

Predominantly Antibody Deficiencies

Gholamreza Azizi¹, Reza Yazdani^{2*}

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Abstract

Primary antibody deficiencies (PADs) are frequent primary immunodeficiencies in humans, characterized by hypogammaglobulinemia, defects in production of specific antibodies, and recurrent infections. Information about PADs is quickly developing, leading to improved diagnoses and

efficient disease management. This study is a review of the pathogenesis, diagnosis, clinical manifestations, and management of PAD disorders such as agammaglobulinemia, common variable immunodeficiency, monogenic defects associated with hypogammaglobulinemia, class switch recombination deficiencies, selective IgA deficiency, subclass immunoglobulin isotypes deficiencies, specific antibody deficiency, and transient hypogammaglobulinemia.

* **Corresponding author:** Reza Yazdani
r_yazdani@sina.tums.ac.ir

1. Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

2. Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran

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Introduction

Predominantly antibody deficiencies (PADs) are frequent primary immunodeficiency diseases (PIDs) that have different etiologies (1, 2). PAD patients have various phenotypes ranging from severe forms (e.g., decreased antibody levels and significantly low B cells) to mild forms (e.g., patients with defect a selective immunoglobulin deficiency with normal serum antibody levels). PAD patients present with

various clinical manifestations, including recurrent respiratory infections, autoimmunity, and gastrointestinal problems (3). These patients also commonly have hypogammaglobulinemia and recurrent infections frequently affecting the respiratory and gastrointestinal tracts (4-6). These patients do not present with opportunist fungal or viral infections (except patients with X-linked

agammaglobulinemia (XLA)) in contrast with those patients who have T-cell deficiencies (7, 8).

Organ damage and mortality caused by bronchiectasis or bronchiolitis obliterans are associated with delays in diagnosis and/or inadequate management (9, 10). Thus, early diagnosis and appropriate management contribute to improving the patients' quality of life. In the present article, the pathogenesis, clinical manifestations, diagnosis, and management of patients with PADs are reviewed.

Pathogenesis

PADs often arise as a result of defects in early B cell development, class switch recombination (CSR), or terminal B cell differentiation (11, 12). B cell development initiates in the bone marrow, where several defined genes are responsible for the early development, and continues in secondary lymphoid organs.

Defects in early B cell development lead to blockages in B cell differentiation, profound reduced mature B cell counts, strong hypogammaglobulinemia, and the early onset of recurrent bacterial infections (13-15). CSR and somatic hypermutation (SHM) are involved in the production of high affinity IgG, IgA, and IgE immunoglobulins in secondary lymphoid organs. In recent years, mutations of genes involved in CSR and SHM such as CD40Ligand (CD40L), CD40, inhibitor of κ light polypeptide gene enhancer in B-cells, kinase gamma (IKBKG), activation-induced cytidine deaminase (AID), and Uracil N glycosylase (UNG) have been reported. Defects in the involved CSR genes lead to reductions in IgG, IgA, and IgE levels and recurrent bacterial infections but a normal

or increased IgM level (16). Finally, some genes, including the CD19-B cell receptor (BCR) complex (CD19, CD21 and CD 81), TACI, BAFF-R, TWEAK, MSH5, and CD20, are responsible for the terminal stages of B cell development (17). Defects in these genes result in manifestations of PADs. Defects in the genes involved in PAD disorders are provided in **Table 1**.

1. Agammaglobulinemia

1.1. X-linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) is characterized by a reduced number of peripheral B cells and severe decreases in all serum antibody levels caused by mutations in the *Bruton's tyrosine kinase (BTK)* gene. Mutations in *BTK* lead to the development and differentiation of B cells in bone marrow (18). Given that the blockage of B cell development is observed in bone marrow (19), there is a profound reduction in B cells less than 1% in the periphery blood of these patients.

1.1.1. Clinical Manifestations

Clinical manifestations in PAD patients are commonly observed between the ages of 6-12 months, when the transfer of maternal IgG is decreased. XLA patients suffer from significantly low levels of B cells; thus, the absence of lymph nodes or lymph node hypoplasia is also observed in most XLA patients. Typically, some clinical complications such as recurrent otitis media, sinusitis, bronchitis, pneumonia, bronchiectasis, and gastrointestinal problems (particularly chronic diarrhea) manifest in XLA patients (20). Upper and

lower respiratory tract infections are the most common complications in affected patients (6, 21), with pneumonia occurring most frequently in XLA patients (22). *Giardia lamblia* is commonly isolated from stool samples from XLA patients with chronic diarrhea. Although some patients may be asymptomatic, the diarrhea may continue for weeks

(23). Some studies have reported that arthritis has been also observed in almost 20% of XLA patients. Other complications such as meningitis, lymphoproliferative disorders, autoimmunity, and neutropenia with lower prevalence rates can also occur in XLA patients (3).

Table 1. Antibody deficiency disorders

Disease		Molecular defect(s)
<i>I. Severe reduction in all serum Ig isotypes with profoundly decreased or absent B cells</i>	BTK deficiency	BTK
	μ Heavy chain deficiency	μ Heavy chain
	λ5 deficiency	λ5
	Igα deficiency	Igα
	Igβ deficiency	Igβ
	BLNK deficiency	BLNK
	PI3 kinase deficiency	PIK3R1
<i>II. Severe reduction in at least two serum Ig isotypes with normal or low number of B cells</i>	Thymoma with immunodeficiency	Unknown
	CVID	Unknown
	ICOS deficiency	ICOS
	CD19 deficiency	CD19
	CD81 deficiency	CD81
	CD20 deficiency	CD20
	CD21 deficiency	CD21
	TACI deficiency	TACI
	LRBA deficiency	LRBA
	BAFFR deficiency	BAFF-R
	TWEAK	TWEAK
	NFκB2 deficiency	NFKB2
	WHIM syndrome	Gain-of-function mutations of CXCR4
<i>III. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells</i>	CD40L deficiency	CD40L (TNFSF5)
	CD40 deficiency	CD40 (TNFRSF5)
	AID deficiency	AICDA
	UNG deficiency	UNG
<i>IV. Isotype or light chain deficiencies with generally normal numbers of B cells</i>	Ig heavy chain mutations and deletions	Mutation or chromosomal deletion at 14q32
	κ Chain deficiency	Mutations in κ gene
	IgA with IgG subclass deficiency	Unknown
	Selective IgA deficiency	Unknown
	PRKC-δ deficiency	PRKCD
	Activated PI3K- δ	PIK3CD
<i>V. Specific antibody deficiency</i>	IgG subclass deficiency	Unknown
		Unknown
<i>VI. Transient hypogammaglobulinemia of infancy with normal numbers of B cells</i>		Unknown

BTK: Bruton tyrosine kinase, CVID: Common variable immunodeficiency, WHIM Warts, hypogammaglobulinemia, infections, myelokathexis syndrome, Ig: immunoglobulin

1.1.2. Diagnosis

XLA patients have low to undetectable antibody serum levels along with almost undetectable concentrations of peripheral B cells (<2%) (24, 25). A few XLA patients could demonstrate >2% peripheral B cells and/or near normal immunoglobulin levels; in these cases, the specific antibody response to specific antigens is evaluated for further identification. To confirm XLA, BTK measurement could be helpful in these patients. Molecular analysis of the *BTK* gene should always be done to define the mutation, if any, causing the disease.

1.1.3. Management

Similar to all antibody deficiency disorders, immunoglobulin replacement therapy (IRT) is vital in XLA patients. A dose of 400 mg/kg/dose every 3 to 4 weeks is usually sufficient to keep IgG levels >500 mg/dL (26). However, IRT has some limitations, as it contains only non-antigen-specific IgG. In addition, it has been indicated that affected patients under treatment with IVIG therapy may develop lung complications (chronic lung disease). Some XLA patients need antibiotics for a long time. Antibiotic prophylaxis is necessary to prevent infections, even when IVIG therapy is used regularly. Today, using antibiotics, regular IRT, and an early diagnosis can improve the quality of life of these patients with fewer complications.

1.2. Autosomal recessive agammaglobulinemia (ARA)

In addition to XLA patients recognized by mutations

in the *BTK* gene, autosomal recessive agammaglobulinemia (ARA) occurs in 10% of XLA patients with a clinical phenotype but no mutation in the *BTK* gene. ARA is a genetically heterogeneous disorder identified by a profound decrease in all antibody classes and a lack of peripheral B cells (13, 24) caused by mutation in the m heavy chain, Iga (CD79A), Igb (CD79B), I5 (IGGL1), B-cell linker protein (BLNK), subunits of phosphoinositide 3-kinase (phosphatidylinositol 3-kinase regulatory, phosphatidylinositol-3-kinase delta, and phosphatase and tensin homolog), and transcription factor E47 (transcription factor 3) (27).

1.2.1. Clinical Manifestations

The clinical features are the same as those observed in the XLA patients. Bacterial infections of the respiratory and gastrointestinal tracts manifest in these patients when maternal antibody titers decrease. Patients do not develop opportunistic infections, indicating normal cellular immunity. Similar to XLA patients, ARA patients develop meningoencephalitis due to enterovirus infection. Mutation in the *mu heavy chain* is more frequent than other autosomal recessive genes responsible for ARA. Clinical manifestations in patients with *mu heavy chain* deficiency are similar to those in XLA patients, but with severe phenotypes (19, 28). Pneumonia is frequently seen in ARA patients, like XLA patients. However, it was recently demonstrated that paralysis following live polio vaccination is significantly higher in ARA patients than in XLA patients. Furthermore, ARA is diagnosed at an earlier age than XLA (3).

1.2.2. Diagnosis

Normal *BTK* protein and sequence of the encoding gene *BTK* distinguish ARA from XLA. When *BTK* mutation analysis results are negative and/or when female patients are recognized, other known genes should be analyzed (μ heavy chain, *Iga* (*CD79A*), *Igb* (*CD79B*), *I5* (*IGGL1*), *BLNK*).

1.2.3. Management

IRT is required for ARA patients, like with other humoral immunodeficiencies. A dose of 400 mg/kg/dose every 3 to 4 weeks is usually sufficient to keep IgG levels >500 mg/dL. Any infectious episode in ARA should be immediately treated with antibiotics. In XLA and ARA, antibiotics must be used for a long time. Antibiotic prophylaxis is necessary to prevent infections, even when IVIG therapy is used regularly.

2. Common variable immunodeficiency

Common variable immunodeficiency (CVID) is the most common clinically significant primary immunodeficiency disorder. It is identified by low immunoglobulin levels, impaired specific antibody production, and an increased susceptibility to recurrent and chronic infections (4, 5). CVID patients also develop other complications such as autoimmunity, lymphoproliferative disorders, gastrointestinal infections, and cancers (29, 30). Despite several years of investigations into the pathogenesis of CVID, the exact etiology of this disease is still unknown. Previous studies have indicated that mutations in several genes, such as the CD19-B-cell receptor complex (CD19, CD21, and

CD81), B cell activating factor receptor, lipopolysaccharides responsive beige-like anchor (LRBA), tumor necrosis factor receptor superfamily member 13b (TNFRSF13B or TACI), tumor necrosis factor receptor superfamily member 13c (TNFRSF13C or BAFFR) and MutS homolog 5 (MSH5), E. coli, IKAROS family zinc finger 1, CCA-adding transfer RNA nucleotidyltransferase 1 and CD20 have been observed, however, these genes have been seen in less than 10% of CVID patients (31, 32). Today, mutations in these genes seen in CVID patients are categorized as monogenic defects.

2.1. Clinical Manifestations

The most common clinical manifestations in CVID patients are recurrent respiratory infections, autoimmunity, lymphoproliferative disorders, and cancers. Age at onset of symptoms is variable, ranging from childhood to late adult life (4, 5). Normal sized or enlarged tonsils and lymph nodes in CVID patients distinguish them from XLA patients (33). Various clinical manifestations in CVID patients are explained in the following sections.

2.1.1. Respiratory disease. Most CVID patients experience respiratory complications, especially otitis media, sinusitis, or pneumonia commonly by encapsulated bacteria (4, 5, 34). More than 80% of CVID patients manifest at least one episode of chronic sinusitis, and 70% have had recurrent otitis media before diagnosis (35, 36), while pneumonia and bronchiectasis are observed in 70-80% and 37.5-73% of CVID patients, respectively (37-42). Measuring these parameters may guide the physician and result in more aggressive treatment for patients

susceptible to infections and lung disease. Some CVID patients might present lymphoid interstitial pneumonitis (LIP) in their airways (43, 44). Granulomatous lung disease and lymphoid interstitial pneumonia are associated with a high rate of lymphoproliferative disease and are indicators of a worse prognosis (45, 46).

2.1.2. Gastrointestinal disease. Inflammatory and gastrointestinal disorders have been observed in some CVID patients (47), the most common of which are watery diarrhea and severe enteropathy, seen in approximately 20% and 10% of patients, respectively (48). Nodular lymphoid hyperplasia, inflammatory bowel diseases, sprue-like illness with flat villi, giardiasis, and nonspecific malabsorption have also been observed in CVID patients. Cellular deficiency increases the risk of such symptoms in CVID patients (47). *Helicobacter pylori* is an important pathogen in CVID patients; it leads to chronic active gastritis involving both the antrum and the corpus (49).

2.1.3. Autoimmune diseases. Approximately 20% to 25% of CVID patients develop autoimmunity or polyautoimmunity (34, 50, 51). The most frequent autoimmune disorders observed in CVID patients is autoimmune cytopenia such as idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), and autoimmune neutropenia (52). Several studies have investigated the mechanism of autoimmune diseases in CVID, but the exact mechanism of autoimmunity in these patients is still unclear. High doses of IRT along with a short course of corticosteroids is useful for most

CVID patients with ITP and AIHA. However, this kind of therapy should be utilized carefully due to a higher incidence of medical complications associated with the use of immunosuppressive drugs in these patients (5).

2.1.4. Cancers. Some CVID patients develop malignancies, especially lymphoma. Malignancies of the gastrointestinal tract and the lymphoid tissues are the most common involvements in these patients (51, 53-57). Lymphoma is commonly observed in childhood; gastric cancer is frequently seen in the fourth decade of life (58).

2.2. Diagnosis

CVID is diagnosed in patients more than 4 years of age (excluding transient hypogammaglobulinemia of infancy) who exhibit clinical manifestations directly attributable to immune dysfunction (59). Of note, the exclusion of other well-defined causes of hypogammaglobulinemia is important in diagnosing CVID. Secondary causes of hypogammaglobulinemia should also be ruled out. Overall, reduced IgG and profound decreases in IgA with or without low IgM are the most important laboratory criteria for suspecting CVID. Moreover, the assessment of specific antibodies after immunization with protein and polysaccharide vaccines is vital to determining the ability of patients to produce specific antibodies. To assess peripheral B cells counts, flow cytometry is useful, especially for patients with significant hypogammaglobulinemia. B cell abnormalities in CVID patients are variable, as almost 13% of CVID patients have a <3% B-cell count in peripheral blood,

while B cell counts in others may be normal or decreased (5).

2.3. Management

The most important treatment for CVID patients is IRT (60) as either IVIG (60) or subcutaneous (SCIG) (61). This immunoglobulin prophylaxis can be utilized on a regular basis to keep a trough level of at least 400-500 mg/dL. A dose of 400-600 mg/kg every 3-4 weeks is commonly required. Patients with severe sino-pulmonary infections might need higher doses of immunoglobulin to prevent bronchiectasis (62). Antibiotic therapy along with IRT might be indicated for long-term use.

3. Monogenic Defects Associated with Hypogammaglobulinemia

3.1. LRBA Deficiency

LRBA plays an important role in vesicle trafficking and signal transduction of cells that are vital for the normal function of the immune system, particularly increasing responses against LPS-containing bacteria (63). This disease is characterized by defective antibody production, autoimmunity, and gastrointestinal problems.

3.1.1. Clinical Manifestations

Patients with LRBA deficiency develop an early-childhood onset of recurrent infections (particularly respiratory infections), autoimmune disorders (especially ITP and AIHA), and gastrointestinal symptoms like IBD (64, 65). Bronchiectasis, growth retardation, and CNS granuloma formation are other complications associated with this disease.

3.1.2. Diagnosis

Hypogammaglobulinemia (low serum IgG and IgA and normal or reduced IgM levels) is an important finding in patients with LRBA deficiency. These patients have a normal number of B cells and decreased numbers of switched memory B cells. Molecular analysis for the *LRBA* gene should be conducted to recognize mutations in these patients.

3.1.3 Management

Patients with LRBA deficiency receive IRT similar to CVID patients. Recently, it has been demonstrated that sirolimus could be used to treat severe enteropathy refractory in these patients (66).

3.2. CD19 Complex Deficiencies

The CD19 Complex comprises CD19, CD21, CD81 (TAPA-1), and CD225 molecules. This complex leads to the recruitment of cytoplasmic signaling proteins to the membrane and reduces the threshold for B cell receptor signaling pathways upon antigen binding (67, 68).

3.2.1. Clinical Manifestations

Hypogammaglobulinemia and impaired specific antibody production in these patients lead to recurrent respiratory and gastrointestinal infections (69-72). CD19 deficient patients manifest a late onset immunodeficiency along with autoimmune nephritis, significantly decreased B cells, selective IgG1 deficiency, reduced IgM levels, autoimmune cytopenia, increased naïve B cells, and reduced CD27+ memory B cells (73). Patients with CD21 deficiency develop persistent recurrent infections in

the respiratory tract, myalgias, chronic diarrhea with weight loss, sore throat, and splenomegaly (74). CD81-deficient patients develop progressive glomerulonephritis and demonstrate a normal B cell count and an absence of CD19⁺ B cells, reduced memory and transitional B cells, and normal transcriptional levels of *CD19* (75).

3.2.2. Diagnosis

Patients with CD19 complex deficiencies develop clinical manifestations similar to those of CVID and are susceptible to recurrent infections, particularly those caused by bacteria in the respiratory and gastrointestinal tracts. Nephritis has been also seen in some affected patients. Hypogammaglobulinemia is present in these patients along with low IgA and/or IgM levels and a lack of B cell responses to antigens. By using flow-cytometric analyses, reductions in CD19⁺ B cells and CD21⁺ B cells are found in CD-19-deficient and CD-21-deficient patients, respectively. The absence of normally spliced CD81 transcripts and increased levels of alternatively spliced transcripts are characteristic for CD81-deficient patients (75).

3.2.3. Management

IRT is recommended for these patients (76). It is commonly utilized in doses similar to other hypogammaglobulinemia disorders (77). Antibiotic prophylaxis, including co-trimoxazole, may be used in these patients (76).

3.3. Other Monogenic Defects Associated with Hypogammaglobulinemia

Currently, there are several new monogenic disorders leading to partial defects in antibody production. These defects present with recurrent respiratory infections, hypogammaglobulinemia or IgG subclasses deficiency, and/or a lack of antibody responses to vaccines, thus resembling a CVID phenotype (15). Defects in the TACI, ICOS, BAFF receptor, NFKB2, TWEAK, MOGS, TRNT1 and TTC37 genes have been reported to be associated with hypogammaglobulinemia.

3.3.1. Clinical Manifestation

Patients with ICOS deficiency have presented with hypogammaglobulinemia, lymphocyte infiltration, autoimmunity, malignancy, as well as immune cell defects including reduced memory and class-switched B-cell counts and defects in antibody production (IgG1 and IgE) in response to immunization, suggesting a reduced germinal center formation (73, 78). The histopathology of patients' lymph nodes revealed severely aberrant and vestigial germinal centers (79, 80).

TACI deficiency has been described in up to 10% of CVID patients and in individuals diagnosed with IgG subclass and IgAD deficiency (81). Autoimmunity was present in 40% and lymphoproliferation in 60% of patients with TACI deficiency. Moreover, the frequency of lymphomas was higher in these patients than in patients with other monogenic defects associated with a partial antibody deficiency.

Mutations in the BAFFR gene have been reported to cause a late onset antibody deficiency and lymphopenia, leading to respiratory and

gastrointestinal tract infections as well as autoimmunity, malignancy, and granuloma (81). BAFFR-deficient patients suffer from a defect in the short-lived plasma cells (except IgA secreting plasma cells from mucosal tissues), long-term humoral memory (except of IgA+ memory), reduced specific antibody responses to polysaccharide antigens, and a relative increase in transitional B cells (82).

TWEAK deficiency is an autosomal dominant PAD that manifests with numerous warts, B cell lymphopenia, chronic thrombocytopenia, and intermittent neutropenia. Its immunologic abnormalities include increased frequencies of double-negative and CD8+ T cells, with a majority of B cells having a naïve phenotype along with decreased IgA and IgM levels, and a lack of antibody response to T cell-dependent and T cell-independent vaccines (83).

To date, two different heterozygous mutations with dominant patterns of inheritance were reported to cause antibody deficiency in the NFKB2 gene. NF- κ B2 plays a critical role in the development and function of T and B cells; the lack of this transcription factor leads to decreased frequency of memory B cells, reduced Ig levels, defective specific antibody responses, the presentation of atopy or asthma, and autoimmunity.

Patients with PKC δ deficiency suffer from common bacterial infections (sinusitis and otitis), intermittent fevers, and chronic infections with EBV along with hepatosplenomegaly and persistent generalized lymphadenopathy. The progression of autoimmunity

(with elevated levels of different autoantibodies) with a subsequent “intermittent lupus-like rash” and confluent erythematous macules over the trunk and extremities has also been reported.

3.3.2. Diagnosis

All of the above-mentioned monogenic defects manifest with CVID-like symptoms. The analysis of serum Igs revealed diminished IgA and IgM levels as well as IgG deficiency or IgG subclass deficiency. Patients are unable to respond to either T-dependent or T-independent vaccinations; however, special features may provide main clues as to the diagnosis, including increases in double-negative and CD8+ T cell subsets (in CD19 deficiency), severe autoimmune adrenal insufficiency (NF- κ B2 deficiency), lymphoproliferative disorders (TACI deficiency), B cell lymphopenia with normal IgA serum levels and IgA1 plasma cells (BAFF-R deficiency), increased levels of inflammatory markers, defective FAS activity, and double-negative T cell proliferation reminiscent of ALPS (PKC δ deficiency). Next generation sequencing of CVID patients may help identify the mutation and facilitate the correct diagnosis of monogenic defects. Looking for truncated proteins by western blot analysis may also lead to a timely diagnosis.

3.3.3. Management

Management strategies for the above-mentioned monogenic PADs involve preventing and treating infections, boosting the immune system by IVIG replacement therapy, and providing timely treatment for the underlying cause of the immune

problem (e.g., autoimmunity or cancer). In recent years, HSCT has been introduced as a permanent cure for monogenic PADs with severe complications.

4. Immunoglobulin Class Switch Recombination Deficiencies Affecting B Cells

Immunoglobulin class switch recombination deficiencies (CSR-Ds), also called “hyper IgM (HIgM) syndrome,” are the consequence of various defects impairing the CSR machinery. CSR-Ds selectively results from an intrinsic B-cell defect caused by mutations in Activation-Induced Cytidine Deaminase (*AICDA* or *AID*), Uracyl-DNA Glycosylase (*UNG*), post-meiotic segregation 2 (*PMS2*), INO80 complex subunit (*INO80*), MutS E. coli homolog 6 (*MSH6*), and other still undefined genes (81, 84-86). They are defined by the presence of elevated or normal serum IgM levels contrasting with low serum levels of IgG and IgA. Recurrent and chronic bacterial infections, lymphoid hyperplasia, and autoimmunity are clinically characteristics of the disease. Compared to CSR-D due to defects in the CD40-mediated signaling, the above-mentioned CSR-Ds have a better prognosis, and most bacterial infections can be controlled by IVIG replacement therapy. However, some of them could be associated with malignancies (81).

4.1. Clinical Manifestations

Recurrent bacterial infections that predominantly affect the respiratory and gastro-intestinal tracts are the main complications in patients with CSR-Ds. *Streptococcus pneumoniae* and *Giardia lamblia* are the most prevalent microorganisms causing

respiratory and gastro-intestinal infections, respectively. The onset of symptoms generally occurs during early childhood, even though some patients may be diagnosed in adulthood. In contrast to patients with CD40L or CD40 deficiency (which is characterized with abnormal T cell responses), neither susceptibility to opportunistic infections nor neutropenia are observed in these patients. Unlike patients with agammaglobulinemia, CSR-D patients do not appear to develop severe enteroviral infections, suggesting that IgM acts as an initial barrier against enteroviruses. Interestingly, IgM has also been shown to efficiently protect against some bacterial infections, such as non-typable *Haemophilus influenzae* (87). Other complications, such as lymphadenopathies and autoimmune/inflammatory disorders, are also frequent.

4.2. Diagnosis

The laboratory diagnosis of CSR-D is based on a normal or elevated serum IgM level and low serum IgG, IgA, and IgE concentrations. Although the IgG response to protein infectious or vaccinal antigens is impaired, antibody responses are restricted to the IgM isotype with the presence of antibodies to polysaccharide antigens and non-typable *Haemophilus influenzae* (87, 88). Nearly all patients have normal circulating B cell counts, while analyses of subpopulations have revealed an absence of switched B cells (IgM(-), IgD(-)). B cells normally proliferate upon in vitro activation but cannot undergo CSR, indicating the existence of a defect in the CSR machinery (89). In all patients, a T-cell immunodeficiency should be excluded, because T-cell disfunctions lead to a secondary CSR-D (4).

Phenotyping and the functional evaluation of T cells, such as CD40L expression on activated T cells, are required before making a diagnosis of CSR-D caused by an intrinsic B-cell defect.

4.3. Management

Similar to patients with hypogammaglobulinemia, the foundation of treatment for CSR-Ds is IVIG replacement therapy that effectively reduces the incidence and severity of complications. IVIG can be used on a regular basis to maintain a trough level of 400-500 mg/dL in patients. Subcutaneous IgG (SCIG) replacement is another route of IgG replacement therapy. However, lymphoid hyperplasia requires surgical resection in case of impressive enlargement, as observed in AR AID deficiency which Ig substitution does not prevent. Nor does IgG substitution prevent autoimmunity which requires steroids therapy, immunosuppressive and rituximab (monoclonal anti-CD20 antibody) therapies. In these patients, antibiotics are generally administered rather than a prophylactic treatment during infectious episodes.

An accurate diagnosis based on clinical history, biological and genetic testing is essential to setting up an adequate follow-up strategy and prevent complications. In addition, it allows a prenatal diagnosis in severe forms of CSR-Ds, especially PMS2-deficiency. New genetic approaches, such as next generation sequencing, will very likely allow the delineation of the molecularly undefined CSR-Ds.

5. Selective IgA Deficiency

Selective immunoglobulin A (IgA) deficiency (sIgAD) is the most common PID, occurring in approximately 1 in every 500 individuals (90, 91). It is defined as a serum IgA level of less than 0.07 g/l and normal serum IgM and IgG levels (92-95). Although, the nature of the basic defect in sIgAD is unknown, the defect is presumed to result from impaired switching to IgA or a maturational failure of IgA-producing lymphocytes. Many affected sIgAD patients are asymptomatic, whereas select patients suffer from recurrent mucosal infections, autoimmune and allergic diseases (95, 96).

Both sIgAD and CVID often coexist in members of the same family, and some patients initially present with IgAD and subsequently develop CVID (91, 97-105). Therefore, the involvement of hereditary factors and genetic associations are assumed to be involved in the pathogenesis of IgAD and CVID (106-108).

A fundamental defect in patients with sIgAD is the failure of IgA-bearing B lymphocytes to mature into IgA secreting plasma cells; sadly, its mechanism is still not understood. However, isotype switching and terminal B cell differentiation into IgA-secreting plasma cells using cytokines such as transforming growth factor beta (TGF- β) (109) or IL21 (110) may indicate that cytokine plays a key role in this process.

Genetic defects of TACI have also been identified in a few patients with IgAD and CVID, possibly causing defective isotype switching (111). Although the former point has been questioned, molecular findings have demonstrated impaired mu switch (S)

to S alpha rearrangements in peripheral B lymphocytes in some sIgAD subjects (112, 113). sIgAD can be a presentation of other forms of PIDs, such as ataxia-telangiectasia, mucocutaneous candidiasis (114, 115), and IgG2 subclass deficiency (116).

Moreover, transient or permanent sIgAD may develop after therapy with certain drugs including carbamazepine, sulfasalazine, gold, phenytoin, valproic acid, zonisamide, penicillamine, hydroxychloroquine, and NSAIDs (nonsteroidal anti-inflammatory drugs) (114, 117). sIgAD has also been reported in patients with chromosome 18 abnormalities (118). Moreover, Epstein-Barr virus and congenital rubella infections have been implicated in a few cases of acquired IgAD (119).

A subgroup of patients with sIgAD exhibited concurrent IgG subclass deficiency along with defective specific antibody production. These patients have higher rates of recurrent infections and bronchiectasis which require more effective monitoring (120). It has been reported that severe infectious complications and autoimmunity may be present in sIgAD patients with a low frequency of switched memory B cells (121, 122). A reduced number of regulatory T cells in these patients have been correlated with autoimmunity.

As maintained above, sIgAD in some patients may develop into CVID. A similarity of the underlying B-cell defect and familial aggregation of these two disorders proposes a common genetic background which may be associated with the HLA A1-B8-DR3-DQ2 haplotype. It has been reported that sIgAD

patients with severe infections (who also have IgG subclass deficiency or specific antibody deficiency) and autoimmune disorders (who also have defective switched memory B cells or regulatory T cells) are at higher risk for the development of CVID (97, 98, 108, 123, 124).

5.1. Clinical Manifestations

It has been reported that approximately two thirds of sIgAD patients remain asymptomatic (125). The association of concomitant defects (including defects in specific antibody production against protein and polysaccharide antigens, deficiency of IgG subclasses, and defects in mannan-binding lectin) in individuals with sIgAD may predispose them to recurrent infections (126-129).

In symptomatic sIgAD patients, infections include recurrent viral infections, frequent sinopulmonary and gastrointestinal infections (91, 128). Invasive infections such as meningitis, septicemia, and osteomyelitis are not generally features of IgAD. As mentioned, patients with sIgAD also have a higher frequency of autoimmune diseases (130), and, potentially, malignancies (56). Interestingly, a lack of severe infection in sIgAD patients may be attributed to a compensatory increase in secretory IgM in some cases (90, 91).

5.2. Diagnosis

The diagnosis of sIgAD is defined as a serum IgA level less than 7 mg/dL with normal serum levels of IgG and IgM in a patient older than 4 years in which other causes of hypogammaglobulinemia have been excluded. In children aged 6 months to 4 years, it

should be confirmed at the age of 4 years that serum IgA levels are persistently low before a diagnosis of sIgAD is made. sIgAD patients, especially those lacking secretory IgA, which is associated with an impaired polysaccharide responsiveness or IgG subclass deficiencies, may develop recurrent sinopulmonary and GI tract infections. IgA-deficient patients may be evaluated for specific antibody production against protein and polysaccharide vaccines. Therefore, secretory IgA and IgG subclass should be measured to determine if there is a concomitant functional antibody deficiency and if the patient would benefit from the administration of IVIG.

5.3. Management

No therapy is recommended for asymptomatic sIgAD patients. The use of prophylactic antibiotics can be considered in sIgAD patients with a history of infections (131). Aggressive antimicrobial therapy is indicated in all sIgAD patients at the time of severe infections. Moreover, routine vaccination is not contraindicated in patients with sIgAD. The use of IVIG replacement therapy for patients without a demonstrable impairment of specific antibody response is controversial (128, 131, 132). In sIgAD patients with inadequate responses to antimicrobial therapy and sIgAD patients with a concomitant specific antibody defect, a trial of gamma globulin should be considered (92). Gamma globulin should be administered with a low IgA product and with caution and, potentially, pre-medication. If the gamma globulin is given subcutaneously, the

existence of anti-IgA antibodies is not a contraindication (132, 133).

6. Other Immunoglobulin Isotypes Deficiencies

6.1. IgG subclass deficiency

IgG subclass deficiency is defined as a reduction in one or more IgG subclasses in the presence of a normal level of total IgG (134). Most patients show a normal IgM level, while in some patients, abnormal IgG subclasses are associated with IgA deficiency (129). Approximately 2% of normal populations have an IgG subclass deficiency of one or more IgG subclasses; thus, the clinical significance of IgG subclass deficiency in patients with recurrent infections remains unclear (134, 135). It is recommended that a low level of one or more IgG subclasses without clinical presentations generally not be considered sufficient for a diagnosis of PID.

6.1.1. Clinical Manifestations

Recurrent respiratory tract infections such as sinusitis, bronchitis, and otitis media are the most frequent symptoms observed in these patients (136-139). Severe systemic infections including pneumonia, sepsis, meningitis, and cellulitis are less common, but some patients present with frequent viral infections. Patients with IgG subclass deficiency frequently encounter allergic disease (140), and many patients are atopic; asthmatic bronchitis is also associated with the respiratory infections.

6.1.2. Diagnosis

In patients with recurrent respiratory tract infections

and normal IgG levels, the IgG subclasses should be evaluated and their levels compared with those of age-matched healthy controls. In some cases, the total IgG level may be low, and care should be taken to determine whether a diagnosis of CVID might be more appropriate. Patients with IgG2 subclass deficiency commonly have impaired responses to polysaccharide vaccines, especially the pneumococcal polysaccharide vaccine (139). In these patients (with recurrent infections and low levels of one or more IgG subclasses), an impaired antibody response to vaccination is considered the most important determinant of disease (135). To rule out other PIDs, tests for cellular immunity, phagocytic function, and complement activities should be performed.

6.1.3. Management

Asymptomatic patients with IgG subclass deficiency and normal antibody responses to polysaccharide antigens have no need of therapy, but patients with recurrent and chronic respiratory infections need to be treated with prophylactic antibiotics, especially in winter. IVIG replacement therapy is occasionally necessary in cases with a failure of continued antibiotics, severe symptoms, and persistent radiographic abnormalities.

6.2. Specific Antibody Deficiency with Normal Immunoglobulin Concentrations

Specific antibody deficiency (SAD) is a PID characterized by abnormal IgG antibody responses to polysaccharide antigens following vaccination and recurrent infection, but with normal IgA, IgM, total

IgG, and IgG subclass levels (141-143). It has been reported that SAD may be the most common PID observed among children with increased susceptibility to infection (144-146). Although the basic origin of SAD remains obscure, there is some evidence of genetic involvement in certain families and an association with certain Gm and Km IgG allotypes (147). Some studies have also reported a defect in the B-cell repertoire (148) and marginal zone of the spleen (149). The high frequency of allergic disease in SAD patients suggests that this disorder may be caused by immune dysregulation with impaired response to polysaccharide antigens (150).

6.2.1. Clinical Manifestations

Although patients with SAD develop recurrent bacterial respiratory infections, systemic infections such as pneumonia, sepsis, or meningitis are less common. These patients frequently show asthma-like symptoms caused by chronic sinusitis. It has been reported that nearly all children with SAD have at least one form of allergic disease, most frequently allergic rhinitis (150). These patients usually exhibit normal growth and development.

6.2.2. Diagnosis

The hallmark of SAD is diminished antibody responses to polysaccharide antigens following vaccination. The interpretation of anti-pneumococcal antibody concentration results is based on antibody increases over pre-immunization concentrations and on final concentrations following vaccination. It was suggested that high pre-immunization antibody

concentrations to a specific serotype are less likely to increase after immunization (151). Adequate antibody responses to individual pneumococcal serotypes are defined as a post-immunization antibody titer of 1.3 $\mu\text{g/mL}$ or higher or at least 4-fold over baseline (151, 152). In patients immunized with heptavalent pneumococcal conjugate vaccine, it is important to measure antibody responses against at least six serotypes present only in the polysaccharide vaccine.

6.2.3. Management

Immunization with conjugate pneumococcal vaccines may be helpful for SAD patients. It has been reported that patients who fail to respond to the polysaccharide vaccine usually respond to the conjugate vaccine when immunized after 2 years of age (153). In symptomatic SAD patients, immunoglobulin therapy should be considered to control and prevent infections.

6.3. Transient Hypogammaglobulinemia of Infancy

Transient hypogammaglobulinemia of infancy (THI) is a form of hypogammaglobulinemia appearing after birth. THI is defined as a prolonged delay in IgG production by infants that extends to the age of 2 or 3 years (154, 155). THI is also defined as a low level of IgG (less than 2SD below the age-related mean) in an infant beyond 6 months of age that extends to the age of 2 or 3 years (with or without a reduction in IgA and/or IgM), in whom other PIDs have been ruled out.

6.3.1. Clinical Manifestations

Some infants and young children with THI are asymptomatic and have normal responses to vaccine antigen; however, the clinical manifestations of symptomatic THI patients include bacterial sinopulmonary infections and other respiratory tract infections (156). THI is also associated with meningitis, sepsis, or invasive infections at a lower frequency (156, 157). Infants are usually protected by trans-placentally-acquired maternal IgG for the first 3 to 6 months of life, until the natural degradation of the maternal antibodies occurs.

6.3.2. Diagnosis

The definitive diagnosis of THI can be made only after the age of IgG (and in some cases IgA and/or IgM)-level correction; before that, infants with a decreased IgG concentration have hypogammaglobulinemia of infancy that may become THI. Although most THI patients spontaneously recover their IgG levels and have a benign clinical course, some patients do not recover and develop CVID, sIgAD, or other forms of dysgammaglobulinemia (154).

Laboratory diagnosis of THI is confirmed by IgG levels below the fifth percentile for the patient's age (158). It has been recommended that measurements be repeated to eliminate misdiagnosis due to laboratory error (159). A decreased IgG level is sometimes associated with a low IgA level and, less often, with a low IgM level (157). Evaluation also includes the enumeration of lymphocyte subsets by flow cytometry and the measurement of specific antibody response to polysaccharide and protein antigens. In most THI cases, the disease is self-

limited with recovery by 3 years of age. Therefore, no treatment is required for asymptomatic THI patients. If infections begin to occur, the immunoglobulin levels should be monitored at least every 12 months to document their therapy.

6.3.3. Management

For some patients with THI, preventive antibiotic therapy may be indicated. Antibiotic prophylaxis should be the initial mode of preventive therapy; if this fails or is not tolerated, some patients may benefit from IVIG administration, particularly during seasons when respiratory illnesses are more frequent.

Conclusion

PADs are genetic diseases, and affected patients have a variety of first clinical presentations, such as diverse infections, lymphoproliferation, allergy, enteropathy, autoimmunity, and malignancy. Currently, practitioners' awareness about the heterogeneous presentations and diagnostic approach of PAD disorders is poor; therefore, suspected PAD patients are often diagnosed late and suffer severe clinical complications before the certain diagnosis is made.

Conflicts of interest The authors declare that they have no conflicts of interest.

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