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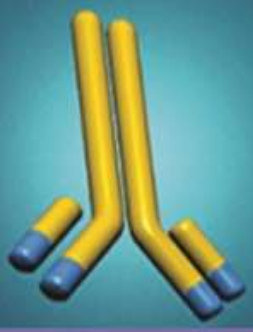

Research Center for Immunodeficiency

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IGJ

Immunology and Genetics Journal

The official journal of RCID: (Research Center for Immunodeficiencies)
and IPIN (Iranian Primary Immunodeficiencies Network)

- Predominantly Antibody Deficiencies
- Multiple Types of Autoimmunity Resulting from the same CD40 Ligand Mutation
- Gastrointestinal manifestations of Iranian patients with LRBA deficiency
- Efficacy of Ganciclovir on CMV Retinitis Complication of Common Variable Immunodeficiency

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Review

Predominantly Antibody Deficiencies

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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.

Keywords Primary antibody deficiencies, pathogenesis, diagnosis, clinical manifestations, management

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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. Severe reduction in all serum Ig isotypes with profoundly decreased or absent B cells	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
	Thymoma with immunodeficiency	Unknown
II. Severe reduction in at least two serum Ig isotypes with normal or low number of B cells	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
III. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells	CD40L deficiency	CD40L (TNFSF5)
	CD40 deficiency	CD40 (TNFRSF5)
	AID deficiency	AICDA
	UNG deficiency	UNG
IV. Isotype or light chain deficiencies with generally normal numbers of B cells	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
	IgG subclass deficiency	Unknown
V. Specific antibody deficiency		Unknown
VI. Transient hypogammaglobulinemia of infancy with normal numbers of B cells		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), l5 (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 *μ 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), l5 (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

ruledout. 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-κB2 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 PKCδ 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 erythematosus 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-κB2 deficiency), lymphoproliferative disorders (TACI deficiency), B cell lymphopenia with normal IgA serum levels and IgA1 plasma cells (BAFF-

deficiency), increased levels of inflammatory markers, defective FAS activity, and double-negative T cell proliferation reminiscent of ALPS (PKCδ 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 pneumonia 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 auto-immune/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-ß) (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 defect (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 administrated 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

IG 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 µg/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

accine 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.

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Original Article

Multiple Types of Autoimmunity Resulting from the same *CD40 Ligand* Mutation

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Abstract

Background/Objectives: Hyper-immunoglobulin M (HIgM) syndrome is a primary immunodeficiency disease in which impaired immunoglobulin class-switch recombination causes normal or high levels of serum IgM versus low or undetectable serum levels of class-switched immunoglobulins.

Methods: The diagnoses of all patients with HIgM in familial cases were evaluated based on genetic testing. Since this syndrome can present with either infectious diseases, malignancies, or autoimmune diseases, all medical complications were recorded in the index patients and relatives.

Results: Surprisingly, the evaluation identified a family with 3 males suffering from CD40 ligand deficiency, and each one had different autoimmune manifestations, including Guillain-barre syndrome and pauciarticular and polyarticular juvenile rheumatoid arthritis.

Conclusions: Based on the results, it is hypothesized that other genetic modifying factors or environmental parameters affecting epigenetics may have a significant role in the presentation of autoimmunity in CD40 ligand deficiency.

Keywords Hyper-IgM syndrome, Autoimmunity, Familial aggregation, Guillain-barre syndrome, Rheumatoid arthritis

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Introduction

Hyper-IgM syndrome (HIgM) can be a primary immune disease (1), or it can be secondary to neoplasia, congenital rubella, or the use of anti-epileptic drugs (2-5). Among primary deficiencies, there are different underlying genetic defects such as X-linked (CD40L, NEMO), autosomal recessive (activation-

duced cytidine deaminase; AIDS, Uracil-DNA glycosylase; UNG, CD40, MSH2, MSH6, INO80) (6, 7) or possibly autosomal dominant (terminal AIDS, PI3KCD, PI3KR1) (8, 9) with impaired class-switching recombination (CSR) and/or somatic hyper-mutation.

Although chronic or recurrent infection is the main presentation of patients with class switch recombination (CSR) defect, autoimmunity is also a major complication, especially in patients with mutations in the *AID* and *NEMO* genes (10). HIgM patients may present with autoimmune arthritis, autoimmune hepatitis, autoimmune cytopenia, hypoparathyroidism, or immune complex nephritis (11, 12). Although CD40L mutation is commonly seen in HIgM, the occurrence of autoimmunity in these patients is rare; it seems that patients most frequently present with autoimmune neutropenia (13, 14). Regarding to other complications, a family was identified with 3 males suffering from X-linked HIgM representing different autoimmune manifestations including Guillain-barre syndrome and pauciarticular and polyarticular juvenile rheumatoid arthritis with the same mutation. The result of this clinical investigation may increase insight into the role of environmental and epigenetic factors in CD40L-deficient patients.

Materials and Methods

Clinical Evaluation

Informed consent for participation in this study was obtained from the patients and their parents in accordance with the principles of the Ethics Committee of Tehran University of Medical Sciences. Patient information was recorded on an evaluation sheet and included patient name, gender, date of birth, age at onset of symptoms, clinical symptoms, age at diagnosis, family history or consanguinity, previous history of medications and vaccinations, and laboratory and molecular data.

Immunological assays

Complete blood count, serum immunoglobulin levels, specific antibody production, lymphocyte subpopulations, and proliferation tests were counted according to standard methods. The CD40L signalling pathway was evaluated using a previously described method (15).

Exome sequencing and analysis

Whole exome sequencing (WES) was performed for the patients. The extracted genomic DNA was randomly fragmented, amplified by ligation-mediated polymerase chain reaction (PCR), and captured and sequenced according to the protocol of the manufacturer as described previously (16). After raw image file processing, sequences were generated and aligned to the human genome reference (UCSC hg 19 version; build 37.1) using the SOAP software (SOAP v.2.21) (17). Duplicated reads were filtered out, and only uniquely mapped reads were kept for subsequent analyses. The SOAPsnp software (v.1.03) was subsequently used with default parameters to

assemble the consensus sequence and call genotypes in target regions (18).

Low-quality single nucleotide polymorphisms (SNP) that met one of the four following criteria were filtered out: a genotype quality of less than 20; a sequencing depth of less than 4; an estimated copy number of more than 2; and a distance from the adjacent SNPs of less than 5 bp. Small insertions/deletions (Indels) were detected using the GATK Unified Genotyper (GATK, v.1.0.4705) (19) following the alignment of quality reads to the human reference genome using BWA (v.0.5.9-r16) (20). For analysis of WES, the protocol described previously for prioritizing candidate variants, predicting their effect on protein, homozygosity mapping, large deletion, and copy number variation detection was followed (16).

The pathogenicity of the disease-attributable gene variant was re-evaluated using the updated guidelines for interpretation of molecular sequencing by the American College of Medical Genetics and Genomics (ACMG), considering the allele frequency in the population database, computational data, immunological/functional data, familial segregation and parental data, and clinical phenotyping (21).

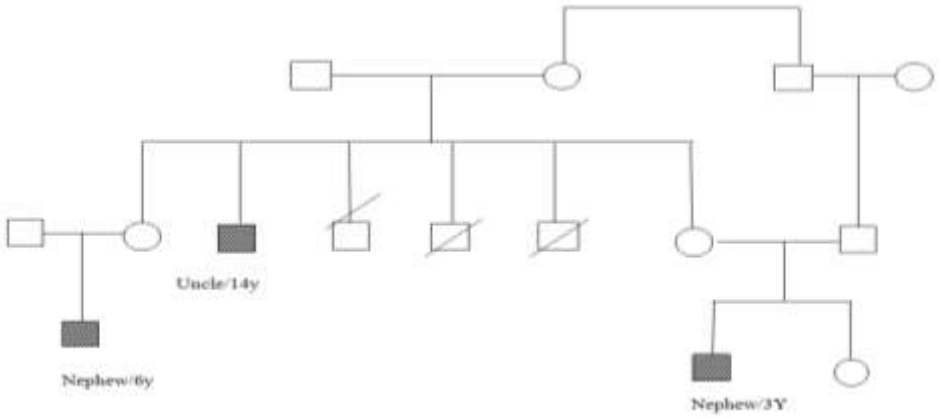
Results

CD40L is the most affected gene among HIgM patients registered in the national registry (21 out of 28 patients with a genetic diagnosis, 75%). Three of these 21 patients (14.2%) belonged to the index family (**Figure 1**). The proband from the index family was a 14-year-old boy who was diagnosed with HIgM at the age of 4 years. His parents were non-consanguineous, and 3 of his brothers had died from recurrent infections and liver problems. The patient had a history of recurrent infection before diagnosis. He had developed pneumonitis (4 times), parotitis, orchitis, sinusitis, and recurrent diarrhea when he was diagnosed with the disease. A complete blood cell count revealed a white blood cell (WBC) count of 10,000/ml with 30% neutrophil, 66% lymphocyte, and 2% eosinophil at the time of diagnosis. The serum concentration of immunoglobulins also showed IgG of 95 mg/dL and IgM of 360 mg/dL, but IgA was not detectable. After diagnosis, the patient received intravenous immunoglobulin (IVIG) regularly every month.

At age 7, he showed symptoms of pharyngitis and tonsil hypertrophy. At age 11, he presented to our center with sudden symmetrical weakness in the upper and lower limbs and ataxic gait. He did not mention any dysesthesia or paresthesia in his limbs, nor did he complain of blurry vision, dysphagia, respiratory distress, or urinary incontinency. On physical examination, the patient was found to be afebrile. His muscle force in distal upper and lower extremities had decreased, but the legs were more affected. Deep tendon reflex in the upper limbs was reduced to one, and the legs were unresponsive to reflex hammer blow, but the patient had no sensory loss. The patient did not mention any recent respiratory infection, diarrhea, vomiting, or

urinary tract infection. His laboratory data showed a leukocyte count of 7,600/ml with 55% neutrophils. His urine analysis was normal and urine culture was negative. A cerebral spinal fluid collection through lumbar puncture was performed for the patient, and the results are demonstrated in **Table 1**. An electromyography was also done. The results indicated an axonal-type Guillain-barre syndrome, and the patient was given 40 grams of IVIG for 2 consecutive days. He improved and his symptoms disappeared. The patient was discharged after one week in a generally good condition.

Figure 1. Pedigree of 3 patients with X-linked hyper-IgM syndrome associated with different autoimmune disorders



Three months later, the patient presented again to our center with complaints of abdominal pain in the right upper quadrant associated with nausea and vomiting. The pain was worse at postprandial times. These symptoms had continued from the previous week. He also complained of massive non-bloody diarrhea from the previous day. In his physical exam, his vital signs were stable and he was not icteric. He had a leukocyte count of 7,000/ml with 56% lymphocytes. His liver enzymes were 15-fold higher than normal, and alkaline phosphate and gamma glutamyl transpeptidase (GGTP) were also higher than normal (**Table 1**). A stool exam revealed fecal occult blood of 2+ and infection with Blastocystis hominis. An abdominal ultrasonography showed mild dilation of the intrahepatic biliary ducts and dilation and thickness of the gallbladder. It also showed cholangitis and constriction of ducts which were consistent with hydrops of the gallbladder. The patient was treated conservatively and referred for an elective cholecystectomy.

Two nephews of the proband were also diagnosed as having HIgM syndrome. The first nephew was a 5-year-old boy who was referred to our department at the age of 11 months with swelling and pain in the right hip, left ankle, and right wrist. He also mentioned a history of recurrent

respiratory infections and diarrhea. One month later he presented with bilateral and symmetrical arthritis of the same joints. The affected joints had limited movements, and he had no fever or any other constitutional symptoms. The patient's tonsils were smaller than normal, and no lymphadenopathy was detected. He had no signs of skin rashes or eye involvement. Based on immunoglobulin titers and his positive family history, the patient was diagnosed with HIgM, and he was also included in the diagnostic criteria for polyarticular juvenile idiopathic arthritis (JIA). Thus, prednisolone was initiated as the main treatment for his JIA, and he was also placed on IVIG treatment (**Table 1**).

The second nephew of the proband was a 3-year-old boy whose parents were first-degree relatives. He presented to our department at the age of 1 year with fever and recurrent non-bloody diarrhea. He also had a history of three admissions to the hospital for sinopulmonary infections during the previous 6 months. The measurement of immunoglobulins indicated IgM of 83 mg/dl, IgA of 2, and IgG of 47 mg/dl. The patient was also diagnosed with HIgM and placed on treatment. At age 3 years, he was referred to our hospital for pain and swelling of wrists and ankle joints from 2 weeks prior to this visit. There was no deformity in his joints, but a mild swelling of the soft tissue with no tenderness was observed in his ankles and wrists. Based on the laboratory data, he was also diagnosed with pauciarticular-onset JIA and placed on prednisolone and 3 high doses of IVIG for treatment; his symptoms gradually improved. A genetic analysis of all of the patients was performed, and the results showed a known mutation in the *CD40L* gene within exon 5 of the TNFH domain of the protein, at c.499 G>C (p.G167R).

Table 1. Auto-antibody titers, liver enzymes, and cerebrospinal fluid analysis (CSF) for the index patient

Parameters	**Results**
Volume of CSF, ml	50
Lactate of CSF, mg/dl	11
Glucose of CSF, mg/dl	45
Protein of CSF, mg/dl	22
WBC of CSF/ul	1
RBC of CSF/ul	228
Direct smear of CSF	Neg
CSF culture	Neg
Aspartate aminotransferase, IU/L	615
Alanine aminotransferase, IU/L	568
Alkaline phosphatase, IU/L	1308
Gamma-glutamyl transferase, IU/L	285
IgM, mg/dL	34
IgA, mg/dL	6
IgG, mg/dL	0
Anti-nuclear antibody (ANA), IU/ml	Neg
Rheumatoid factor (RF), IU/ml	Neg
Anti-cyclic citrullinated peptides (CCP), IU/ml	Neg
Smooth muscle antibody (SMA), IU/ml	Neg
Anti-neutrophil cytoplasmic antibodies (ANCA), IU/ml	Neg
Anti-liver-kidney microsomal type 1 (LKM1), IU/ml	Neg

Discussion

One major type of autoimmunity with c.499 G>C (G167R) mutation is a different type of autoimmune arthritis. About 9% of HIgM patients develop arthritis during their lifetimes (22). Most cases are affected by polyarthritis, but monoarthritis, oligoarthritis, tenosynovitis, subcutaneous nodules, and periarticular masses can be seen (23-25). There are a lot of hypotheses about the mechanism of autoimmunity and arthritis in HIgM patients. CD40 receptors which are on B cell surfaces can also be revealed on cells like macrophages, endothelial cells, fibroblasts, and other cells in inflamed joints (26). Unlike the activation of B cells which is exclusively dependent on CD40-40L interaction, these cells can be activated by other stimuli, like TNF-α (27). Based on these observations, some scientists believe that infections and unregulated cytokines in CD40L patients can activate cells other than B cells, like fibroblasts, macrophages, endothelial cells, and osteoclasts, which can represent inflammatory arthritis. Some others believe that the interaction between CD40 and CD40L has a protective and regulatory role in immune responses to autoantigens (26). Recently, a new model suggested that infections can affect thymus function and induce autoreactive T cells, which can cause arthritis in mice (28).

Although some physicians refer to this disease as rheumatoid arthritis, there are a lot of reasons that arthritis in HIgM patients is different from classic idiopathic RA. First of all, the rheumatoid factor (RF) is usually negative in HIgM patients in contrast with RA patients (23-25). It is thought that CD40-40L interaction is essential for the production of this autoantibody, and the absence of this interaction leads to RF negativity in these patients (23). Secondly, a biopsy of the synovial membrane shows synovial hyperplasia and capillary proliferation without lymphocytic or polymorphonuclear infiltration. B cells and plasma cells can rarely be seen, while there are a lot of CD8+ T cells. In contrast, B cells and CD4+ T cells are the main cells in the synovial fluid of classic RA patients (29-31). Thirdly, the HLA findings are incompatible with those of RA patients; for example, HLA A1, B8, and DR3 are more common in HIgM patients than HLA DRB1*04 and DRB1*01 (29, 32).

There are many hypotheses about the factors involved in autoimmune diseases in HIgM which may interpret the autoimmune neurologic disorders as being Guillain-barre syndrome in the proband. Interactions of CD40 L and Fas L with B cell receptors can propel these cells to maturation or elimination (33). Hervé et al. have suggested that impaired peripheral B cell tolerance can be seen in CD40L deficient patients (34). In fact, CD40L on T cells and MHC II are essential in suppressing autoreactive mature naïve B cells which express antibodies with highly positively charged IgH CDR3s. It is suggested that central B cell checkpoints are intact in both patients and the control group, but the peripheral elimination of autoreactive B cells

is decreased due to impaired regulatory T system and B-cell activating factor (BAFF) accumulation. BAFF is a serum cytokine, high levels of which can be seen in autoimmune diseases; BAFF can act as an inhibitor in suppressing autoreactive B cells (35, 36).

Lacroix-Desmazes et al. also believe that the interactions of CD40-CD40L are essential modulators for the selection of autoreactive B cell repertoires (37). They found a significant bias in IgM autoreactivity in HIgM patients versus the normal activity of these immunoglobulins against foreign antigens. They have also suggested that the autoreactivity of the serum IgG of these patients does not differ from that of the control group in the same concentrations.

Kumanogoh et al. studied the defects of T cells by transferring T cells from CD40-deficient mice to syngenic athymic (nude) mice. They observed that the rate of autoimmunity increased in these mice, while it stayed the same when the cells were from wild-type mice. They also noticed lower levels of $CD25^{+}CD45RB^{low}CD4^{+}$ subpopulations (which is essential in the regulatory T cell system) in CD40-deficient mice. Moreover, CD40-deficient antigen-presenting cells fail to provoke T regulatory cells, which this leads to T cell autoreactivity (38).

The proband also suffers from hydrops of the gallbladder associated with Blastocystis hominis infection; however, the probability of the role of autoimmune inflammation in this complication cannot be ruled out. It is evidenced that prolonged diarrhea in CD40L patients can be commonly caused by *Cryptosporidium parvum*, which also can be involved in cholangiopathy or liver cirrhosis (39, 40). Liver involvement seems to be severe in these patients and is estimated to be the cause of death of 75% of patients in the third decade of life (1). This infection can be transported from the bowels to the bile duct retrogradely or it can be transported to the liver by portal blood (41). Some studies have stated that the excessive proliferation of IgM-producing plasma cells can cause a kind of autoimmunity against the liver, gallbladder, and gastrointestinal tract in response to parasites in CD40L patients (42). It is suggested that primary biliary cirrhosis is more prevalent in these patients, which involves small and medium-sized intrahepatic bile ducts and leads to inflammation and progressive fibrosis due to remarkably high levels of pentameric IgM (43, 44). It is also distinguished with anti-mitochondrial auto-Abs (AMA) in about 90% of affected individuals (45). Cellular immunity also has a role in the pathogenesis of this disease, as it has been found autoreactive T cells in the patients (46). This disease can be more common in HIgM patients due to the higher rate of infections seen in these patients, because their antigens can mimic the superficial antigens of biliary ducts (47, 48). Unfortunately, in our patient, the surveys were not completed to understand which one of the pathologies, autoimmunity, infection, or malignancy of ducts, was responsible for the hydrops of the patient's gallbladder.

Until 2011, the database of CD40L mutations causing X-linked hyper-IgM syndrome (X-HIgM) contained over 250 public entries about different known mutations of this gene (http://bioinf.uta.fi/CD40Lbase). Most of the detected mutations occur in the extracellular TNFH domain encoded by exon 5. It is noteworthy that there is no specific correlation between clinical presentations and the site of the mutation; in other words, each mutation can cause any manifestation of the disease (49). The gene mutation in our patients is a known missense mutation in exon 5, which is related to the TNFH domain of the CD40L. This gene mutation was reported to be responsible in other patients with tonsillar atrophy and low IgM levels but without autoimmunity (50). This comparison also represents the role of epigenetics or environmental factors (like different infections) in the final manifestation of the disease.

Monthly treatments with IVIG and intravenous antibiotics (400–600 mg/kg/month) seem to be useful in decreasing the severity of infections and the related mortality, but they have failed to prevent autoimmune disorders (51). Recent studies have suggested that the autoimmunity of X-linked HIgM can be cured with bone marrow transplantation; unfortunately, however, the conditioning regimen can be toxic to the liver itself and can be fatal in patients who already have a liver complication of the disease (52, 53).

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

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Original Article

Gastrointestinal manifestations of Iranian patients with LRBA deficiency

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Abstract

Background: Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency is a rare genetic primary immunodeficiency (PID) disease caused by mutation in the *LRBA* gene. The most important symptoms in patients include autoimmunity, recurrent infections, hypogammaglobulinemia, and enteropathy.

Methods: A total of 19 LRBA patients were enrolled in this longitudinal study. All recorded data for clinical presentation, demographic information, laboratory and gastrointestinal findings were collected.

Results: In this study, 11 females and 8 males (from 16 unrelated families) with LRBA deficiency were evaluated. The most common gastrointestinal symptoms were gastroenteritis, chronic or bloody diarrhea with abdominal pain, vomiting, anorexia, and FTT. The most important pathologic finding was colitis that was seen in 4 patients. Gastritis, esophagitis, gastroesophageal reflux disease, celiac-like disease, and normal upper endoscopy were documented equally in 2 patients. Also seen was enteritis in 3, proctitis, ileitis, and cryptitis in 1, and villous atrophy in 3 of the LRBA patients.

Conclusion: A variety of gastrointestinal conditions may be the most frequent complications in patients with LRBA deficiency.

Keywords LRBA deficiency, primary immunodeficiency, enteropathy, autoimmunity

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Introduction

LRBA (Lipopolysaccharide-responsive beige-like anchor protein) deficiency is a rare genetic primary immune deficiency disease (PID) resulting from biallelic loss-of-function mutations in the LRBA gene. Immunological abnormalities in patients are decreased IgG antibody production, impairment of specific antibody response, increased apoptosis in B lymphocytes, and defective activation and proliferation of T-cells. In the majority of patients, low B-cell subset counts, especially in switched memory B cells and plasmablasts, have been reported (1, 2). LRBA deficiency has a wide spectrum of clinical phenotypes and manifestations (3-5), including immune deficiency, lymphoproliferation, autoimmunity, and gastrointestinal complications (1, 6).

The most common gastrointestinal symptoms in LRBA deficiency are reported to be chronic and intractable diarrhea (7), chronic active gastritis, active colitis (6, 7), inflammatory bowel disease (IBD) (3, 8), gastric carcinoma and malignant melanoma (9), malabsorption, and failure to thrive (FTT) (10). Recent reports of LRBA deficiency cohorts proposed that enteropathy is a predominant gastrointestinal complication in these patients with a frequency rate ranging from 62% - 76.5% [2, 7, 8].

Until now, there has been no report on gastrointestinal manifestations in patients with LRBA deficiency; therefore, the current study evaluated gastrointestinal manifestations in Iranian patients with LRBA deficiency.

Patients and Methods

All 19 LRBA-deficient patients enrolled in this longitudinal study were registered in the Iranian Registry of Primary Immunodeficiency (11). The inclusion criterion was a diagnosis of LRBA deficiency, primarily diagnosed according to standard criteria (12). All patients had a homozygous mutation in the LRBA gene and were diagnosed between March 2013 and October 2017. Any LRBA patient or patient's parents who did not want to participate in the study were excluded. After securing approval for the study from the Ethics Committee of Tehran University of Medical Sciences, informed consent was obtained from parents and patients. Patient records, clinical symptoms, molecular, laboratory, and pathologic data as well as gastrointestinal manifestations and symptoms of the patients were evaluated. Moreover, either an endoscopic or a colonoscopy procedure was performed, and biopsy samples were sent for pathologic study.

Immunological evaluation

Serum immunoglobulin levels and specific antibody responses to tetanus, diphtheria toxoids, and pneumococcal polysaccharide vaccines as well as complete blood counts were measured in all patients according to standard laboratory methods (13, 14). Immunologic evaluations of B-

and T- cell subsets (CD markers) and regulatory T cells were done by flow cytometry. Autoantibody and immunoglobulin levels were also evaluated.

Statistical analysis

Values were presented as frequency (number and percentage), mean ± standard deviation (SD), and median (interquartile range, IQR), as appropriate. The Fisher's exact and chi-square tests were used for 2 × 2 comparisons of categorical variables, and the Mann-Whitney U test was used to compare numerical variables. The Shapiro-Wilk test was used to check the assumption of normality for a variable, and the parametric or nonparametric test was done according to the normality assumption. Statistical analyses were performed using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

Results

Demographic data

This longitudinal study evaluated 19 patients (11 females and 8 males from 16 unrelated families) from Iran with LRBA deficiency. Patients were followed for a median of 13 years per patient (range 1.3 to 33 years). At the time of the study, the median (IQR) age of patients was 15 (6-25) years (**Table 1**). At the time of analysis, 13 patients (68.4%) were alive and 6 patients (31.6%) had died, mostly due to pneumonia, respiratory failure, or gastrointestinal bleeding. All patients were born to consanguineous parents (100%).

Clinical manifestations

The most common presentations of immunodeficiency at the onset of disease were respiratory tract infection (n=7; 36.8%), chronic diarrhea (n=4; 21.1%), autoimmunity (n=3; 15.8%), failure to thrive (FTT) (n=1; 5.3%), allergy and asthma (n=2; 10.5%), and fever (n=2; 10.5%). The median (IQR) age at the primary onset of symptoms was 2.0 (0.55-2.0) years, and the age at the time of diagnosis was 7.0 (4.5-11.5) years (patient data illustrated in **Table 1**). During the follow-up of patients, the main LRBA phenotypes were chronic diarrhea and enteropathy, infection, autoimmunity and lymphoproliferative disease (**Figure 1**).

All patients (19 of 19) had a history of infectious complications. Infection manifestations were bacterial and viral pneumonia in 14 (73.7%), otitis media in 13 (68.4), sinusitis in 13 (68.4%), meningitis in 3 (15.8%), brain abscess in 1 (5.3%), septicemia in 2 (10.5%), and oral candidiasis in 4 (21.1%) patients. Patients 10 and 14 (P10 and P14) had Giardia lamblia, and P13 had nematode parasite infection with Trichostrongylidae.

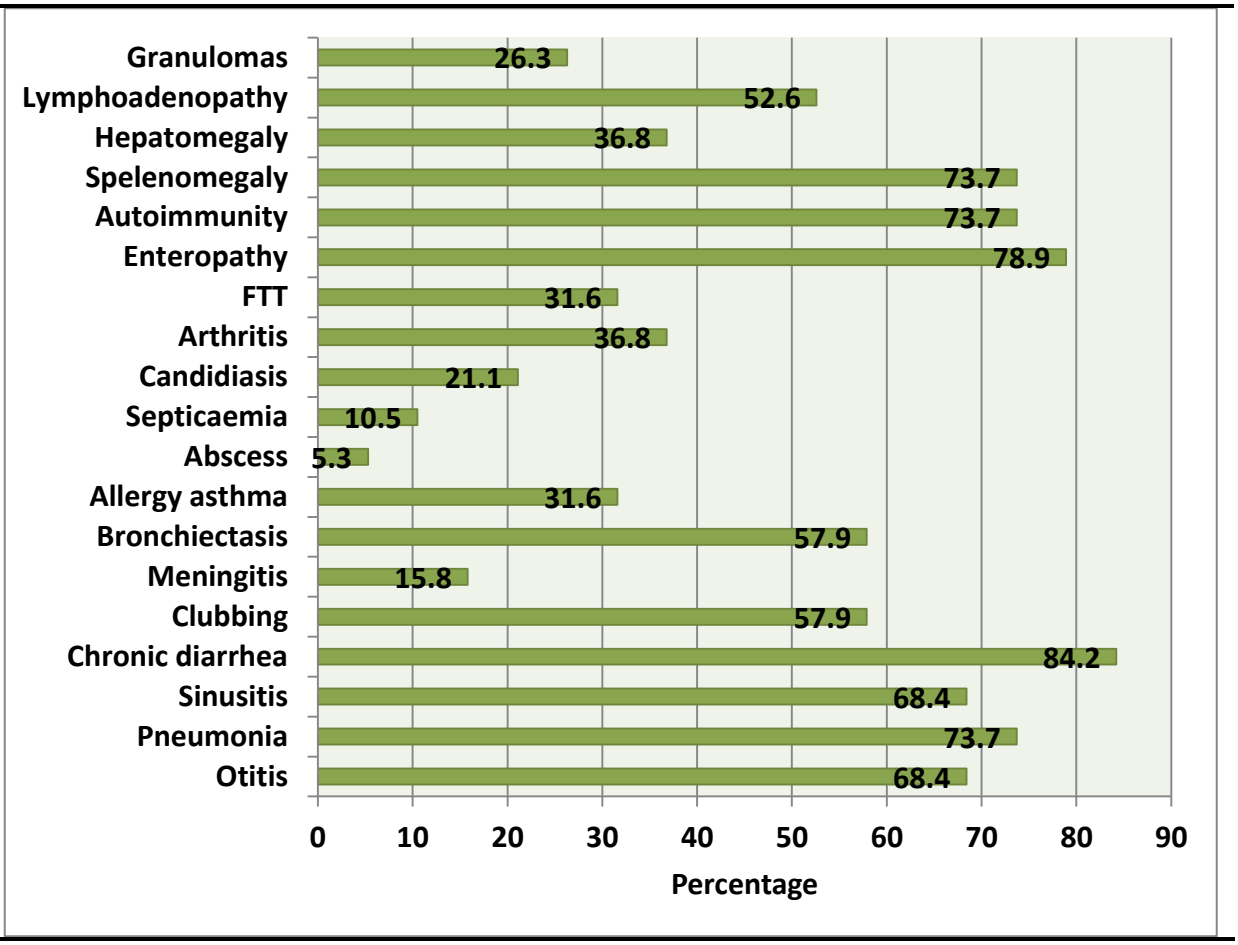
Pulmonary infection was the most common respiratory infection by a median (IQR) of 0.33 (0.02-0.51) episodes per year. P3, P4, and P17 had Cytomegalovirus pneumonia, and P7 was infected with Epstein-Barr virus and had Pseudomonas septicemia.

Table 1. General data of patients with LRBA deficiency

ID	Sex	Dx	Age (y)	AOO (y)	AOD (y)	A/D	YOF	Zygosity	CDNA mutation	Amino acid changes	CADD score**	Reference	Type of autoimmunity
P1	F	CVID	6	0.0	5	A	5.7	Homozygous	C.1383_1384insAAAGTTAACGTTAGCAGATAGAAGGAAATGATAAA	P.S462LfsX7	32.0	(17)	-
P2	F	CVID	30	2	12	A	28	Homozygous	C.C6607T	P. R2214X	35.5	(17)	-
P3	M	CSD	15	2	4	D	13	Homozygous	C.G175T	P. E59X	37.0	(17)	ITP/AIHA
P4	M	CSD	6	0.6	4	A	5.4	Homozygous	C.544C>T	P. R182X	38.0	(17)	IDDM
P5	F	CVID	13	0.5	6	A	12.4	Homozygous	C.5623delA	P. I1875SfsX14	35.0	(17)	JRA
P6	F	Normal Ig	1.8	0.5	0.6	D	1.3	Homozygous	Large deletion (Exon41)	-	-	(17)	ITP
P7	M	CVID	13	0.5	4	A	12.5	Homozygous	Large deletion (Exon41)	-	-	(17)	ITP/AIHA
P8	F	CVID	22	3	11	D	19	Homozygous	C. 4729+2dupT	-	7.5	(17)	AIHA/ITP/AIT
P9	F	Normal Ig	19	5	10	A	14	Homozygous	C. 4729+2dupT	-	7.5	(17)	ITP/AIHA/Neutropenia
P10	M	CVID	27	2	10	A	25	Homozygous	C.C4814G	P.S1605X	34.5	(17)	-
P11	M	Nor mal Ig	35	2	34	A	33	Homozygous	C.C4814G	P.S1605X	34.5	(17)	-
P12	F	CVID	21	1	21	A	20	Homozygous	C.C4814G	P.S1605X	34.5	(17)	AIHA/ITP/MS
P13	M	CVID	16	2	8	A	15	Homozygous	C.C544T	P.R182X	38.0	(17)	JIA
P14	M	CVID	19	2	7	D	16	Homozygous	C.G175T	P.E59X	37.0	(17)	ITP/AIHA
P15	F	CVID	11	3	5	D	6	Homozygous	C. 1014+1G>A	-	26.5	(17)	JRA
P16	F	CVID	19	2	17	D	17	Homozygous	Large deletion (Exon 1-2 deletion)	-	-	(17)	Myasthenia Gravis
P17	M	CVID	12	2	7	A	10	Homozygous	C.743_744insAAGA	P.D248EfsX	36.0	(17)	AIHA/ITP
P18	F	CVID	4	1	3	A	2	Homozygous	C.C4814G	-	-	New patient	-
P19	F	CVID	2	1	1	A	2	Homozygous	NM-001199282: exon 29, C.4638delc	-	-	New patient	ITP/AIHA

Dx, Diagnosis at the time of mutation analysis; AOO, age of onset; AOD, age of diagnosis; A/D, alive or dead; YOF, years of follow-up; IHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura; JRA, juvenile rheumatoid arthritis; MS, multiple sclerosis; IDDM, insulin-dependent diabetes mellitus; AIT, autoimmune thrombocytopenia. All patients had consanguineous parents

Figure 1. Clinical manifestations of LRBA-deficient patients



Cholecystitis was reported in P7, P12 had acute hepatitis, and allergic problems were seen in P6,

P8, P14, and P16. P10 was infected with Helicobacter pylori, and disseminated varicella infection, oral thrush, brain abscess, Pseudomonas aeruginosa, Pneumocystis jirovecii and CMV were seen in P17. Disseminated leishmaniasis and hypertriglyceridemia was also reported in P19.

In the current study, 14 (82.3%) patients had a history of lymphoproliferative disorders, including, hepatomegaly, splenomegaly, lymphadenopathy, and granuloma. Non-caseating granuloma was reported in five patients (26.3%), and three patients presented with granulomatous-lymphocytic interstitial lung disease. All three of them had a history of lung infection with the CMV virus. Multiple hepatic, splenic, adrenal, and pulmonary granuloma were seen in P13.

A variety of autoimmune, endocrine, neurological, hematological, and rheumatologic disorders were reported in 14 (73.7%) patients with LRBA deficiency (**Table 1**). Atopic disorders including allergic dermatitis, food allergies, urticaria, asthma, and insect sting

allergies were also documented in six of the 19 (31.6%) patients evaluated. Bronchiectasis was reported in 11 (57.9%) and clubbing in 11 (51.7%) of the LRBA patients. P5 had septic arthritis.

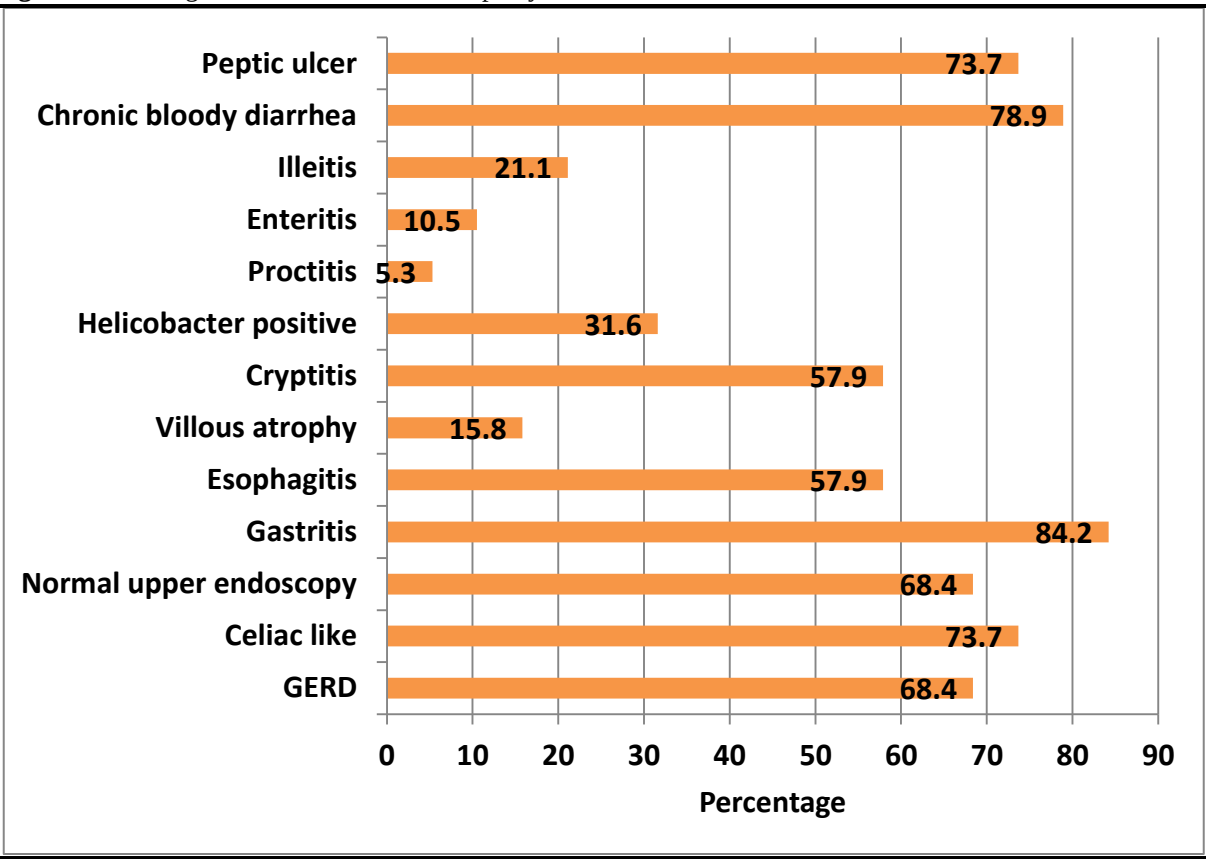
Gastrointestinal manifestations

The most common gastrointestinal symptoms in LRBA patients were gastroenteritis (84.2%), chronic or bloody diarrhea with abdominal pain, vomiting, anorexia (84.2%), and FTT (31.6%). Chronic diarrhea was found in 16 patients (84.2%) patients, 11 of whom (57.8%) manifested three or more episodes of diarrhea during follow-up. Gastrointestinal symptoms were reported in 15 (78.9%) patients, and enteropathy proven by biopsy was seen in nine patients (47.3%). Chronic active gastritis, chronic non-crypt destructive colitis, active colitis, villous atrophy, and intestinal inflammation were the most common and important findings in the patients' pathology reports. Six patients had FTT, while five of these six patients had a history of enteropathy. Endoscopy or colonoscopy was performed on 15 (78.9) LRBA patients with gastrointestinal symptoms (based on patient symptoms and signs). The most common enteropathic conditions were inflammatory bowel disease (IBD) seen in 8 (47.3%) patients and celiac-like disease in 2 (12.5%) patients (**Figure 2**).

The most important pathologic finding in biopsies was colitis seen in four patients (25%). Gastritis, esophagitis, GERD, celiac–like disease, and normal upper endoscopy were documented equally in 2 (12.5%) patients. Enteritis was seen in 3 (17.6%), proctitis, ileitis, and cryptitis in 1 (6.3%), and villous atrophy in 3 (18.8%) LRBA patients. H. pylori was found in one of the patients after an endoscopic procedure (6.3%), and peptic ulcer was seen in another patient. Chronic bloody diarrhea was also seen in one patient (6.3%) (**Figure 2**).

Twelve patients had an overlap of autoimmune and enteropathy disease. It was found that age at onset of enteropathy was less than that of autoimmunity (2.5 [1.0-5.0] vs. 3.0 [2.0-6.0] years); however, the differences were not significant. According to the assessments, none of the patients with GERD had autoimmune cytopenia, but 50% of non-GERD patients had an autoimmune cytopenia. The incidence of autoimmune cytopenia in those with celiac-like disease was 50% compared to 42.9% in those who did not have celiac-like disease. The prevalence of autoimmune cytopenia in those with enteritis disease was 66.7% compared to 42.9% in those who did not have enteritis. In patients with villous atrophy, 2 patients (66.7%) had autoimmune cytopenia, but in patients who did not have villous atrophy, 5 patients (38.5%) had autoimmunity. Moreover, autoimmune cytopenia was seen in 25% of patients with colitis and in 50% of those without it.

Figure 2. Pathologic manifestations of enteropathy in LRBA disease



The prevalence of rheumatologic disorders in patients with gastritis was 0%, but 14.3% of patients who did not have gastritis had a rheumatologic disorder (p=0.350). None of the patients with GERD, celiac-like disease, or enteritis had rheumatologic disorders, but 21.4% of patients without these diseases had rheumatologic disorders. The incidence of rheumatologic disorders in patients with villous atrophy was 0% compared to 23.1% in those who did not have villous atrophy. Rheumatologic disorders were seen in 25% of patients with colitis, but in only 16.7% of patients who did not.

Discussion

LRBA deficiency has several clinical phenotypes, the most of which are chronic diarrhea, autoimmune disorders, hypogammaglobulinemia, respiratory tract infection (15), organomegaly, or combinations of these phenotypes (2, 4, 6, 16). Bal et al. described six symptomatic patients with LRBA deficiency, including autoimmunity (6/6), organomegaly (6/6), and chronic diarrhea (5/6). In other study, Azizi et al. reported pneumonia (76.5%), lymphoproliferative disorders (82.3%), and enteropathy (76.5%) as the main clinical phenotypes of LRBA deficiency (17, 18). Gámez-Díaz et al. described 13 LRBA patients

with enteropathy (61.9%) (2), while in the current study 15 patients (78.9%) had a history of enteropathy and 8 patients (42.1%) had a diagnosis of IBD. This represents a higher percentage of enteropathy in the current study due to the focus on LRBA patients with gastrointestinal complications. Therefore, LRBA patients may be associated only with enteropathy symptoms without infectious complications, and gastroenterologists, immunologists, and rheumatologists should be aware of the clinical symptoms of this disease.

Before the discovery of LRBA gene mutations, most LRBA patients were diagnosed with CVID. In a study by Gámez-Díaz et al. (2), 41% of patients with LRBA had a previous diagnosis of CVID. Lopez-Herrera et al. reported on five patients who had a childhood-onset CVID diagnosis (6). In the current study, however, 14 (73.7%) LRBA patients had a primary diagnosis of CVID. Therefore, most CVID patients with autoimmune complications and enteropathy may have defects in the LRBA gene.

The current study is the first pathological study of gastrointestinal involvement in LRBA patients. Biopsies were performed in 15 (78.9%) patients with persistent gastrointestinal symptoms. The most enteropathy-type complications were celiac-like disease and IBD. The pathologic findings of gastrointestinal biopsies included colitis, GERD, celiac-like disease, gastritis, esophagitis, villous atrophy, cryptitis, proctitis, enteritis, ileitis, and peptic ulcer. One patient tested positive for Helicobacter pylori, and 2 patients had a normal upper gastrointestinal endoscopy. Burns et al. and Alangari et al., in two different reports, showed that duodenal villous atrophy, lymphocytic colitis or Crohn's-like disease occur in LRBA patients (15, 19, 20). This data indicates that LRBA can affect any part of the gastrointestinal tract, from the mouth to the anus.

Usually, in pathologic studies of biopsies, the infiltration of inflammatory cells in the mucosal membrane of the digestive system are critical findings for a diagnosis of inflammatory complication in the gastrointestinal tract. It was reported that in the histology of jejunum mucosa in coeliac and IBD in CVID, LRBA, and XLA patients, the lack of plasma cells is typical and most striking, while an increased number of intra-epithelial lymphocytes, granulomas, and crypt distortions should be observed. Because of these differences, inflammatory gastrointestinal diseases in CVID and LRBA patients are named "coeliac-like", "Crohn's-like", "sprue-like", and so on. This should be considered in the pathologic examination of a gastrointestinal biopsy by an expert pathologist when a question of LRBA disease exists.

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

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Case Report

Efficacy of Ganciclovir on CMV Retinitis Complication of Common Variable Immunodeficiency

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Abstract

Common variable immunodeficiency (CVID) is a heterogeneous disease with different clinical phenotypes that is characterized by hypogammaglobulinemia, abnormal antibody response, and susceptibility to bacterial infections as well as severe viral infections and autoimmunity.

Here we report a case of CVID with autoimmune hemolytic anemia presenting with blurred vision and cytomegalovirus retinitis which improved after treatment with ganciclovir.

Keywords CVID, CMV retinitis, hypogammaglobinemia, ganciclovir

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Introduction

Common variable immunodeficiency (CVID) is a collection of primary immunodeficiency diseases characterized by hypogammaglobulinemia and impaired antibody response. The majority of CVID patients present between the ages of 20-40 years, but 20-50% are under the age of 20 years, according to population genetic studies (1). Delays in diagnosis and proper treatment lead to severe irreversible complications (2).

Factors such as consanguinity and early-onset disease can determine a subgroup of patients characterized with poor prognoses, more complications, and in need of aggressive treatment (3). In CVID patients, several conditions can occur, including recurrent

bacterial/viral infection, autoimmunity, lymphocytic infiltration, and malignancy (4-8). The pathophysiology of CVID is still unknown (9); however, treatment universally commences with immunoglobulin replacement therapy and prophylactic antibiotic therapy. This treatment improved patient survival rates, but it cannot manage particular non-infectious complications of the disease (10-11).

Cytomegalovirus (CMV) is a DNA virus of the herpes viridian family. It causes severe infection in immunocompromised patients (12-13). Severe CMV infection is a rare condition in CVID patients usually with the coincidence of other non-infections complications (14). CMV infections in lymph node (lymphadenitis), lung (pneumonitis) and gastrointestinal tract (enteropathy) have been reported (14). Here we report a CVID patient with CMV retinitis associated with autoimmune hemolytic anemia.

Case report

Our patient is an 11-year-old boy with a history of chronic diarrhea, recurrent pneumonia, recurrent otitis media, and subcutaneous abscess. He is the second child of unrelated parents with no history of primary immunodeficiency in his family. He received vaccines without complications. He had a history of mastoiditis and surgical drainage in the third year of life. The first presentation was severe watery chronic diarrhea and failure to thrive (FTT) at 23 days after birth. He was healthy until the diagnosis of primary immunodeficiency in his second year of life. At his first immunological evaluation, a tentative diagnosis of selective IgA deficiency was made (IgA=5 mg/dl, IgM=54 mg/dl, IgE=33 IU/ml, IgG=2102 mg/dl).

At the age of 7 years, autoimmune hemolytic anemia, thrombocytopenia, and hepatosplenomegaly were added to his clinical picture. There was no evidence of anti-platelet antibody, and Coombs' test and all microbiological evaluations were negative. The patient was then treated with systemic corticosteroid. Recurrent pulmonary bacterial infection was the prominent clinical picture afterwards, leading to the boy's frequent hospitalization. Chest computed tomography (CT) scan revealed pulmonary bronchiectasis. Aspergillums grew in bronchoscopy and fungal cultures of bronchoalveolar lavage (BAL), and with the administration of an antifungal (amphotricin-B) the patient improved. In the second immunological evaluation, pan-hypogammaglobinemia was seen, and intravenous immunoglobulin therapy was initiated with a diagnosis of CVID. Specific antibody responses to tetanus and diphtheria toxin were impaired. Flow cytometry of the peripheral lymphocytes showed normal B cells and T cells (**Table 1**). Upon physical examination, the patient had a failure to thrive, huge hepatosplenomegaly, and diffuse wheezing and rales in both lungs. In the child's extremities, severe clubbing and acral cyanosis were observed, and diffuse flat warts on his trunk were also recorded.

At the age of 10 years, the child presented with blurred vision. In an ophthalmologic consultation, cotton-wool spot was reported, suggestive of CMV retinitis (**Figure 1**). To make a definite diagnosis, a virology investigation was performed which measured the CMV polymerase chain reaction (PCR) in a blood sample. The result was positive, and CMV retinitis was confirmed. For treatment of this complication, intravenous ganciclovir was administered, after which, significant improvement was achieved without complications.

Table 1. Laboratory Data of the Patient at the Time of Diagnosis of CVID

Immunologic parameters	Results
IgA, mg/dl	5
IgM, mg/dl	24
IgG, mg/dl	452
IgE, IU/ml	11
Anti-tetanus Ab, IU/ml	<0.1
Anti-diphtheria Ab, IU/ml	<0.1
Anti-pneumococcal Ab, mg/L	<0.1
CD3+ T cells, in lymphocytes	56%
CD4+ helper T cells, in lymphocytes	30%
Regulatory CD4+ T cells, in T cells	2.2 %
CD8+ cytotoxic T cells, in lymphocytes	37%
CD16+ NK cells, in lymphocytes	5%
CD19+ B cells, in lymphocytes	3%
Switched memory B cells (CD19+CD27+IgD-, in total B-cells) 5	0.3%

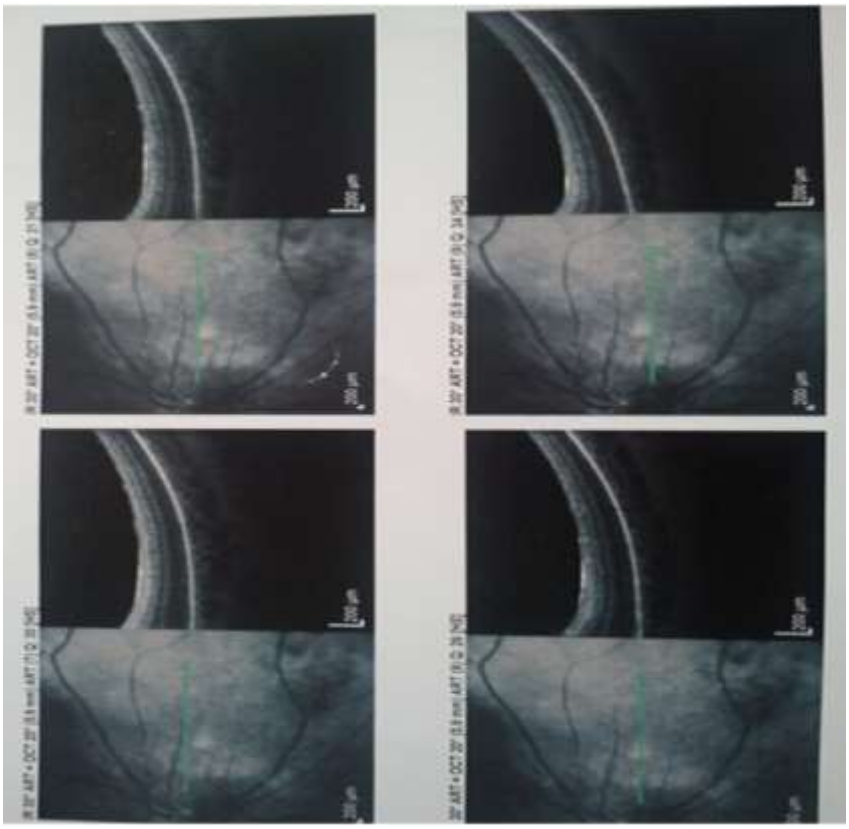

Figure 1. Optical Coherence Tomography in ophthalmologic evaluation revealed cotton-wool spot

Discussion

Common variable immunodeficiency is a heterogeneous disorder characterized by pan-hypogammaglobulinemia, abnormal antibody response, and profound susceptibility to bacterial infection (1). Diagnostic delay in CVID may result in severe irreversible complications; thus, early diagnosis and appropriate treatment can lead to a better prognostic outcome (2). Recurrent bacterial infections in the gastrointestinal and respiratory systems are major clinical pictures in CVID patients (15). Hematologic and ophthalmologic complications of CVM infection are seen in an estimated 8.6% and 5.5% of immunocompetent patients, respectively (15). There is no evidence that CMV infection is highly prevalent in CVID, but associations of reduced immunoglobulin production and herpes virus infection have been highlighted in patients with immune dysregulation syndromes (15-16).

Our patient presented with early onset CVID and a diagnosis of progressive antibody deficiency. His clinical presentations were chronic watery diarrhea, FTT, autoimmune hemolytic anemia, and recurrent bacterial infections which are typically recorded among other CVID patients. However, he was selective IgA deficient and progressed to CVID, which indicated a gradual increase in the severity of his condition usually associated with T-cell defects. The patient experienced blurred vision, and in an ophthalmologic evaluation, evidence confirmed CMV retinitis. Based on the patient's ophthalmologic consultation, intravenous ganciclovir was administered.

The authors have recently reported another case of CVID with macrophage activating syndrome and CMV retinitis associated with retinal detachment (15). Because of diagnostic delay, the patient in that case experienced retinal detachment and visual impairment despite appropriate treatment (15). In the current case, however, treatment was effective, indicating that treatment of retinitis due to CMV infection is individualized and the location of active retinitis and immune status are important factors in treatment (15). Current anti-CMV drugs available are ganciclovir, valganciclovir, foscarnet, cidofovir, fomivirsen, ganciclovir implants, and oral valganciclovir (15, 17). In our patient, CMV retinitis was significantly improved with intravenous ganciclovir without any visual impairment.

Conclusion

Early diagnosis of CVID and its complications, such as CMV retinitis, and appropriate treatment with intravenous ganciclovir can prevent irreversible changes in the retina.

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

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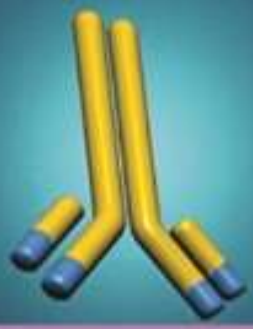

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