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COMMON VARIABLE IMMUNODEFICIENCY AND LIVER INVOLVEMENT

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Abstract

Common variable immunodeficiency (CVID) is a primary B-cell immunodeficiency disorder, characterized by remarkable hypogammaglobulinemia. The disease can develop at any age without gender predominance. The prevalence of CVID varies widely worldwide. The underlying causes of CVID remain largely unknown; primary B-cell dysfunctions, defects in T cells and antigen presenting cells are involved. Although some monogenetic defects have been identified in some CVID patients, it is likely that CVID is polygenic. Patients with CVID develop recurrent and chronic infections (e.g., bacterial infections of the respiratory or gastrointestinal tract), autoimmune diseases, lymphoproliferation, malignancies, and granulomatous lesions. Interestingly, autoimmunity can be the only clinical manifestation of CVID at the time of diagnosis and may even develop prior to hypogammaglobulinemia. The diagnosis of CVID is largely based on the criteria established by European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency (ESID/PAGID) and with some recent modifications. The disease can affect multiple organs, including the liver. Clinical features of CVID patients with liver involvement include abnormal liver biochemistries, primarily elevation of alkaline phosphatase (ALP), nodular regenerative hyperplasia (NRH), or liver cirrhosis and its complications. Replacement therapy with immunoglobulin (Ig) and anti-infection therapy are the primary treatment regimen for CVID patients. No specific therapy for liver involvement of CVID is currently available, and liver transplantation is an option only in select cases. The prognosis of CVID varies widely. Further understanding in the etiology and pathophysiology will facilitate early diagnosis and treatments to improve prognosis.

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Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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Keywords

common variable immunodeficiency; CVID; primary immunodeficiency; B cell; hypogammaglobulinemia; infection; autoimmunity; granuloma; liver involvement; nodular regenerative hyperplasia; alkaline phosphatase

1. INTRODUCTION

The immune system is a complex and highly regulated system to protect our body from pathogens and maintain immune homeostasis (1–4). When part of the system is either absent or not functioning properly, it can lead to immunological disorders such as immunodeficiency (5–9). Immunodeficiency disorders are either congenital or acquired. A congenital, or primary, disorder is one you were born with. Compared to other human immune defects, common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency disorder in adults (10–13). While the circulating B cell count is normal in most patients with CVID, the disease is characterized by defects in B-cell differentiation, leading to decreased counts of plasma cells and memory B cells, and low levels of circulating immunoglobulins (Igs). Hence, remarkable hypogammaglobulinemia is the hallmark of CVID. However, the underlying mechanisms of CVID remain largely unknown.

Clinically, CVID is highly variable and heterogeneous. Some key features include a) the low plasma cell numbers and immunoglobulin levels leading to infections primarily by bacteria in the respiratory and gastrointestinal tracts; b) autoimmune disorders despite the immunodeficient state; and c) risks of malignancies. Taken together, these presentations indicate both B and T lymphocytes are involved in the pathogenesis of CVID. The predominant organs involved include the lungs, gastrointestinal tract, hematological system and the liver. The liver involvement ranges from mildly elevated liver enzymes to severe hepatic decompensation and liver failure (14–18). The diagnostic criteria for CVID have been established and subsequently revised. Due to the diverse clinical manifestations and rarity of CVID, the diagnosis of CVID and in particular liver involvement is often delayed, leading to severe organ damage and poor prognosis (19). Thus, early recognition and appropriate clinical management is required to improve the clinical outcome and prognosis. Here, we discuss the epidemiology, pathogenesis, clinical manifestations, diagnosis and treatments with emphasis on the liver involvement of CVID.

2. EPIDEMIOLOGY OF CVID

Antibody related primary immunodeficiency disorders account for over 50% of all immunodeficiency patients (20, 21). Selective Immunoglobulin A deficiency (SIgAD) is the most common antibody related primary immunodeficiency. However, 80% of SIgAD patients are asymptomatic. The second most common is CVID, which accounts for 11.7% to 36.3% of all primary immunodeficiency (12, 13, 20, 22, 23). The estimated incidence and prevalence of CVID are 2–10/100,000 (10, 24) and 1–10/100,000 population (21, 25–27), respectively.

The prevalence of CVID varies widely worldwide. The reported prevalence ranges from 30.2/100,000 in USA (13), 1.3/100,000 in the United Kingdom, 0.7/100,000 in France (20, 23), 0.13–0.28/100,000 in Taiwan and 0.25/100,000 population in Japan (22, 28). The actual prevalence may be even higher due to delay in diagnosis, more effective treatments available and subsequent better prognosis and longer survival (28).

3. ETIOLOGY AND PATHOGENESIS OF CVID

Although the underlying causes of CVID remain largely unknown, primary B-cell dysfunctions, defects in T cell and antigen presenting cells (APCs) are involved in the pathogenesis. Thus, CVID is considered a group of highly heterogeneous disorders (24, 26, 29).

3.1 Defects in B cells

CVID is mainly characterized by defects in B cell differentiation to plasma cells and memory B cells, including impaired up-regulation of CD70 and CD86 in naive B cells (30), BCR signaling (31, 32), toll-like receptors (TLRs) signaling, and interferon (IFN)-α signaling (33–36). Consequently B cells lose their activation, proliferation and differentiation capacities to become plasma cells and memory B cells, leading to poor humoral immunity and recurrent infections. Significantly reduced level of plasma cells in the bone marrow has been observed in 94% of CVID patients, and correlates with serum IgG levels (37). Although it is not specific to CVID, the paucity of plasma cells is included in the new diagnostic criteria (21). Moreover, reduced count of switched memory B cells (CD27+IgM-IgD-), which is associated with infections, autoimmunity, immune cytopenia, granulomas, lymphadenopathy and splenomegaly is common (33, 38–42), and is included as one of the parameters in the classification of CVID (33, 38, 42–44). In addition, $CD21^{low}$ B cells, which include a proportion of auto-reactive cells, are also detected in CVID patients, and are believed to be associated with autoimmunity (24, 42, 45).

3.2 Defects in T cells

In addition to B cell defects, CD4+ and CD8+ T cells, T-helper, and regulatory T (Treg) cells are also involved in the pathogenesis of CVID (46). Specifically, the numbers of CD4+ and Treg cells are decreased while CD8+ T cells are increased. Alterations of T cell functions, including decreased proliferative responses to mitogen and antigens stimulation, increased activation and apoptosis of T cells, and abnormalities in cytokine production have been demonstrated (18, 46). A recent study reveals that impairment in cytokine production of T cells may be responsible for the decreased level of memory B cells in a subset of patients with CVID (47). In addition, dysfunctions of TCR signaling, TLRs signaling, interleukin (IL)-4 signaling and FcγRIIa signaling are also detected in T cells of CVID patients (7, 46). More importantly, the suppressive function of Treg cells from CVID patients with autoimmune disease is attenuated, which may partly account for autoimmune manifestations in CVID patients (45, 48). When opportunistic infection happens, and/or CD4+ lymphocyte count falls below 200/μL, it is named late-onset combined immunodeficiency (LOCID) (21, 49, 50).

3.3 Defects in antigen presenting cells (APCs)

The number and function of dendritic cells (DCs) are also decreased in CVID patients. Both myeloid and plasmacytoid DCs are markedly reduced in CVID patients (6, 51), which correlates with increased incidence of autoimmunity, granulomas and splenomegaly (51). DCs from CVID patients are less responsive to antigen stimulation and suffer from impaired differentiation, and inability to up regulate maturation markers, co-stimulatory molecules, and cytokine production (e.g. IL-12), which are key components for the activation of T cells (52). In addition, defective TLRs signaling had also been observed in DCs of CVID patients (35). These defects in DCs lead to impaired antigen presentation and subsequent adaptive immune responses.

3.4 Genetics

Unlike many other primary immunodeficiency disorders, most CVID patients do not have any distinct genetic background (10, 26, 33). About 5–25% patients with CVID have a positive family history, and most of them are presented with autosomal dominant inheritance (10, 21, 29, 33). Thus far, some monogenetic defects responsible for a small proportion of CVID or CVID-like patients have been identified, including *ICOS, TNFRSF13B (TACI), TNFRSF13C (BAFF-R), TNFRSF7 (CD27), CD18, CD19, MS4A1 (CD20), CR2 (CD21), CD81, LRBA, Msh5, PRKCD, PLCG2, NFkB1, NFkB2, PIK3R1, VAV1, IKZF1 (IKAROS), IRF2BP2, CTLA-4, PIK3CD, BLK, RAC2, TNFSF12 (TWEAK), CXCR4, IL-21, IL-21R, FANC* and *RAG1* (10, 24, 27, 49, 53–57). However, it is more likely that CVID is a polygenic rather than a monogenic disorder (24). Testing of these genes in CVID patients is not recommended because their mutations are rare and sometimes found in healthy individuals (10, 27, 58). In addition, other studies suggest an association between SIgAD and CVID, raising the possibility of common genetic background (10, 21). Recent high throughput genomic and epigenomic studies have identified several loci as well as genes and pathways on possible shared genetic basis of CVID and autoimmunity (59). However, their small sample size, diverse clinical phenotypes and different cell types examined limit these studies. Continued and coordinated efforts with larger sample size and in-depth analysis on broad variety of immune cell types will facilitate the discovery of reliable genetic biomarkers panel for disease monitoring and subgroup stratification, prognosis and treatment progress.

4. CLINICAL MANIFESTATIONS OF CVID

CVID is the most frequent symptomatic primary immunodeficiency disorder with heterogeneous clinical manifestations. While recurrent infection is a major characteristic, the frequencies of autoimmune disorders and malignancies are on the rise among patients with CVID.

Although CVID can be diagnosed at any age, its onset commonly ranges from 20 to 40 years of age (10, 23, 29, 49, 58), with a pediatric onset age peaking before 10 years old (26). There appears to have an earlier onset in male (26, 28, 29), but no gender predominance is observed overall (10, 24, 26, 28). Diagnosis is commonly delayed, with a significant number of patients being diagnosed 4–8 years after the initial onset (21, 23, 26, 29, 49) and some

even over 10 years (49, 60). The delay in diagnosis is partly due to its heterogeneity in clinical presentation; while recurrent infections are commonly recognized as CVID, other clinical manifestations (i.e., autoimmune diseases, lymphoproliferative disorders and malignancies, gastrointestinal or liver involvement) often lead to misdiagnosis. However, recent data suggest that the diagnostic delay is decreased (26, 29). Importantly, the clinical presentation may vary over time and different clinical features may appear sequentially making the accurate diagnosis of CVID challenging.

4.1 Infections

Primary hypogammaglobulinemia is the serological hallmark of CVID and leads to increased susceptibility to encapsulated bacteria. More than 90% of the CVID patients manifest as various infections, often before diagnosis (10, 29, 58, 60) (Table 1).

The respiratory tract is the most frequently infected organ (10, 29), which often manifests as sinusitis, bronchitis, pneumonia and chronic bronchiectasis. Ultimately, lung impairment may require surgical treatment (i.e. lobectomy) (26) and accounts for a large proportion of CVID fatality (21, 61). The gastrointestinal tract is the second most common infected organ and often manifests as enteritis or gastritis, with transient or persistent diarrhea, and may have lower level of serum IgA (29). In addition, meningitis, encephalitis, septicemia, skin abscess, urinary or urine cervical infections, empyema, osteomyelitis, otitis, joint, ear, nose and throat infections are common in CVID patients (21, 29).

Bacteria are the predominant microbes isolated from patients with CVID. They include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catharralis* and *mycoplasma species* from the respiratory tract, and *Giardia lamblia, Salmonella, Campylobacter jejuni, H pylori, Clostridium difficile*, and *Yersinia enterolitica* from the gastrointestinal tract (10, 29, 58, 62). Virus and mycobacterium are also occasionally detected (29, 63–66).

4. 2 Autoimmunity

Autoimmunity is a common complication of CVID, found in about 20–30% of the CVID patients (18, 21, 45, 67) (Table 1). Importantly, it can be the only manifestation of CVID at the time of diagnosis, and may even develop prior to hypogammaglobulinemia (21, 45). Autoimmune diseases secondary to CVID are more common in female than male patients (18, 24). Primary T-cell defects and increased autoreactive B cells have been implicated in the pathogenesis of autoimmunity (24).

The most frequent autoimmune condition associated with CVID is cytopenia, including idiopathic thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) or Evan's syndrome (both ITP and AIHA); autoimmune neutropenia is rare. Both systemic autoimmune diseases (rheumatoid arthritis, juvenile rheumatoid arthritis, seronegative arthritis, Sjogren syndrome, systemic lupus erythematous, Behçet's disease), and organ specific autoimmune diseases (thyroiditis, vitiligo, uveitis, vasculitis, inflammatory bowel disease-like diseases and primary biliary cholangitis (PBC) have also been documented (18, 21, 24, 45, 67–69). Interestingly, $CD21^{low}$ B cells are increased in the peripheral blood of CVID patients (70). Given the high prevalence of $CD21^{low}$ B cells in autoimmune disorders,

$CD21^{low}$ B cells may represent a link between autoimmunity and CVID (71–73) and potentially an optional target for the therapeutic intervention of CVID patients with autoimmune disorders.

4.3 Lymphoproliferation and malignancies

CVID patients also show an increased risk of lymphoproliferation and malignancies (Table 1). Benign lymphoproliferation (linked to hepatomegaly, splenomegaly or lymphadenopathy) is observed in more than 20% of CVID patients (21) and patients may require splenectomy or lymphadenectomy for final diagnosis (18, 26). Cervical, mediastinal or abdominal lymphadenopathies are frequent in CVID patients; histological findings include atypical or reactive lymphoid hyperplasia and granulomatous lesions (21). Lymphoma is observed in 3–10% of CVID patients, and is mainly presented as B-cell non-Hodgkin lymphoma (26, 58, 74, 75). Mucosa-associated lymphoid tissue lymphomas (MALTomas) have also been reported (58, 76–78). Solid tumors are also frequently observed in CVID patients. Gastric cancer is the most notable and at 10–47 higher risk than general population (58, 75, 79–82). In addition, breast, skin and other cancers were also reported (26). Malignancies are the major cause of death in CVID patients (80) and thus surveillance is a mandatory lifelong task.

4.4 Granulomatous lesions

8–22% of the patients with CVID develop non-caseating granulomatous lesions (27, 83) (Table 1), which are believed to be a result of abnormally activated and aggregated macrophages (45). Mostly these lesions affect the lungs, lymph nodes, and liver. However, involvements of bone marrow, kidney, brain, spleen, skin, gastrointestinal tract, and eyes have also been reported (83, 84). When granuloma occurs in the lungs concomitant with lymphoid infiltrations, it is named granulomatous and lymphocytic interstitial lung disease, which sometimes is misdiagnosed as sarcoidosis (83, 85). The level of serum Ig, which is elevated or normal in sarcoidosis patients, is then included for differential diagnosis (85). Granulomatous lesions are associated with autoimmunity, and may have a poorer prognosis (10, 26, 83).

4.5 Gastrointestinal involvement

CVID patients may be presented with chronic, intermittent or persistent diarrhea, steatorrhea, bloating, weight loss, and loss of minerals and fat-soluble vitamins. Besides gastrointestinal infections, autoimmune enteropathy (AIE) and granulomas have also been detected (10, 21, 26, 86), and are often misdiagnosed as malabsorption, celiac disease, or IBD (18, 86, 87). Histologic evaluation includes villous atrophy, crypt distortion with increased lymphocyte infiltration, crypt apoptosis with loss of goblet cells, lymphoid aggregates or hyperplasia, granulomas, and paucity of plasma cells, which is only present in about two-thirds of CVID patients (21, 87). Steroid or immunomodulators may be used in treating patients with AIE, however the efficacy is still uncertain (21, 26). Due to the lack of specificity, CVID patients with AIE may have a long delay in diagnosis (26).

4.6 Liver involvement

At least 10% of CVID patients present with liver involvement. Infections, autoimmune reactions, lymphoproliferation and malignancies, granulomas, infiltration of inflammatory cells, and intrahepatic biliary obstruction have been reported as contributors of the liver damage in CVID (10, 21, 25). Moreover, liver damage is strongly associated with lymphocytic enteropathy in CVID patients (14), suggesting a pathogenic role of the gut-liver axis (16).

The clinical evidence for liver involvement in CVID ranges from elevated alkaline phosphatase (ALP) (14, 86) to nodular regenerative hyperplasia (NRH), liver cirrhosis, and portal hypertension (14, 21, 45, 86, 88). In addition, CVID patients may develop liver cancer (45, 89). *Cunningham* reported that significant liver dysfunction was evident in 11.9% of the CVID patients, including hepatitis C patients infected by Ig infusions (18); while in a separate cohort, 44% of the CVID patients had abnormal liver biochemistries (14). NRH is a common lesion observed in the liver of CVID patients and can lead to chronic cholestasis, non-cirrhotic portal hypertension or liver cirrhosis (86, 90–92). Patients with liver involvement may remain asymptomatic or complain of fatigue, nausea, vomiting, jaundice, pruritus, ascites, edema, hepatomegaly, splenomegaly and esophageal varices (14, 15). Clinically, some CVID patients have been diagnosed with chronic hepatitis (62, 93, 94), autoimmune hepatitis (24, 45, 86, 95), PBC (18, 24), primary sclerosing cholangitis (PSC) (96), hepatopulmonary syndrome secondary to cryptogenic liver disease (97), portal hypertension (98), liver cirrhosis (14, 17) and even liver failure (14). Importantly, CVID patients with hypogammaglobulinemia often have low or undetectable levels of specific autoantibodies (45). Therefore, the diagnosis of specific liver diseases in CVID can be difficult and often requires a liver biopsy. In particular the diagnosis of PBC which presents with elevated alkaline phosphatase and relies on the anti-mitochondrial antibodies (AMA) for diagnosis, should be considered despite negative AMA testing. In addition, the testing for hepatitis C should include a HCV viral load, as the anti-HCV antibody may be falsely negative. In light of the association of autoimmunity and CVID, data on genome wide association studies on hepatic autoimmunity may shed light on potential genetic markers (99). The clinical manifestations of liver involvement are summarized in Table 2.

5. DIAGNOSIS

The European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency (ESID/PAGID) criteria have been largely used for the diagnosis of CVID. The diagnostic items include: (a) chronic and recurrent infections; (b) remarkably decreased levels of IgG and either IgM or IgA isotypes (at least 2 standard deviations below the mean for age); (c) onset of immunodeficiency at an age of 2 or more than 2 years old; (d) absence of isohemagglutinins and/or poor response to vaccines; (e) other causes of primary immunodeficiency and hypogammaglobulinemia secondary to drugs (e.g., glucorticoid), infections, malignancies, and lymphangiectasias must be excluded (100). Important attention should be paid to exclude other causes of hypoimmunoglobulinemia, including CID (101–104) (Table 3).

To improve the diagnosis, some additional criteria have been proposed (21, 105–108). Among these, the International Consensus Document (ICON) criteria are listed in Table 4. The ICON criteria set the onset age at more than 4 years old to further exclude some atypical primary immunodeficiency disorders, for example, X-linked agammaglobulinemia (XLA), and add histologic and genetic evidences (21).

When liver abnormalities are present, the underlying causes should be investigated. Possible causes for liver abnormalities include infections, autoimmune reactions, lymphoproliferation, malignancies, deposition of iron, copper and fat, intake of alcohol, drugs and toxins (Table 2). Infectious agents including, bacteria, parasites, hepatitis virus (A–G), Epstein-Barr virus (EBV), cytomegalovirus and human acquired immunodeficiency virus (HIV), should be tested. Biopsy should be conducted if necessary. Among the various causes of liver abnormality, infections, autoimmunity, lymphoproliferation and malignancies may be considered liver involvement of CVID due to the increased susceptibility to these complications described above.

Laboratory tests

Significant reduction of IgG level is the diagnostic hallmark of CVID, defined as at least 2 standard deviations below the mean for the age - or below 5g/L for adults - in at least 2 measurements more than 3 weeks apart (10, 21). Low levels of either IgA or IgM (at least 2 standard deviations below the mean for the age or below 0.8g/L, 0.4g/L, respectively) are required (10, 21). Importantly, due to the variability of serum Ig, age and region should be taken into the adjustment of reference range. Only up to 21% of the CVID patients may have minimal-to-undetectable levels of all Ig isotypes at presentation (21), hence suspected patients should be tested repeatedly.

Moreover, CVID patients commonly have normal count of circulating B cells (21, 49), an important difference between CVID and XLA. Less frequently, slight elevation or reduction in circulating B cells is also observed. Significant reduction (<1%) is only observed in 10% of patients with CVID, indicative of remarkably poor prognosis, and differential diagnosis with XLA is required (10, 21, 25). Similarly, most patients have normal counts of T cells and NK cells, but decreased count of CD4+ T cells (including naive CD4+CD45RA+) and increased count of CD8+ T cells have been described (10, 109).

Liver tests/examinations

ALP is the most commonly elevated liver enzyme; to our knowledge, only one study has been published, and included only a small number of patients (14). However, elevation of ALP in CVID patients may also be caused by osteomalacia as a result of enteropathy or granulomatous disease (14). Elevation of bilirubin and transaminases has been observed (110).

Ultrasonography, computed tomography scan, or magnetic resonance imaging can be used to examine for structural changes in the liver, and signs of NRH, cirrhosis and portal hypertension (110). It is important to exclude hepatic malignancies. Finally, endoscopy should be performed to exclude esophageal varices in portal hypertension patients when necessary.

The common indications for liver biopsy in CVID patients include elevation of transaminases, hepatomegaly, and splenomegaly (16, 110). In some cases, the biopsy usually shows disturbance of liver structure, nonspecific portal and lobular inflammation, interface hepatitis, lymphocyte infiltration without plasma cells, granulomas, fibrosis, macrovesicular steatosis and neogenesis of biliary ducts (15, 16, 95, 110). NRH is the most frequent lesion (14, 92, 111), occurring in 5–81% of CVID patients (14, 91, 92). Two studies describing histological liver characteristics in CVID have been published. First, *Ward et.al*. reported, among 16 CVID patients with liver biopsy, 13 of them presented with NRH (2 of them also had liver cirrhosis), and 2 with granulomatous hepatitis. Further, among the 13 patients with NRH, 12 had elevated levels of both ALP and gamma glutamyl transpeptidase (γ-GT), and the level of ALP in 6 patients slowly increased over years. NRH was associated with lymphoproliferation, enteropathy, abnormal liver function tests, cytopenia and granulomas (14). Second, *Malamut et.al*. reported that 84% of CVID patients presenting with non-fibrosing architectural abnormalities, which is consistent with NRH (90). Regardless of its frequent appearance in the liver, NRH is a not a specific lesion of CVID, and is also present in other diseases or in the general population (14). Recently, however, it has been reported that indolent proliferation of cytotoxic T cell in the liver sinusoid associated with NRH is more specific for CVID (110). The current tests and examinations of liver involvement in CVID are summarized in Table 2.

Responses to Vaccines

Responses to vaccines should be evaluated in all CVID patients before starting Ig replacement therapy. Qualitative and quantitative assessments of both T-dependent and T-independent responses are required (21). In addition, isohemagglutinins may also be detected, especially after Ig infusion (21).

Genetic analysis

Patients with CVID do not have any specific genetic background or markers, so genetic analysis is not recommended for CVID patients (21). It can be used in the exclusion of other primary immunodeficiency disorders, such as XLA (*Btk* mutation).

6. TREATMENT FOR CVID AND LIVER INVOLVEMENT

Replacement therapy with Ig and anti-infection treatment remain the main clinical inventions for CVID. In addition, the treatments for other complications may also be needed.

Replacement therapy

Hypoimmunoglobulinemia is the main underlying cause of infections in CVID; the primary treatment is replacement with intravenous Ig (IVIG) or subcutaneous Ig (SCIG) (112). The recommended dosage is 400–600mg/kg intravenously, every 3–4 weeks or 100–200 mg/kg subcutaneously, every week (27). In some patients, the dose has to be adjusted to reduce the severity of infections (113, 114). During treatment, the level of IgG should be higher than 7 g/L (26). Although anaphylactic reactions may happen in some CVID patients with absent IgA due to the formation of anti-IgA antibody complex with IgA, allergy testing of it is not a routine procedure (21). Over the years, the survival of CVID has improved greatly, largely

attributed to the use of Ig (10, 115). In the past, when blood derived Igs were used, transmitted infections were of concern (116). Finally, it should be noted that replacement therapy with Ig is effective for infections and probably for autoimmunity, but less for other CVID complications (10, 26, 45, 58).

Anti-infection treatment

Antibiotics should be administered based on the drug-sensitive tests in case of bacterial infections.

Treatments for other complications

Corticosteroids or immunomodulators should be administered in case of autoimmune diseases. Note that lower doses and shorter periods of treatment are often required (18, 67). Although it induces a potential increased risk of immunodeficiency, splenoectomy may be considered when necessary (29, 41, 45, 117).

Corticosteroids, or in combination with immunomodulators should be used in case of granulomas (118–120). In addition, infliximab may be used in the treatment of some selected CVID patients with granulomas (83, 119–121).

No specific therapy for liver involvement of CVID exists thus far, ursodeoxycholic acid can also be used when biliary damage is identified histologically (15, 24). Commonly accepted treatment for complicated cirrhosis, including liver transplantation, might be applied. Similarly, esophageal varices should be treated if required. Successful liver transplantation in end-stage liver disease has been reported (122–125). Meanwhile, periodic follow-up of liver function is recommended in case of liver involvement.

Allogeneic peripheral stem cell transplantation

Some successful cases of allogeneic peripheral stem cell transplantation have been reported (126), however the current experience is limited.

7. PROGNOSIS OF CVID AND LIVER INVOLVEMENT

The 20-year-survival of CVID patients after diagnosis is 64% for male patients and 67% for female patients (18). The median age at death was 42 and 44 years old for males and females, respectively with lung failure, lymphomas, cancers and severe infections as the primary cause of death (18, 21, 25).

The prognosis of CVID depends on various factors, including the age of onset and diagnosis, diagnostic delay, malignancies (26) and the initial level of IgG and B cell count in the peripheral blood (18). Non-infectious complications, such as granulomas, gastrointestinal and liver involvement and lung diseases may indicate poor prognosis (10, 26). A deeper comprehension of the etiology and pathophysiology will aid in the early diagnosis and appropriate treatments to improve prognosis (105).

Abbreviations

AIE	autoimmune enteropathy
AIHA	autoimmune hemolytic anemia
ALP	alkaline phosphatase
CID	combined immunodeficiency
CVID	common variable immunodeficiency
GLILD	granulomatous and lymphocytic interstitial lung disease
IBD	inflammatory bowel disease
ICON	International Consensus Document
Ig	immunoglobulin
IL	interleukin
ITP	idiopathic thrombocytopenia
IVIG	intravenous immunoglobulin
NRH	nodular regenerative hyperplasia
PBC	primary biliary cholangitis
PSC	primary sclerosing cholangitis
r-GT	gamma glutamyl transpeptidase
SCIG	subcutaneous immunoglobulin
SIgAD	selective Immunoglobulin A deficiency
TLR	toll-like receptor
Treg cell	regulatory T cell
XLA	X-linked agammaglobulinemia

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Table 1

Multi-system manifestations and frequencies of CVID

Manifestations	**Mount Sinai Hospital (n = 248, 1999) [18]**	**DEFI network (n=252, 2008)[29]**	**Mount Sinai Hospital (n=473, 2012) [25]**	**ESID Database (n=902, 2014) [26]**
Infections	90%	>90%	94%	Not specified
Pneumonia	76.6%	58%	40%	32%
Bronchiectasis	27%	37%	11.2%	23%
Gastrointestinal involvement	21.4%	47%	>15.4%	9%
Autoimmunity	22%	>18%	28.6%	29%
Splenomegaly	Not specified	38%	Not specified	26%
Cancers	8%	8.7%	7%	5%
Lymphoma	8.9%	6.3%	8.2%	3%
Granuloma	8%	14%	9.7%	9%
Splenectomy	6%	6.0%	8.2%	2%

Table 2

Clinical manifestations, laboratory tests/examinations for liver involvement of CVID and possible causes of liver abnormalities

Clinical manifestations	Abnormalities in laboratory tests	Abnormalities in liver examinations	Possible causes of liver abnormalities
A: Asymptomatic	A: Liver function tests	A: Imaging examinations	● Infections (bacterium, parasite, hepatitis virus (A–G), Epstein-Barr virus, cytomegalovirus, human acquired immunodeficiency virus, etc)
B: Symptomatic	● Increased level of ALP, r-GT	● Structural alterations on ultrasonography, CT scan, or MRI	● Autoimmunity
● Fatigue	● Increased level of ALT, AST and bilirubin	● Esophageal varices on endoscopy B: Histology	● Lymphoproliferation
● Nausea	● Decreased level of albumin B: Coagulation markers	● Non-specific inflammation	● Malignancies
● Vomiting	● Increased PT, APTT	● NRH	● Dysfunction of metabolism (deposition of copper, iron, fat, etc.)
● Jaundice	● Decreased level of fibrinogen	● Granuloma	● Drugs
● Pruritis		● Portal hypertension	● Toxins
● Ascites		● Liver cirrhosis	● Alcohol
● Edema			● Etc.
● Hepatomegaly			
● Splenomegaly			
● Bleeding as a result of esophageal varices			

Note: ALP: alkaline phosphatase; **r-GT**: gamma glutamyl transpeptidase; **ALT**: alanine transaminase; **AST**: aspartate transaminase; **PT**: prothrombin time; **APTT**: activated partial thromboplastin time; **CT**: computed tomography; **MRI**: magnetic resonance imaging; **NRH**: nodular regenerative hyperplasia.

Table 3

Features of primary hypogammaglobulinmia in the differential diagnosis of CVID

Disorder	Presentation	Mechanism
Selective IgA deficiency	Decreased level of IgA; normal level of other Ig isotypes and count of B cells; usually onset age > 4 years old	Unknown, possible defects in terminal differentiation of IgA+ B cells
X-linked agammaglobulinemia	Decreased levels of all Ig isotypes and count of B cells; male children, usually onset age < 2 years old	Mature defects in development of pre-B cell to B cells due to *Btk* genetic mutation
Autosomal recessive agammaglobulinemia	Similar as XLA; female children	Dysfunction of pre-B cell receptor complex; no *Btk* mutation
Transient hypogammaglobulinemia of infancy	Decreased level of IgG and/or IgA, IgM; nearly normal antibody generation; normal count of B cells	Unknown, postponed production of Ig isotypes
X-linked hyper-IgM syndrome	Increased level of IgM, decreased level of IgG or IgA isotypes; male children	Defects in Ig isotype switch of B cells due to *CD40LG* genetic mutation in T cells
Non-X-linked hyper-IgM syndrome	Similar as XHIGM but without gender predominance	*AID* or *UNG* genetic mutation
X-linked severe combined immunodeficiency, XSCID	Decreased level of all Ig isotypes; decreased count of T and NK cells; nonfunctional B cells; male children	Genetic defects in *IL-2Rγ*
Deficiency of adenosine deaminase	Decreased level of all Ig isotypes and count of T, B and NK cells	Genetic defects in *ADA*
Good syndrome	Decreased levels of all Ig isotypes and count of B cells; thymoma	Unknown
X-linked lymphoproliferative syndrome	Decreased level of IgG subclasses, increased levels of IgA, IgM prior to Epstein-Barr virus (EBV) infection; EBV susceptibility; mononucleosis; lymphoma; aplastic anemia; male children	*SH2D1A* or *XIAP* genetic mutation

Table 4

International Consensus Document (ICON) criteria for CVID (2015)[21]

A.	**Must meet all major criteria**
	● Hypogammaglobulinemia: serum IgG below 5 g/L for adults
	● No other causes of primary immunodeficiency
	● Age at diagnosis > 4 years
B.	**Clinical manifestations indicative of immunodeficiency (one or more criteria)**
	● Recurrent, severe or unusual infections
	● Poor response to antibiotics
	● Breakthrough bacterial infections in spite of prophylactic antibiotics
	● Infections in spite of immunization with the appropriate vaccine
	● Bronchiectasis and/or chronic sinus disease
	● Inflammatory disorders or autoimmunity
C.	**Supportive laboratory evidence (three or more criteria)**
	● Concomitant deficiency or reduction of serum IgA (<0.8 g/L) and/or IgM (<0.4 g/L)
	● Presence of B cells but reduced memory B cell subsets and/or increased $CD21^{low}$ subsets by flow cytometry
	● IgG3 deficiency (<0.2 g/L)
	● Impaired vaccine responses compared to age-matched controls
	● Transient responses to vaccines compared to age-matched controls
	● Absent isohaemagglutinins (if not blood group AB)
	● Serological support for autoimmunity in section B
	● Sequence variations of genes predisposing to CVID
D.	**Presence of any one of relatively specific histological markers of CVID (not required for diagnosis but presence increases diagnostic certainty)**
	● Lymphoid interstitial pneumonitis
	● Granuloma
	● Nodular regenerative hyperplasia (NRH) of the liver
	● Nodular lymphoid hyperplasia of the gut
	● Absence of plasma cells on gut biopsy