential – specially for absolute lymphocyte count, platelet count and size Coombs test (if patient is anemic) Bone marrow aspiration and biopsy (if suspected lymphoma or myelodysplasia)
Biochemistry	Renal function test Liver function test Serum calcium Urine analysis
Microbiology	Direct culture of sputum, pus and body fluids (e.g., blood, urine, CSF, and so on) and antibiotic sensitivity test for bacterial infections Indirect or serological assay, for example, ELISA ELISA for hepatitis B, C virus and HIV Molecular detection of pathogen by PCR Stool examination for parasites; for example, *Giardia lamblia*
Radiology	Chest X-ray HRCT lung, abdomen Ultrasonography abdomen MRI of central nervous system, abdomen
Clinical	Evaluation by clinical immunologist and genetic counseling
Others	Spirometry, carbon monoxide diffusion test, blood gas analysis, bronchoscopy, and so on, for lung functions Esophagogastroduodenoscopy and colonoscopy for gastrointestinal tract Routine cancer screening Thyroid stimulating hormone (if excessive fatigue) Fecal fat (if malabsorption) Sweat test (to exclude cystic fibrosis)

Data taken from [3,31,56,128–131].

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In vitro *T-cell proliferation assay*

T cells isolated from peripheral blood are cultured to assess lymphocyte proliferation response to mitogens, for example, photohemagglutinin or pokeweed antigen. Certain microbial antigens, for example, *Candida albicans*, tetanus toxoid, etc. can also be used as an alternative. After adding ^{3}H thymidine to culture preparation. the cells are counted in a scintillator. Alternatively, 5-bromo-2′-deoxyuridine (Brdu) may be used and after incubation, the cell proliferation may be assessed by measuring the optical density [67]. A much easier flow cytometric approach can also be used by labeling cells with carboxyfluorescein succinimidyl ester (CFSC) dye. CFSC labels the long-lived intracellular molecules; hence, when CFSC-labeled cell divides, the daughter cells contain half the CFSC-labeled molecules thereby leading to decrease in fluorescence [68].

Though the test gives useful information regarding integrity of T-cell function, it is not mandatory for the diagnosis of CVID as only 20% of the patients will have impaired proliferative responses. Moreover, these are the patients with low $CD4^+$ T-cell count and normal to raised $CD8^+$ T-cell count [69].

Flow cytometric analysis of lymphoid cells

Flow cytometric analysis has become a part of standard diagnostic workup for CVID [70]. A detailed analysis of the lymphocyte population is important for assessment of severity of immune turbulence, identification of large monoclonal populations and disturbances in early B-cell differentiation that results in very low numbers of peripheral blood B cells. Before extensive B-cell phenotyping, full blood cells counts and lymphocyte counts should be done using a hematology analyzer.

Lymphocyte subset analysis

Absolute counting of $CD4^+$, $CD8^+$ T cells, B cells and NK cells in whole blood or peripheral blood lymphocytes preparation using a small lymphocyte panel (Table 8) is strongly

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Table 7. Specific immunologic tests for common variable immunodeficiency.

Test	Procedure
Flow cytometric lymphocyte subset analysis	CD45, CD3, CD4, CD8, CD19, CD16/CD56
Immunoglobulin subclass analysis	IgG1, IgG2, IgG3, IgG4, IgA1, IgA2
Flow cytometric B-cell subset analysis	Naïve B cells ($CD19^+$ $CD27^-$ IgD^+) Class-switched memory B cells ($CD27^+$ IgD^- IgM^-) Nonswitched memory B cells ($CD27^+$ IgD^+ IgM^+) IgM memory B cells ($CD27^+$ IgM^+ IgD^{dull}) Transitional B cells ($CD38^{+++}$ IgM^{++}) Plasmablasts ($CD38^{+++}$ IgM^-) Mature B cells ($CD21^+$) $CD21^{lo}$ B cells
Functional antibody test	Protective levels of IgG against two or more vaccines, such as tetanus, diphtheria, hepatitis A and B, rabies, *Haemophilus influenza*, pneumococcal polysaccharides, *Streptococcus pneumoniae*, bacteriophage ΦX174 Isoagglutinin titers (antiA and/or AntiB)
In vitro lymphocyte proliferation	Peripheral blood lymphocyte proliferation responses to one or more stimulants, that is, Phytohemagglutinin, Concanavalin A, Poke weed, *Candida albicans*, Tetanus toxoid
Biopsy	Lymph node or intestinal biopsy for noncaseating granuloma and/or nodular lymphoid hyperplasia
Flow cytometric analysis for protein expression	ICOS BAFFR CD19
Molecular genetic testing by gene sequencing/PCR	ICOS TACI TNFRSF 13C CD19

Data taken from [3,24,31,128,129].

recommended as a preliminary test [71]. This also helps in calculating absolute numbers of different subpopulations. Reference ranges of the percentage of various circulating lymphoid cells in adult population are given in Table 9.

B-cell phenotyping

For B-cell phenotyping, lymphocytes may be gated using different surface markers, such as CD19, CD20 and CD22. Since CD19 is present on all circulating B cells, it is used most commonly. Up to six different subsets of B cells can be distinguished by using a panel of surface markers. After gating the CD19-positive cells, different B-cell subsets should be distinguished using combinations of markers (Table 9). This distinction is important as CVID has been classified into its variants based on the alteration in one or other B-cell subsets. Three classification systems: Freiburg, Paris and EUROClass classification are based on phenotyping of B-cell subsets [72–74].

Freiburg classification divides CVID patients with >1% $CD19^+$ cells into two groups: Group I patients with <0.4% of $CD27^+$ IgM^- IgD^- class switched memory B cells and Group II patients with >4% of these cells. Group I has been further divided into those with >20% $CD21^+$ B cells as Group Ia and those with <20% $CD21^+$ B cells as Group Ib. The Freiburg classification was developed to discriminate CVID patients with differentiation defects of early peripheral B cells from those with memory B cells. Paris classification is based on quantification of class switched memory B cells and total $CD27^+$ B cells including marginal zone like B cells. It assigns patients into three phenotypes: M0 with reduced nonclass switched memory B cells (<11%) and class switched memory B cells (<8%) in the peripheral blood, M1 with reduced class switched but normal nonclass switched memory B cells and M2 with nearly normal percentage (>11%) of naïve/memory B cells or not fitting into above two categories. EUROClass was aimed to provide a consensus classification by introducing new criteria as well as combining features of both the above classifications. It discriminates the patients with <1% $CD19^+$ B cells from the great majority of patients with higher numbers of B cells. Patients with >1% $CD19^+$ B cells are further divided into those with severe deficiency of switched memory B cells (<2% of $CD19^+$ B cells) and those with >2% of switched memory B cells. EUROclass also divides patients on the basis of percentage of $CD21^{low}$ B cells into those with below and above 10% of $CD19^+$ B cells (Figure 3).

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Table 8. Peripheral blood reference values of various lymphocyte subsets in adults.

CD marker expressed	Lymphocyte subset	Reference range (%)
CD45+	Total lymphocytes	35-40
$CD3^+$	T cells	50–80
$CD3^+$ $CD4^+$	$CD4^+$ T cells	28–50
$CD3^+$ $CD8^+$	$CD8^+$ T cells	15–35
CD4+/CD8+	T helper/T cytotoxic cell ratio	0.7–3
$CD3^+$ $CD25^+$	Activated T cells	0.5–6
$CD16^+$ $CD56^+$	NK cells	5–30
$CD19^+$ $CD45^+$	B cells	5–19
$CD19^+$ IgM^- IgD^-	Class switched B cells	8–31
$CD19^+$ IgD^+ $CD27^-$	Naïve B cells	42–82
$CD19^+$ IgD^+ $CD27^+$	Marginal zone like B cells	7–32
$CD19^+$ IgD^- IgM^- $CD27^+$	Class switched memory B cells	6–29
$CD19^+$ $CD38^-$ $CD21^{low}$	$CD21^{low}$ B cells	0.9–7
$CD19^+$ IgM^{++} IgD^{++} $CD24^{++}$ $CD38^{++}$	Transitional B cells	0.6–3
$CD19^+$ $IgM^{+/-}$ $CD27^{++}$ $CD24^-$ $CD38^{+++}$	Plasmablasts	0.4–3

Data taken from [71,132,133].

Up to 90% of CVID patients may have normal or only marginal reduction in their peripheral B-cell counts. In 5–10% of patients, the peripheral B-cell counts, however, are drastically low (<1% of lymphocytes). Flow cytometric classification of these patients may reveal defects of early B-cell differentiation, disturbed germinal center functions causing reduction in switched memory B cells, disrupted marginal zone B-cell differentiation leading to selective decrease in IgM memory B cells. Expansion of circulating $CD21^{low}$ B cells is associated with splenomegaly and granulomatous disease [70]. Expansion of transitional B cells is associated with lymphadenopathy [74].

T-cell phenotyping

T-cell defects may be seen in up to 50% of CVID patients [75]. Hence, T-cell phenotyping by flow cytometry has also been suggested by few investigators. Besides reduction in total T-cell counts, naïve T cells ($CD45RA^+$ $CD4^+$)

Table 9. Examples of antibody panels for preliminary screening B- and T-cell phenotyping.

Panel	FITC	PE	PerCP	APC
Preliminary lymphocyte count				
P1	CD8	CD4	CD45	CD3
P2	CD19	CD16/56	CD45	CD3
B-cell phenotyping				
B1	CD27	Anti-IgD	CD19	Anti-IgM
B2	CD38	CD21	CD19	Anti-IgM
Activated T cells				
T1	CD69	IgG1 isotype	CD3	CD4
T2	CD69	ICOS	CD3	CD4
T3	CD69	CD40L (CD154)	CD3	CD4

APC: Antigen presenting cell; FITC: Fluorescein isothiocynate.
Data taken from [71,134].

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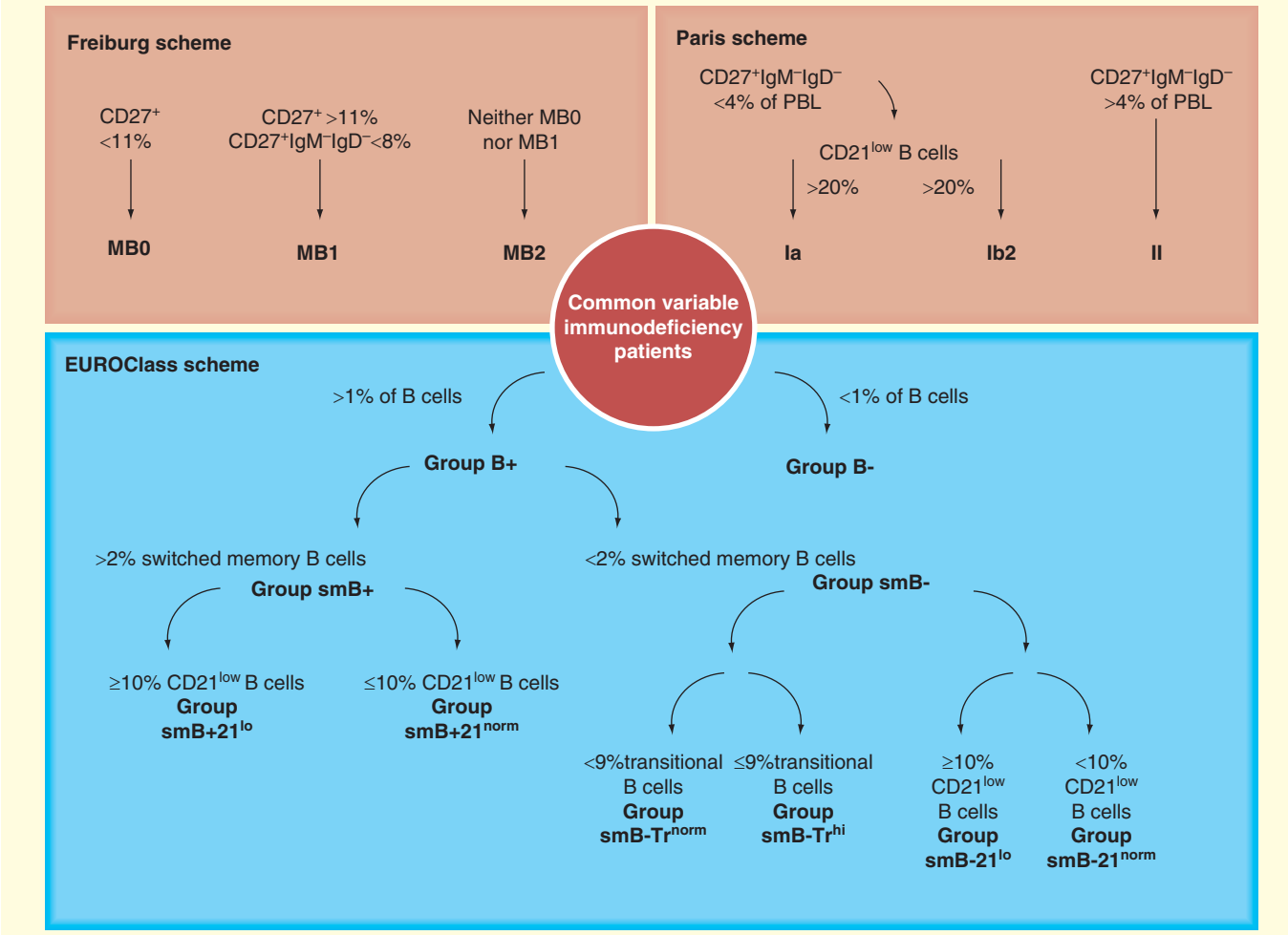

Figure 3. B-cell phenotype-based classification of common variable immunodeficiency.

are also reduced. On the basis of naïve T-cell counts, patients may be separated into three groups: <15%, 16–30% and >30% of $CD4^+$ T cells. The patients with more severe reduction in naïve CD4 T cells have decreased thymic output of $CD4^+$ T cells, decreased switched memory B cells, increased $CD21^{low}$ B cells, splenomegaly and granulomatous disease [76]. More than 50% of patients show decrease in CD4/CD8 ratio (<1.0) due to increased $CD8^+$ and reduced $CD4^+$ lymphocytes [75]. In addition, patients of CVID with splenomegaly and chronic inflammation may also show reduced T_{reg} [77,78].

Exclusion of other defects by flow cytometry

Flow cytometry may also be used to exclude other conditions mimicking CVID. For analysis of CD40 deficiency which also leads to class switch recombination defect, CD40 expression may be examined after gating on B cells. Similarly, in CD40L deficiency, another cause for class switch recombination defect, $CD4^+$ T cells after stimulation may be evaluated. The nonactivated T cells with reduced expression of CD40L suggest its deficiency. However, CD40L deficiency is extremely rare and should be considered only if male patient with positive family history presents with increased serum IgM. ICOS deficiency that closely mimics CVID may be analyzed after T-cell stimulation and gating on $CD4^+$ T cells. Similarly, BAFFR deficiency, CD19 deficiency etc. can also be easily excluded by flow cytometry. Flow cytometry results for TACI deficiency, however, are unreliable. Hence, genetic sequencing is a better option for its analysis [79].

Future research

The diagnosis of CVID is often delayed due to varied clinical symptomatology of the disease and absence of a specific biomarker. Hence, futuristic research on CVID requires establishment of more precise diagnostic criteria and search for an appropriate immunological marker to diagnose the condition. Although B-cell phenotyping is used for classification of CVID, a significant variation in B-cell memory subsets in different studies renders it far from perfect. The knowledge regarding the role of cytokines, DCs and NK cell defects and T_{reg} in CVID, even if evaluated in previous

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studies need further clarification. CVID is a multifactorial disease and it is likely that multiple genetic abnormalities contribute to its pathogenesis. The pinpointing of exact disease-modifying factor contributing to the complications of CVID particularly autoimmunity and malignant predisposition may be facilitated in future owing to the availability of advanced techniques like DNA and RNA expression arrays. Epigenetic studies and sequencing of familial clusters may also provide additional information related to the disease pathogenesis. Targeted sequencing of existing pathways that have been used with great success in discovering other forms of PIDs may prove to be fruitful in CVID as well.

Expert commentary

Recent advances in diagnostics have provided us valuable information on multifactorial causation, spectrum of complications and progression of CVID. The course and management of the CVID has also improved after the introduction of IG replacement therapy. However, still a long path remains to be traversed as the cases of CVID being reported presently probably represent only the tip of iceberg, particularly in the developing nations. Intensification of collaborative and interactive efforts is required to seek out the hidden cases. This may be easier if we have a specific biomarker for the disease. Moreover, further research is warranted to find out the culprits leading on to defective immune system after adolescence. An increasing awareness and interest among the clinicians and immunologists will certainly expedite the evolution of advanced diagnostic tools, which will aid to combat this chronic and debilitating disease.

Five-year view

The diagnosis of CVID is often neglected due to its rarity and ignorance about its presentation. Therefore, an increased awareness about this entity and a high index of suspicion are prerequisites for its timely detection. The appropriate training of the doctors as well as the laboratory personnel may also help in the prompt recognition of this type of immune defect. Regular follow-ups, periodic serum IGs measurement, blood counts, monitoring for lung function, and so on, are done, but there are no set rules on monitoring for CVID. There is no agreement on use of chest X-ray or MRI for lung monitoring, and also there is controversy regarding duration and interval in monitoring in different studies. A consensus among clinicians and immunopathologists may be important for formulation of guidelines for diagnosing and monitoring of CVID in the coming years. The cost of IG replacement therapy is beyond the reach of poor men. The therapy could be affordable if private sectors come forward and join hands with the government for local manufacture of IGs. Also it is important to measure the disease burden particularly in developing countries for health planning, research and allocation of limited resources. Registries are required in different countries to estimate the disease prevalence. It is hoped that ongoing efforts from clinicians, immunologists and scientists all will contribute to our understanding of CVID. This may not only aid in improving the quality of life in the patients but also help to reduce the physical and psychological effects of CVID. It is hoped that as the technology accelerates, the task of chipping away at this mountain will be attained.

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Key issues

- Common variable immunodeficiency (CVID) is the one of the most common symptomatic primary immunodeficiency disorder in adults but is underreported.
- A diagnosis of CVID should be considered in all patients with recurrent infections, particularly in those with similar illness in other family members.
- Radiological investigations may provide information on severity of the disease and preliminary quantitative IGs assay should be done in all suspected cases.
- Although there is a long list of laboratory measures available, they should be utilized judiciously after a detailed clinical evaluation of the patient.
- Flow cytometry has been found to be most informative and serves as the standard diagnostic tool for CVID patients.
- So far, no single genetic factor has been found to be exclusively associated with CVID, and genetic analysis is required mostly to exclude other conditions.
- Reporting of more number of cases, awareness among clinicians and education of patients about management of disease is needed for disease control.

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