HOSPITAL CHRONICLES 2016, 11(1): 1–5

REVIEW

Clinical Heterogeneity of Common Variable Immunodeficiency

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ABSTRACT

Common variable immunodeficiency (CVID) is the most common, clinically relevant, primary immunodeficiency (PID). In the western world the incidence of this disease is about 1:50000. CVID is characterized by hypogammaglobulinemia which involves in all cases immunoglobulin G (IgG), in about 70-80% of cases immunoglobulin A (IgA) and in about 50% of cases immunoglobulin M (IgM). Additionally, patients with CVID develop weak or no immunization responses against polysaccharide (mainly) and protein antigens. Clinical manifestations of CVID may present either early in childhood or late in adulthood, usually between the third and fourth decade of life. The range of CVID clinical manifestations is broad. Underlying CVID should be considered mainly in cases of patients who present with recurrent or persistent bacterial infections of the upper or lower respiratory tract. The possibility of underlying CVID has also to be examined during laboratory investigation of various clinical syndromes, such as lymphadenopathy, hepatosplenomegaly, chronic diarrhea, or malabsorption, and also of autoimmune cytopenias such as idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia. It is noteworthy, that autoimmune diseases and malignancies in the form of lymphoma and neoplasm of the gastrointestinal tract occur with increased incidence in CVID patients in comparison to the general population. Treatment strategy of CVID patients should not be limited to immunoglobulin substitution therapy (administered either intravenously or subcutaneously), but it also has to target effective management of infections and early diagnosis of occurring malignancies (lymphomas and gastrointestinal tumors) through systematic patient monitoring. With regard to life expectancy of CVID patients, two recently published large retrospective studies showed that CVID patients suffering only from infections had prolonged overall survival compared to those who presented with other CVID clinical manifestations. Exclusion of all potential causes of secondary hypogammaglobulinemia is mandatory for establishing the diagnosis of CVID. Also, in some CVID cases, differential diagnosis from other PID may be required, such as X-linked agammaglobulinemia (XLA), antibody deficiency with increased IgM (Hyper-IgM syndrome), and X-linked lymphoproliferative syndrome (XLP).

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KEY WORDS: *Primary immunodeficiencies; hypogammaglobulinemia; common variable immunodeficiency*

Abbreviations
AHA = autoimmune hemolytic anemia
CVID = common variable immunodeficiency
FC = flow cytometry
HSCT = hematopoietic stem cell transplantation
Ig =immunoglobulin
ITP = idiopathic thrombocytopenic purpura
MM = multiple myeloma
PID = Primary Immunodeficiency Diseases
XLA = X-linked agammaglobulinemia
XLP = X-linked lymphoproliferative syndrome

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Manuscript received February 24, 2015; Revised manuscript received October 4, 2015; Accepted November 20, 2015

INTRODUCTION

Primary immunodeficiencies (PID) form a heterogeneous group of diseases characterized by varying deficits, which relate commonly with specific immunity and are

Conflict of Interest: none declared

located either in B-lymphocytes, or in T-lymphocytes, or both. Rarely may innate immunity deficits be responsible, in which case they are associated with phagocytes, NK cells, cytokine receptors and complement factors. According to the most recent classification of the International Union of Immunological Societies (IUIS) of 2004, which has been updated in 2009, 2011 and 2014, PID are categorized into 8 groups, which are presented in Table 1.[1-4] The vast majority of PID cases are diagnosed during childhood. Only a small fraction of PID cases are diagnosed in adulthood. These patients are almost exclusively suffering from primary antibody deficiencies, such as common variable immunodeficiency, selective immunoglobulin A deficiency, selective deficiency of immunoglobulin G subclasses, or specific antibody deficiency.[5,6] In adults, common variable immunodeficiency (CVID) attracts most of the interest, mainly because of its clinical heterogeneity (a disease with many faces). Herein, a brief presentation of CVID will be described, focusing on the range and the specific features of its clinical manifestations.

COMMON VARIABLE IMMUNODEFICIENCY - GENERAL DATA

Common variable immunodeficiency is characterized by hypogammaglobulinemia which in all cases concerns immunoglobulin G (IgG), in about 70-80% of cases it concerns immunoglobulin A (IgA) and in about 50% of cases it concerns immunoglobulin M (IgM). Additionally, patients with CVID develop weak or no immunization response against polysaccharide (mainly) and protein antigens. CVID is the second most common primary antibody deficiency, after the selective deficiency of IgA, but the most common symptomatic antibody deficiency with an estimated incidence in about 1/50000.[6-10] Notably, the epidemiological data of almost all primary immunodeficiencies (including CVID) should be evaluated with caution, because they are considerably under diagnosed. In most CVID cases (approximately 85-90%) no inheritance is documented. In these patients causative mechanisms are practically unknown. In a minority of CVID patients with documented disease, inheritance with mutations in specific genes (CD19, ICOS, TACI, BAFFR, MSH5) associated with B-Lymphocyte ontogenesis and differentiation have been detected.[6,11]

The clinical manifestations of CVID may present either early in childhood or late in adulthood (usually between third and fourth decade of life).[6-10] It is estimated that about 50% of CVID patients are diagnosed in adulthood. The range of CVID clinical manifestations is very broad (Table 2). Underlying CVID should be considered mainly in cases of patients who present with recurrent or persistent bacterial infections of the upper or lower respiratory tract (otitis, sinusitis, bronchitis, pneumonia), which are not adequately treated by common antibiotics.[6-10] Also, young adults with chronic obstructive pulmonary disease or bronchiectasis should also be examined for underlying CVID. Additionally, the possibility of underlying CVID has to be examined during laboratory investigation of various clinical manifestations (lymphadenopathy, hepatosplenomegaly, chronic diarrhea, malabsorption) and autoimmune cytopenias, such as idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AHA).[6,8,10] It is noteworthy that autoimmune diseases and malignancies (lymphomas and neoplasms of the gastrointestinal tract) occur with increased incidence in CVID patients in comparison to the general population.[6,8,10] Treatment strategy of CVID patients should not be limited to immunoglobulin substitution therapy (administered either intravenously or subcutaneously), but it also has to target effective management of infections and early diagnosis of occurring malignancies (lymphomas and gastrointestinal tumors) through systematic patient monitoring.[6]

As previously indicated, CVID clinical phenotype is both heterogeneous and complex.[6-10] In the last few years, data from large patient registries have revealed that clinical phenotyping may aid in separating CVID patients into biologically relevant categories.[10,12,13] Two main CVID clinical phenotypes were identified, CVID 1 characterized by infections and CVID 2 in which inflammatory, autoimmune and/or hematologic complications also develop.[10,13] With regard to life expectancy of CVID patients, the same studies showed that CVID patients

TABLE 1. Classificationof Primary Immunodeficiencies (PID)

Combined T and B-cell immunodeficiencies
Congenital syndromes associated with specific immunity deficiencies
Predominantly antibody deficiencies
Diseases of immune dysregulation
Congenital defects of phagocyte function, number or both
Defects associated with innate immunity
Autoinflammatory disorders
Complement deficiencies

TABLE 2. Clinical Manifestations of Common Variable Immunodeficiency

Respiratory disease
Gastrointestinal disease
Hematological complications
Autoimmune complications
Other complications
Malignancies

suffering only from infections had prolonged overall survival compared to those who presented with some other clinical manifestations of CVID.[10,12,13] Exclusion of all potential causes of secondary hypogammaglobulinemia is mandatory for establishing CVID diagnosis.[14] Also, in some cases differential diagnosis of CVID from other PID may be required, such as X-linked agammaglobulinemia (XLA), antibody deficiency with increased IgM (Hyper-IgM syndrome), and X-linked lymphoproliferative syndrome (XLP).[15]

SECONDARY HYPOGAMMAGLOBULINEMIA

The main groups of diseases including cases of patients who are likely to develop secondary hypogammaglobulinemia are malignant diseases, and protein-losing gastrointestinal or renal disorders. Also, therapeutic interventions often cause hypogammaglobulinemia.[6,14]

MALIGNANT DISEASES

From this group of diseases, hematologic malignancies mainly induce secondary hypogammaglobulinemia. Low-grade lymphomas, especially chronic lymphocytic leukemia and follicular lymphoma, are well known causes of occasionally severe hypogammaglobulinemia.[6,14] The same applies to some multiple myeloma (MM) cases (light chain MM and non-secretory MM) and to several primary systemic (AL) amyloidosis cases.[6,14] Finally, apart from the previously mentioned hematological malignancies, another known cause of occasionally severe hypogammaglobulinemia is thymoma. In these cases, hypogammaglobulinemia is not restored after surgical removal of the tumor.[6,14]

PROTEIN-LOSING DISORDERS

It is well known that protein loss can occur via two main routes, the urinary and the gastrointestinal tract. Hence, hypogammaglobulinemia due to protein loss occurs mainly in cases of nephrotic syndrome, inflammatory bowel disease, intestinal lymphangiectasia (Waldman disease) and gastropathy with protein loss (Menetrier syndrome).[6,14] Malnutrition, a condition which is related to reduced protein intake and its increased catabolism, has also been associated with hypogammaglobulinemia.[14] Finally, extensive burns and injuries have rarely been associated with hypogammaglobulinemia.[14]

THERAPEUTIC INTERVENTIONS

Therapeutic interventions (transplants, drugs) have become the major causes of secondary immunodeficiency.[6,14] Hematopoietic stem cell transplantation (HSCT) has been associated with disorders of all components of the immune system.[16] Autologous HSCT (Auto-HSCT) is first or second line treatment option for patients suffering from several hematological malignancies (multiple myeloma, Hodgkin's disease, non-Hodgkin lymphoma). Allogeneic HSCT (Allo-HSCT) is a curative treatment option for several hematological malignancies, especially for a large number of patients with acute leukemia who are in first or second complete remission.[16] Due to myeloablative conditioning regimen, patients who undergo HSCT develop severe leukopenia which is restored usually quickly, but restoration in normal range of CD4 T-lymphocytes and B-lymphocytes is delayed. The result of sustained B-lymphopenia is the occurrence of hypogammaglobulinemia, which is further prolonged in patients undergoing Allo-HSCT (compared with patients undergoing Auto-HSCT), both because of stronger myeloablation and immunosuppression resulting from the conditioning regimen, and because of immunosuppressive treatment against either acute or chronic graft versus host disease, or both.[16] Patients undergoing organ transplant (especially renal transplantation), receive immunosuppressive treatment in order to prevent the occurrence of graft rejection. This immunosuppressive therapy has been associated with lymphopenia and hypogammaglobulinemia, mainly because of the effects of azathioprine and corticosteroids.[14] Among medications, corticosteroids were probably the first ones associated with acquired immunodeficiency. Lymphopenia (absolute or selective) and hypogammaglobulinemia are well known consequences of prolonged administration of corticosteroids.[6,14] The administration of monoclonal antibodies against CD20 has been associated with both B-lymphopenia and prolonged hypogammaglobulinemia.[14] Several drugs have been associated with secondary hypogammaglobulinemia, secondary selective IgA deficiency and secondary IgG subclasses deficiency.[6,14] Anti-infammatory (sulfasalazine, gold salts, chloroquine, D-penicillamine, non steroidal anti-inflammatory drugs) and anticonvulsant (phenytoin, carbamazepine, sodium valproate) drugs are included within this group.[14] From the above, it is clear that primary consideration for adult patients presenting with hypogammaglobulinemia should be the exclusion of all possible causes of secondary immunodeficiency.

LABORATORY INVESTIGATION FOR COMMON VARIABLE IMMUNODEFICIENCY DIAGNOSIS DOCUMENTATION

Laboratory testing for CVID diagnosis documentation includes the following:

A) Serum protein electrophoresis. Quantification of the major immunoglobulin classes (IgG, IgA, IgM); IgG subclasses quantification; anti-A and anti-B iso-hemagglutinin titration; evaluation of serum IgG antibody levels against bacterial polysaccharide and protein antigens, before and after immunization.[6-8,10]

B) Total lymphocyte absolute number measurement; B, T and

NK cells measurement by flow cytometry (FC); T and B cells specific subpopulation (CD4, CD8, CD4/CD45RO, CD4/CD45RA, CD19/CD27, CD19/CD21) measurement also by FC. These subpopulations may exhibit alterations in CVID patients (in comparison with the general population).[6,8] Particularly, in many CVID patents' peripheral blood, CD4/CD45RA T cells and CD19/CD27 B cells are low compared with the general population. Also, in some CVID patents' peripheral blood, CD19/CD21 B cells may be detectable. Finally, testing should be done for CD40L (CD154) expression by FC too, if it is appropriate in certain cases.[6,8]

C) Testing for the presence or the absence of specific proteins (BtK, SAP) by the Western blot technique, if it is appropriate.[6,7,11]

D) Testing for the presence or the absence of mutations in specific genes (Btk, SH2D1A, CD40L) by molecular techniques.[6,11] This specific laboratory testing and the aforementioned testing for the presence or the absence of specific proteins (BtK, SAP, CD40L) by FC and Western blot technique are helpful in order to distinguish CVID from other PID (XLA, Hyper-IgM syndrome, XLP), if necessary.

CLINICAL PRESENTATION OF COMMON VARIABLE IMMUNODEFICIENCY

The range of CVID clinical manifestations is broad, including acute and chronic infections, inflammatory and autoimmune diseases, and an increased incidence of cancer and lymphoma.[6-10]

RESPIRATORY DISEASE

Upper and lower respiratory tract infections (mainly due to polysaccharide encapsulated bacteria) are the most common clinical manifestations encountered in CVID patients (about 70% of them), and in a significant proportion of them (about 30%) the only ones present.[6-10] Finally, with regard to the respiratory system, the presence of lung infiltrates (usually imaged by chest radiographs) is not uncommon. These infiltrates usually correspond to nonspecific granulomas (differential diagnosis of sarcoidosis is required), while rarely represent nonmalignant lymphoid infiltrates.[6,8,10]

GASTROINTESTINAL DISEASE

The remarkable probability of CVID diagnosis in the context of laboratory investigation for syndromes of chronic diarrhea (10-40% of cases) and malabsorption needs to be emphasized.[6,8,10] Chronic diarrhea usually has an infectious etiology, due to Salmonella, Shigella, Cambylobacter, Cryptosporidium, or Giardia Lamblia.[6] In some cases, differential diagnosis between CVID and diseases such as Crohn's disease, ulcerative colitis and celiac disease accompanied by hypogammaglobulinemia, may be extremely difficult. Nodular lymphoid hyperplasia of the bowel (polyclonal hyperplasia of Peyer's patches) is relatively common in CVID patients.[6,8,10] Atrophic gastritis, with or without concomitant pernicious anemia, is less common in CVID patients. Liver involvement is not very common in CVID patients, and usually is associated with presence of nonspecific granulomas, presence of nodules in the context of modular regenerative hepatitis and presence of histological lesions compatible with primary biliary cirrhosis.[6,8,10]

HEMATOLOGICAL COMPLICATIONS

Hematological complications of CVID are quite common. Splenomegaly is reported in about 30% of CVID cases and lymphadenopathy in about 10-20%, due to involvement with either nonmalignant lymphoid infiltrates or to development of granulomas.[6,8,10] Regarding autoimmune cytopenias, occurrence of ITP is reported in about 10-30% of CVID cases.[6,8,10] Occurrence of AHA is less common. Finally, both Evans syndrome and autoimmune neutropenia are rarely diagnosed in CVID patients.[6,8,10]

AUTOIMMUNE COMPLICATIONS

Apart from the aforementioned autoimmune cytopenias, the following autoimmune diseases have rarely been diagnosed during CVID: autoimmune thyroiditis, nonspecific arthritis clinically resembling rheumatoid arthritis, systemic lupus erythematosus and polymyositis-dermatomyositis.[6,8,10]

OTHER COMPLICATIONS

Very rarely has CVID been associated with the following disorders: allergy syndromes, central nervous system infections and degenerative diseases, urinary tract infections, opportunistic infections, cutaneous manifestations (infections, granulomas) and septic arthritis or osteomyelitis.[6,8,10]

MALIGNANCIES

In the past 30 years, many studies established the association between CVID and both lymphoma and gastrointestinal tract tumors. The cumulative risk of Hodgkin's lymphoma and non-Hodgkin lymphoma affecting patients with CVID has been estimated to range between 2-9%. It has been estimated that among CVID patients, the incidence of lymphoma is about 30 times greater than in the general population. It has also been noted that among CVID patients, the incidence of gastric cancer is about 50 times greater than in the general population.[6,8,10,12,13]

CONCLUSION

As deduced from the data presented in this review, an integrated approach to CVID diagnosis requires a high index

of suspicion for an underlying immunodeficiency, exclusion of all potential causes of secondary hypogammaglobulinemia, profound knowledge of CVID clinical heterogeneity, specialized laboratory testing, and clearly distinguishing CVID from at least three other PID (XLA, Hyper-IgM syndrome, XLP).

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