Predominantly Antibody Deficiencies

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3.1 Introduction

Primary antibody deficiencies (PADs) are the most common types of primary immunodeficiency diseases (PIDs), accounting for approximately half of the diseases [15, 160, 219, 253, 291, 292, 333]. The spectrum of PADs is broad, ranging from patients with a severe reduction of all serum immunoglobulin classes (Ig) and totally absent B cells to patients who have a selective antibody deficiency with normal serum immunoglobulin (Fig. 3.1) [292]. Many of these disorders share a clinical phenotype with common features such as chronic and recurrent infections, chronic inflammation, and autoimmunity [292]. Hypogammaglobulinemia is the major hallmark of patients with PADs, and the main manifestation is recurrent bacterial infections, predominantly occurring in the respiratory and gastrointestinal traces [12, 110, 241]. *(See* Table 1.2 *and* Fig. 1.9 *for updated classification of predominantly antibody deficiencies)*

The infections are usually caused by pyogenic bacteria with *Haemophilus influenza, Moraxella catharrhalis, Streptococcus pneumonia, Staphylococcus aureus, and Pseudomonas aureginosa* being the most common species. Unlike patients with T-cell deficiencies who have increased susceptibility to opportunist infections, patients with antibody deficiencies do not have

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N. Rezaei et al. (eds.), *Primary Immunodeficiency Diseases*, DOI 10.1007/978-3-662-52909-6_3

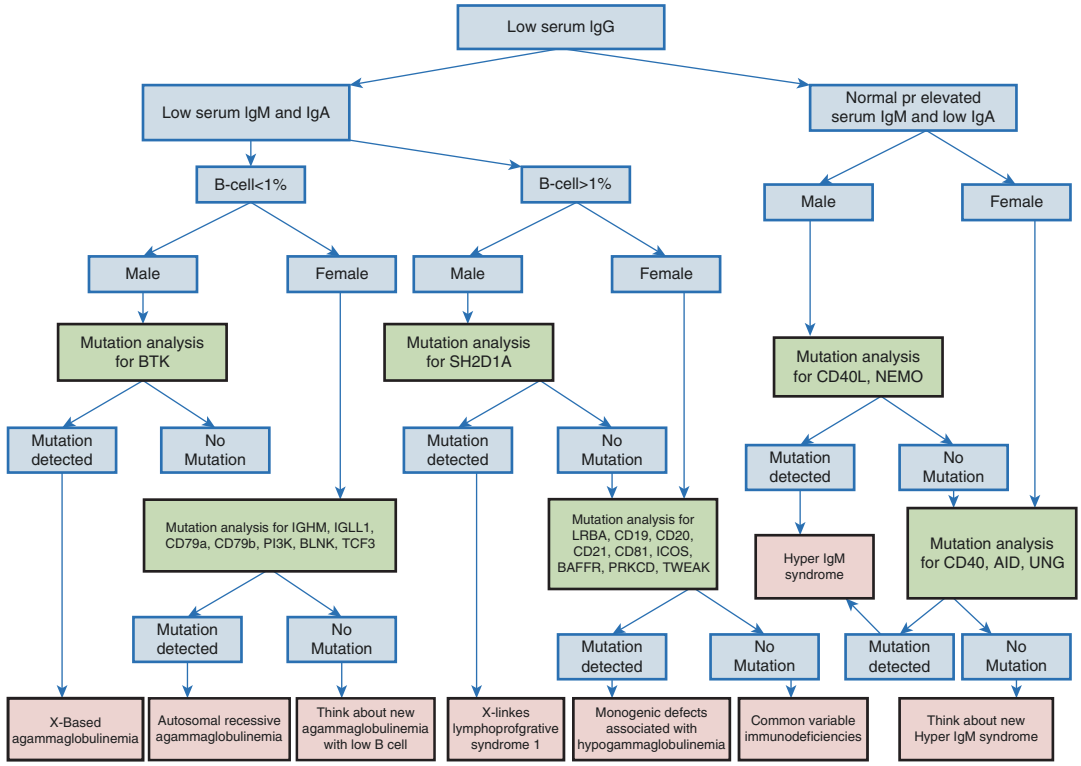

Fig. 3.1 Approach to a patient with hypogammaglobulinemia. †Exclude thymoma, if peripheral blood B cells low. If the patient has findings of clear T-cell deficiency or features like structural defects, abnormal facies or need for remedial education, remember that certain combined immunodeficiencies (e.g., ataxia-telangiectasia, IPEX, ICF, NBS, CARD11, STAT1/GOF), genetic or syndromic immunodeficiencies (e.g., Kabuki, Cornelia de Lange, Roifman) and chromosomal syndromes (Di George/22q11, Jacobsen/11qter, Chromosome 18q sdr, Turner, Down, Wolf-Hirschhorn, Mohr-Traenebjaerg/X22q, OLEDAID/X28q, trisomy 8, monosomy 22, various translocations) may present with immunoglobulin deficiency (Adapted from Seppanen et al. [363])

problems with fungal or viral pathogens, except patients with X-linked agammaglobulinemia (XLA), who are susceptible to enteroviruses and may develop chronic enteroviral encephalomyelitis [267, 339].

Patients are usually free of infection until the latter part of the first year of life, as passively acquired IgG from the mother decreases to below protective levels. Most patients with antibody deficiency can lead normal lives if given replacement gammaglobulin therapy and prophylactic antibiotics. Delays in diagnosis and/or inadequate management may lead to permanent organ damage (*e.g.,* bronchiectasis or bronchiolitis obliterans) or death from overwhelming infection [54, 364].

PADs often arise as a result of defects in early B cell development, class switch recombination or terminal B cell differentiation [1, 307]. B cell development begins in the bone marrow where several defined genes are responsible for the early development and continues in secondary lymphoid organs

The genes involved include Bruton's tyrosine kinase (BTK), Igα, Igβ, λ5, μ heavy chain, B cell linker protein (BLNK), the p85a subunit of phosphoinositide 3-kinase (PIK3R1) and the E47 transcription factor. Mutations in genes involved in early B cell development result in severe forms of PADs, characterized by a block in B cell differentiation before the production of surface Igs, markedly reduced number of mature

B cells in the peripheral circulation, profound hypogammaglobulinemia and early onset of recurrent bacterial infections in affected children [6, 100, 276].

In secondary lymphoid organs, two mechanisms, class switch recombination (CSR) and somatic hypermutation (SHM), are essential for the generation of high affinity IgG, Ig A, and IgE antibodies secreted by plasma cells. Known genes important for CSR and SHM include CD40Ligand (CD40L), CD40, Inhibitor of k light polypeptide gene enhancer in B-cells, kinase gamma (IKBKG), activation induced cytidine deaminase (AID) and Uracil N glycosylase (UNG). Defects in CSR are characterized by low serum levels of IgG, IgA, and IgE leading to recurrent bacterial infections but normal or elevated serum IgM [41].

Terminal stages of B cell development are controlled by a variety of different genes including state of TNF receptor superfamily members (TACI, BAFF-R and potentially TWEAK), the MutS protein homolog 5 (MSH5), the CD19-B cell receptor (BCR) complex (CD19, CD21 and CD 81) and the B cell differentiation antigen, CD20 [180]. The serum level of antibodies is related to expression of LPS-responsive beige-like anchor (LRBA) protein in mature B cells which is necessary for inhibition of early apoptosis plasma cells [243].

Recent advances in the understanding of the genetic basis of B lymphocyte differentiation and identification of the genes involved in primary antibody deficiencies have led to a significant increase in our understanding of the pathogenesis of this group of disorders. Differential diagnosis is important, since some of them have a different prognosis and required a different type of treatment [237].

Immunoglobulin replacement therapy in association with prophylactic antibiotics, is essential to prevent bacterial and viral infections [17, 81, 193]. The purpose of this chapter is to provide current knowledge on the pathophysiology, diagnosis and management of different forms of PADs.

3.2 X-Linked Agammaglobulinemia

(BTK deficiency)

3.2.1 Definition

X-linked agammaglobulinemia (XLA; OMIM*300755) is a rare PID, characterized by absence of circulating B cells with severe reduction in all serum immunoglobulin levels due to mutations in the *BTK* gene (OMIM*300300). Affected patients present an early onset of recurrent bacterial infections. The incidence of the disease varies from 1:100,000 to 1:200,000, depending on ethnicity.

3.2.2 Etiology

XLA represents the prototype for PIDs and was described for the first time by Colonnel Bruton in 1952 [72]; however, the underlying genetic defect was only identified in the early 1990s by two different groups [406, 417]. Bruton's tyrosine kinase (Btk), a member of the Tec family of kinases, was found to be mutated in the majority of male patients with agammaglobulinemia [8, 241, 299, 319, 418]. The animal model deficient for Btk (xid mouse) [327] showed remarkable similarities with the human phenotype and helped to elucidate the pathogenic mechanism responsible for the B cell defect in XLA. B cell development takes place in the bone marrow and depends on the sequential expression of specific gene products that regulate B cell maturation [43, 258, 264]. B cell maturation follows specific steps starting from pro-B to pre-B to immature and then mature B cells that exit the bone marrow and enter the periphery [83]. Pre-B cells express the pre-BCR receptor complex that requires Btk for the initiation of the downstream signalling cascade, necessary for further maturation (Fig. 3.2) [97, 446, 453]. Mutations in *BTK* result in a developmental arrest of B cell

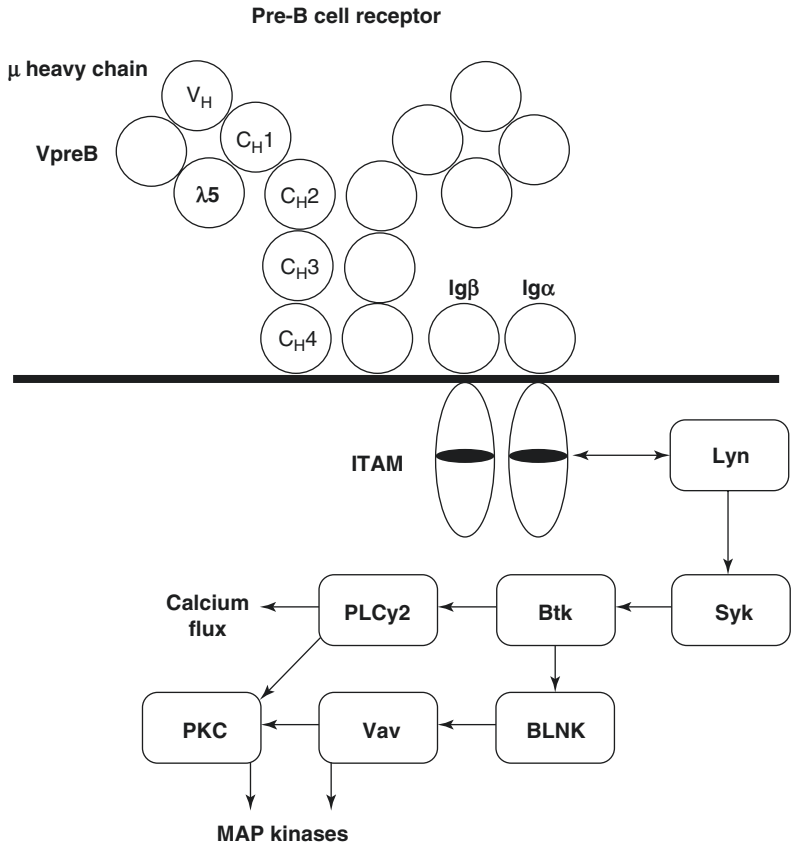

Fig. 3.2 A schematic diagram summarizing the relationships of several molecules whose absence is associated with agammaglobulinemia. Pre- B cells express the pre-BCR, a receptor complex formed by the μ heavy chain, Igα, Igβ, VpreB and λ5, that initiates downstream signalling necessary for B cell differentiation through kinases such as Btk. Mutations in the Btk (BTK), μ heavy chain (IGHM), Igα (CD79A), Igβ (CD79B), λ5 (IGLL1), and B-cell linker protein (BLNK) genes have been described in the patients with agammaglobulinemia

development in the bone marrow at the pro-B to pre-B stage [405]. Studies performed both on patients and animal models have underscored the importance of this check point for B cell maturation in the bone marrow evidencing an accumulation of B cells in the pro to pre-B stage in XLA patients when compared with healthy controls [100]. Since the block in B cell development takes place early in the bone marrow [99], less than 1 % of B cells are detectable in the periphery of these patients. Immunoglobulin levels are very low for all classes and there is virtually no humoral response to recall antigens. BTK deficiency specifically affects the B cell lineage, resulting in reduced size of lymph nodes and tonsils, tissues normally highly populated by B cells. On the other hand, both number and function of T cells are conserved, with the former being slightly increased.

Btk maps on the X-chromosome and mutations can be both familiar and de novo ones; in the first case, mothers of affected individuals are healthy carriers. One case of a female patient with agammaglobulinemia due to *BTK* mutation has been reported so far, due to skewed X-chromosome inactivation.

3.2.3 Clinical Manifestations

The protective role of maternal IgG transferred through the placenta is underscored in XLA: clinical symptoms in affected patients initiate typically between the ages of 6–12 months, when the maternal IgGs are catabolized. Recurrent bacterial respiratory and/or gastrointestinal infections are the hallmark of this disorder. Many patients may remain asymptomatic for the first year of life. Rare cases of young adolescents or even adults affected with XLA, but without symptoms until that age have been reported [181, 223, 383, 408].

Typically, XLA patients suffer from recurrent otitis media, sinusitis, bronchitis, pneumonia and gastrointestinal infections [102]. Frequency of these manifestations is variable based on the different cohorts of patients investigated, however the upper and lower respiratory tract appear to be the mostly affected [241, 280, 319, 382].

Bacterial infections are the hallmark of XLA, both as presenting symptoms and as complications once immunoglobulin replacement therapy, either intravenous (IVIG) or subcutaneous (SCIG) therapy is initiated [7, 332]. Such infections are mainly caused by encapsulated pyogenic bacteria, namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and others. Pseudomonas species has been reported to be the most frequently isolated pathogen in septicemia, followed by *H. infuenzae*, *S. pneumoniae* and *S. aureus*. Septic arthritis in these patients is mainly caused by *H. infuenzae* and *S. pneumoniae* before IVIG therapy, whereas a viral cause is mainly responsible after IVIG therapy. Bacterial meningitis can also complicate the history of these patients, especially before appropriate treatment and is caused by the above-mentioned pathogens as well.

Typically, XLA patients suffer from recurrent infections of the upper and lower respiratory tract. Chronic sinusitis is present in more than 65 % of patients. Recurrent bronchitis and/or pneumonia continue to occur even when IVIG therapy is regularly established, leading to the development of bronchiectasis [241, 280, 319].

Infections of the gastrointestinal tract are also frequent in XLA patients. Giardia lamblia is frequently isolated from stool samples from these patients and unfortunately, its eradication appears unsuccessful, resulting in chronic diarrhea and malabsorption. Similar clinical findings are caused by *Campylobacter jejuni* infections, that can however be accompanied by skin manifestations and fever. The diarrhea may persist for weeks, although some patients may remain asymptomatic. It appears that antibodies are an important line of defense against Campylobacter, explaining the increased susceptibility to this pathogen in XLA patients. Salmonella has also been described as cause of g-i infection in XLA patients [241, 280, 319].

Mycoplasma species are also frequently cause infections in XLA patients, mainly interesting the respiratory and urogenital tract, and in some cases joints. Since the isolation of these microorganisms is often difficult, the course of the infection may be prolonged with consequently severe symptoms at presentation. Frequently, combined infections with Mycoplasma species and other bacteria can increase disease severity. Recurrent bacterial conjunctivitis is also rather frequent (5–8 %), and pathogens involved are the ones so far described.

Besides bacterial infections, viral infections may complicate the natural history of XLA. Affected patients are particularly susceptible to enterovirus, namely poliovirus, echovirus and coxsackie virus. Vaccine associated poliomyelitis after live attenuated oral vaccine (Sabin) has been reported and is complicated by a high mortality rate.

Progressive neurological symptoms in XLA patients, such as ataxia, paresthesias, loss of cognitive skills, neurosensorial hearing loss should always raise the suspicion of enteroviral infection. Enteroviral meningoencephalitis in XLA patients tends to manifest slowly throughout the years, although fulminating infection with fever, headache and seizures has also been reported [175, 278, 349, 442]. The difficulty in isolating the enterovirus from the CSF was thought to be overcome by using PCR techniques; however such method does not always identify the enterovirus. CSF characteristics are usually suggestive (associated with clinical findings) of a viral infection: pleocytosis, elevated protein content and in some cases hypoglycorrhachia. Unfortunately, patients with symptoms of encephalitis may have normal or near-normal CSF findings. Chronic enteroviral infections were more frequent before the initiation of IVIG therapy; however, such infections do still occur. High dose IVIG treatment has been shown to be efficient in controlling the infection and limiting the CNS involvement, however, the limited number of patients studied does not allow statistical conclusions [323]. Intrathecal delivery of IVIG has also been used in some cases for a more prompt and

direct effect. An anti-inflammatory effect of high dose IVIG has been proposed, although it is difficult to demonstrate. MRI or CT scan is usually normal at the onset of symptoms, and has therefore limited diagnostic value. Chronic enteroviral infection eventually results in cerebral edema, diffuse inflammation and progressive cerebral atrophy [175, 278, 349, 442]. Chronic leptomeningitis has been reported in some cases instead of the "classic" findings of encephalitis.

CNS enteroviral infection may also present with peripheral edema and erythematous rash mimicking a dermatomyositis-like syndrome [40]. Biopsy specimens from skin and muscle evidence inflammation. Such manifestations follow the CNS involvement and demonstrate a disseminated enteroviral infection. Involvement of the liver, with an enteroviral hepatitis, ALT increase and hepatomegaly has also been reported, usually associated with rash and fever. Hepatitis C infection from contaminated IVIG preparations has been reported in the early 90s. XLA patients seem to tolerate better the HCV infection when compared with CVID patients. More than a third of the reported patients cleared the infection or remained asymptomatic, whereas only one patient developed hepatic failure, but was co-infected with hepatitis B virus. *Pneumocystis jiroveci* has been documented as a rare cause of pneumonia in XLA patients, mainly debilitated ones [24, 131, 350]. Recurrent pyoderma was recently shown to be the only clinical manifestation of an XLA patient. Chronic gingivitis has also been reported as the only clinical finding in an XLA patient. *Helicobacter cinaedi* bacteremia with macules and no fever was recently reported in an adult patient with XLA.

Arthritis has been reported in almost 20 % of XLA patients [241, 280, 319, 382]. Clinical findings are indistinguishable from RA, including motion limitation, effusion, pain and destructive pannus formation. In some cases, a pyogenic cause has been isolated, although in the majority of the cases no isolates are found. These manifestations tend to respond to IVIG therapy, sometimes at increased doses indicating a potential infectious cause. Antibiotics are usually associated with the IVIG treatment. In many reported cases, an enteroviral or Mycoplasma infection was associated with the rheumatic manifestations. Interestingly, although B cells have been proposed to be involved in RA pathogenesis, no B cell infiltrates were found in the synovium of an XLA patient with RA.

Neutropenia has also been reported in XLA [78, 92, 149, 208]. A Japanese nationwide study showed that 18 % of XLA patients presented neutropenia before IVIG treatment was initiated. In different studies, neutropenia has been reported in a percentage variable form 10–25 %, although the clear involvement of Btk in neutrophil development has not been elucidated yet. Other rare manifestations include glomerulonephritis, alopecia, amyloidosis, von Recklinghausen disease. Conjunctivitis is rather frequent mainly in adult patients, and some report a benefit from IVIG treatment.

3.2.4 Diagnosis

The typical laboratory findings of XLA consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells (>2 %), reflecting the early block in B cell development [22, 103]. Rare cases of patients with peripheral B cells and/or near normal Ig levels have been reported; in such cases specific antibody response to specific antigens is used for further characterization. Once the clinical suspicious is made by the clinical findings, Btk expression levels may be helpful in confirming the clinical suspicion of XLA; molecular analysis of the *BTK* gene should always be performed in order to define the mutation, if any, causing the disease. Once the mutation is defined, carrier diagnosis and prenatal diagnosis can be performed where necessary.

3.2.5 Management

Immunoglobulin replacement therapy is essential in XLA as in all humoral immunodeficiencies. In the past, intramuscular administration was used; current protocols are based on IVIG or

subcutaneous immunoglobulins. It is widely accepted, based on different international studies, that maintaining pre-infusion IgG levels >500 mg/dL assures a notable reduction in the number of infections, reducing the necessity for hospitalizations. Using a dose of 400 mg/kg/dose every 3–4 weeks is usually sufficient to maintain such levels. Several studies have argued on the cut-off level that should be considered protective. Currently, the subcutaneous administration appears very promising for different reasons: First of all, it is well tolerated and is indicated in particular for patients with previous severe adverse reactions to the intravenous preparations. In second place, it is as efficient as the intravenous one and in addition the subcutaneous therapy offers better quality of life, since the administration takes place at the patients' home.

However, the immunoglobulin replacement therapy presents certain limitations. From one hand, it contains only IgG that are not selected on antigen specificity. Secreted antibody deficiency is not replicable. In addition, different studies have shown that after almost two decades of follow-up, patients regularly on IVIG therapy may develop lung complications (chronic lung disease). Therefore, the optimal therapy is still to be determined; on the other hand the role of respiratory physiotherapy is becoming very important as the main strategy in order to maintain and even ameliorate lung function.

Any infectious episode in XLA should be immediately treated with antibiotics. In XLA, patients require frequent therapies with antibiotics, many of which for long periods. In addition, the infectious agent is not always eradicated even though antibiotics may be used for months. Frequently, antibiotic prophylaxis is necessary in order to control the number of infections even when IVIG therapy is performed regularly.

Considering the specificity of the defect in XLA, where Btk is defective in the B cell lineage, the gene therapy approach has been strongly considered. After the complications (leukemia) in two SCID patients treated with gene therapy, a lot of discussions have aroused on the risks involved with such approach. However, recent advances in the field have demonstrated that gene therapy is possible for XLA in the murine model and will probably soon becomes a therapeutic option for affected patients as well.

The introduction of antibiotics and IVIG has completely changed the prognosis of XLA patients. Before the introduction of appropriate therapy, patients would die before the age of 10. Nowadays, the prompt use of antibiotics, regular replacement therapy and an early diagnosis can assure a longer life span with less complications. However, the situation is still rather dramatic. After a follow-up of 17 years, almost 70 % of an Italian group of XLA patients had developed chronic lung disease, either obstructive, restrictive or both [319]. The progressive damage of the lung structure and the consequent functional deterioration result in important limitations for these patients. Recently, lung transplant was performed in a limited number of XLA patients with very good results, a positive follow-up for the first year and significant improvement of the respiratory function.

Malignancy has been reported in XLA as well [39, 140, 241, 280, 319, 382, 409]. The percentage is variable in the different studies. Colorectal cancer has been reported in several patients, although the underlying association with XLA is not well defined yet. Gastric adenocarcinoma has been observed in XLA patients with underlying chronic gastritis. Lymphoid malignancies have been reported but percentages vary in the different cohorts of patients.

3.3 AR-Agammaglobulinemia

(μ heavy chain deficiency, λ5 deficiency, Igα deficiency, Igβ deficiency, BLNK deficiency)

3.3.1 Definition

Autosomal recessive agammaglobulinemia (AR-agammaglobulinemia) is rare form of PID, characterized by severe reduction of all of immunoglobulin classes and absence of peripheral B cells, in the absence of *BTK* mutations [22, 100]. It affects both males and females. However, the

underlying genetic defect is currently known only in a limited number of patients.

3.3.2 Etiology

B cell development takes place in the bone marrow where the sequential expression of specific gene products promotes B cell differentiation from the pro-B to pre-B to immature B to mature B cell that enters the periphery [43, 147, 174, 239, 247, 340]. Pre- B cells express the pre-BCR, a receptor complex formed by the μ heavy chain (*IGHM*; OMIM*147020), Igα (CD79A; OMIM*112205), Igβ (CD79B; OMIM*147245), VpreB and λ5 (*IGLL1*; OMIM*146770), that initiates downstream signalling necessary for B cell differentiation through kinases such as Btk and *BLNK* (OMIM*604615) [97]. Animal models and *in vitro* studies have elucidated the importance of each of the pre-BCR components and associated transcription factors for the transition from pro-B to pre-B stage of maturation and consequently became candidates for the cases of agammaglobulinemia of unknown genetic origin [218, 247, 295, 441, 454].

The first patients with mutations in the mu heavy chain were described in 1996 [448]. A more extensive investigation including large numbers of agammaglobulinemic patients was undertaken in the United States and in Italy in order to define the exact incidence of mu heavy chain mutations within the cohort of patients with agammaglobulinemia of non-defined genetic origin. Approximately 40–50 % of these patients presented mutations in the mu heavy chain locus.

λ5/14.1 together with VpreB comprise the surrogate light chains that are part of the pre-BCR receptor complex, which is essential for early B cell development. Conley et al. reported on the first male patient with mutations in the λ5/14.1 gene causing autosomal recessive agammaglobulinemia [275].

Igα and Igβ form the signalling transducing elements that associate with the pre-BCR and allow the initiation of the downstream signalling cascade, rendering both valid candidates for this disease. In fact, Minegishi et al. reported on the first patient with a mutation in the Igα gene, resulting in alternative exon splicing of the gene product which abolishes the expression of the protein on the cell surface [99]. The second reported male patient had a homozygous alteration at an invariant splice donor site of intron 2, which presumably resulted in the truncation of the protein [431].

Igβ is essential for the downstream signalling cascade after pre-BCR cross-linking both in mice and humans. Recently, two different groups identified patients affected with agammaglobulinemia and mutations in Igβ. Dobbs et al. [132] reported recently on a 15 year old female patient with a hypomorphic mutation in Igβ and a leaky defect in B cell development. Ferrari et al. [154] on the other hand, recently reported on a 20 year old male patient with a homozygous nonsense mutation in Igβ, resulting in a stop codon. Bone marrow analysis of this patient evidenced a complete block of B cell development at the pro-B to pre-B cell transition, closely resembling the one observed in the animal model. In addition, in vitro studies showed that the nonsense Igβ mutation abrogates the expression of the pre-BCR on the B cell surface.

BLNK (also called SLP-65) is activated after BCR cross-linking and initiates the downstream signaling cascade. Since mutations in pre-BCR components have been found to cause agammaglobulinemia and BLNK acts downstream of this complex, it was evaluated as a candidate gene. In fact, Minegishi et al. [277] reported on the first male patient with mutations in BLNK resulting in agammaglobulinemia. Bone marrow analysis showed a specific block at the pro-B to pre-B stage, and additional experiment concluded that BLNK is essential for B cell development once the pre-BCR is expressed.

3.3.3 Clinical Manifestations

Clinical symptoms in patients with μ heavy chain deficiency reminds those of XLA, although apparently in a more sever manner [99, 448]. In fact, age at diagnosis appears younger for this disorder when compared to XLA. Chronic enteroviral encephalitis, recurrent bronchitis, pneumonia,

Pseudomonas aeruginosa sepsis, otitis media and others characterized the onset of the disease. Clinical history ameliorated after regular immunoglobulin replacement therapy was initiated at a regular basis. Chronic infection by Giardia lamblia, resistant to therapy, resulting in anemia and malabsorption is present in one female patient with mu heavy chain deficiency *(*Plebani, personal communication, 2015*)*. Neutropenia has also been reported in almost a third of patients with this disorder. Bone marrow analysis from mu heavy chain deficient patients evidenced an early arrest of B cell development, even earlier to that seen in Btk deficient ones, with almost complete absence of peripheral B cells.

On the other hand, the clinical history of the patient affected with λ5/14.1 deficiency started at the age of 2 months with recurrent otitis media and was found to be hypogammaglobulinemic with absence of peripheral B cells at the age of 5 years, when he was hospitalized for Haemophilus meningitis [275]. Peripheral B cell analysis evidenced less than 0.06 % of B cells. Bone marrow studies showed a specific block at the pre-B to pre-B stage of differentiation.

The first female patient affected with Igα deficiency presented chronic diarrhea with failure to thrive within the first month of life [99]. At 1 year of age, she was hospitalized for bronchitis and neutropenia. Immunological work-up showed severely reduced levels of all immunoglobulin classes and absence of peripheral B cells. Bone marrow analysis evidenced a specific block at the transition from pro-B to pre-B cell. Interestingly, no lymph nodes were detectable during clinical examination. The second patient was a male with a history of respiratory infections, diarrhea and a dermatomyositis-like phenotype [431]. Unfortunately he died of a pulmonary infection.

The patient with the hypomorphic mutation in Igβ presented recurrent lower respiratory tract infections from the age of 5 months [132]. After initiation of the IVIG therapy at the age of 15 months, her clinical history presented a significant amelioration. The patient carrying the nonsense mutation in the Igβ gene was first admitted at the age of 8 months for pneumonia and Salmonella-caused enteritis [154]; his immunological workup evidenced a complete absence of peripheral B cells (CD19 < 1 %) and panhypogammaglobulinemia. IVIG therapy was initiated immediately but the patient's clinical history was complicated by recurrent bronchitis, sinusitis, otitis media and bacterial conjunctivitis.

Clinical history of the single reported patient affected with BLNK deficiency [277], includes recurrent otitis from the age of 8 months and two episodes of pneumonia before the age of 6 months. The first immunological workup evidenced undetectable serum IgG, IgA and IgM levels in the absence of peripheral B cells. Once on regular IVIG therapy and during an 18 year period of follow-up, his clinical history was complicated with chronic otitis and sinusitis, hepatitis C from immunoglobulin reparation, and a protein-losing enteropathy during adolescence.

3.3.4 Diagnosis

The typical laboratory findings of AR-Agammaglobulinemia consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells, as defined by CD19 and CD20 expression (<2 %), reflecting the early block in B cell development [22, 100]. When *BTK* mutation analysis results negative and/or when female patients are identified, sequencing analysis of the other known genes (μ heavy chain, Igα, Igβ, λ5, BLNK) should be performed.

3.3.5 Management

Immunoglobulin replacement therapy is essential in AR-Agammaglobulinemia as in all humoral immunodeficiencies. In the past, intramuscular administration was used; current protocols are based on IVIG or subcutaneous immunoglobulins. It is widely accepted, based on different international studies, that maintaining pre-infusion IgG levels >500 mg/dL assures a notable reduction in the number of infections, reducing the necessity for hospitalizations. Using a dose of 400 mg/kg/dose every 3–4 weeks is usually sufficient to maintain such levels. Several studies have argued on the cut-off level that should be

considered protective. Currently, the subcutaneous administration appears very promising for different reasons: First of all, it is well tolerated and is indicated in particular for patients with previous severe adverse reactions to the intravenous preparations. In second place, it is as efficient as the intravenous one and in addition the subcutaneous therapy offers better quality of life, since the administration takes place at the patients' home.

Any infectious episode in AR-Agammaglobulinemia should be immediately treated with antibiotics. In XLA and AAR, patients require frequent therapies with antibiotics, many of which for long periods. In addition, the infectious agent is not always eradicated even though antibiotics may be used for months. Frequently, antibiotic prophylaxis is necessary in order to control the number of infections even when IVIG therapy is performed regularly.

The introduction of antibiotics and IVIG has completely changed the prognosis of patients affected with AR-Agammaglobulinemia. However, the identification of genetic defects causing autosomal recessive agammaglobulinemia has been accomplished in a limited number of patients and frequently interests single patients; on the other hand, not enough follow-up and observation time is available in order to define specific complications present in these forms, although so far, the prognosis appears similar to that of XLA.

3.4 Other Forms of Agammaglobulinemia with Absent B-Cells

(TCF3 deficiency, LRRC8 deficiency, Thymoma with immunodeficiency)

3.4.1 Definition

The condition of agammaglobulinemia with absent B-cells may be observed in other conditions besides the ones described so far. E47/TCF3 deficiency (*TCF3*; OMIM*147141) was recently described in four patients with agammaglobulinemia and reduced peripheral B cells that expressed CD19, but lacked BCR expression on the cell surface [56]. The leucine-rich repeat-containing 8 (*LRRC8*) is another gene (OMIM*608360) implicated in the pathogenesis of agammaglobulinemia: it was identified in a female patient with agammaglobulinemia and minor dysmorphic features [351].

Thymoma with immunodeficiency or Good's Syndrome (GS) is a rare association of thymoma and combined immunodeficiency [155] classified as "predominantly antibody deficiency", included in the "profoundly decreased or absent B cells" group [22, 103]. It has similar characteristics with common variable immunodeficiency (CVID); nevertheless, GS is associated with a poorer prognosis. Its presentation, usually after the fourth decade of life, can be related with recurrent infections or a casual finding of an anterior mediastinal mass (thymoma). The major immunological defects are hypogammaglobulinemia, few or absent B cells, an abnormal CD4/CD8 T-cell ratio and impaired T-cell mitogenic responses. Hematological disorders and associated autoimmune diseases are also common.

Primary myelodysplastic syndromes (MDS) are heterogeneous clonal hemopoietic stem cell disorders clinically presenting with a varying degree of peripheral cytopenias and an increased probability of leukemic evolution [141]. Hypogammaglobulinemia may be found in a limited number of patients affected with MDS.

3.4.2 Etiology

The broadly expressed transcription factor E47 resulted mutated in the four patients with TCF3 deficiency. The recurrent mutation E555K has a dominant negative effect and results in an autosomal dominant form of agammaglobulinemia. Animal models have underlined the role of transcription factors such as E47 in B cell development [61]. Affected patients carrying the E555K

mutation presented an unusual peripheral B cell phenotype: enhanced CD19 expression with absent expression of BCR. Bone marrow analysis in 2 out of 4 affected patients showed a reduction both in pro-B and pre-B cells, suggesting an earlier developmental arrest than that seen in other forms of agammaglobulinemia [56].

The leucine-rich repeat-containing 8 (LRRC8) is a novel family of proteins with unknown function and consists of four transmembrane helixes with one isolated and eight sequentially located leucine-rich repeats (LRRs). The protein consists of 810 amino acids and shows a higher expression in the bone marrow than in peripheral blood. LRRC8 is expressed on a variety of tissues and cell types. The reported patient presented a chromosomal translocation t(9;20)(q33.2;q12) resulting in the deletion of the eighth, ninth and half of the seventh LLR domains located close to the C-terminal. The patients' parents showed no chromosomal abnormalities. The deletion in almost three LRRs in the C-terminal of the protein, led to the expression of two isoforms, wild type and mutant, in the patient. Experiments with retroviral overexpression of wild type and mutant LRRC8 in mice showed that LRRC8 plays an important role in the early stages of B cell development, especially at the pro-B to pre-B transition, explaining therefore the causative link between mutations in LRRC8 and the agammaglobulinemia found in the patient. The wide expression of LRRC8 in diverse tissues such as brain, heart, liver, kidney, may explain, at least partially, the dysmorphic features described in the reported female patient [351].

Good's syndrome is a rare condition and is typically diagnosed after the fourth decade. The pathogenesis of Good's syndrome remains unclear, although some hypotheses have been proposed. Bone marrow stromal stem cells have been suggested to secrete interferon-like cytokines which alter the growth and differentiation of B cell and thymocyte precursors [232, 397]. Further, autoantibodies or activated T-cells have been proposed to inhibit the production of immunoglobulins by B cells through a similar mechanism to that found in paraneoplastic syndromes associated with thymoma [187, 203]. The decrease in CD8 or CD4 memory T-cells may explain the increased susceptibility to viral infections and predisposition to tumours as described by some authors [155, 214, 215].

It is generally accepted that MDS arise from a hematopoietic stem cell harboring irreversible DNA damage. Despite a plethora of demonstrable progenitor cell anomalies, a definitive, archetypal molecular aberration in MDS clonal hematopoietors, remains elusive. Mutational activity of oncogenes, genetic or epigenetic tumor suppressor gene inactivation, defective ribososmal biogenesis and aberrant cytokine signaling in hematopoietic and bone marrow stromal cells have all been well documented. The concept of an immune-mediated response against normal hematopoietic cells in MDS bone marrow has crystallized because hematopoietic cytopenias of these patients were associated with clinical autoimmune phenomena, T-cell mediated myelosuppression, and cytokine turmoil in bone marrow milieu [144, 161, 162, 176, 427].

3.4.3 Clinical Manifestations

Patients affected with TCF3 deficiency presented a clinical history suggestive of agammaglobulinemia: pneumococcal meningitis, recurrent otitis, vaccine-associated polyomyelitis and arthritis. Associated clinical features included eosinophilic dermatitis and hepatomegaly. Low peripheral B cells and severe hypogammaglobulinemia was observed in all patients [56].

The reported patient with mutations in LRRC8 is a female patient with agammaglobulinemia and 0.6 % of CD20+ B cells in the periphery. She presented with epicantic folds, mild hypertelorism, a high-arched palate and low set ears [351].

Good's syndrome is a rare condition and is diagnosed after the fourth decade [155, 187, 214, 282]. The clinical presentation consists of recurrent infections or it may be a casual finding of an anterior mediastinal mass (thymoma). The major immunological defects are hypogammaglobulinaemia, few or absent B cells, an abnormal

CD4/CD8 T-cell ratio and impaired T-cell mitogenic responses. Hematological disorders and associated autoimmune diseases are also common.

The clinical presentation of MDS is variable [53, 141, 144, 161, 162, 427]. Typically, affected patients present symptoms related to low red and/or white blood cell count such as: fatigue, shortness of breath, pale skin, weakness, malaise, unexplained bleeding, fever and infections that won't resolve. Serological immunological abnormalities like hyper- or hypogammaglobulinemia, positivities of antinuclear antibody, positivities of direct Coombs test, or inverted CD4/8 ratios are found in 18–65 % of patients with MDS. Furthermore, the presence of autoimmune manifestations is a recognized feature of MDS clinical spectrum, with an estimated incidence of 10 %. Such phenomena usually include acute systemic vasculitic syndromes, skin vasculitis with or without fever, arthritis, peripheral neuropathy, glomerulonephritis and relapsing polychondritis.

3.4.4 Diagnosis

The typical laboratory findings of autosomal recessive agammaglobulinemia consist of low to undetectable immunoglobulin serum levels and the almost complete absence of peripheral B cells (<1 %), reflecting the early block in B cell development [22, 100]. In the case of TCF3 deficiency, low peripheral B cells with the typical finding of enhanced CD19 expression in the absence of BCR expression on the cell surface, are rather suggestive. Bone marrow evaluation where available will show an earlier block at the pro-B cell stage. Genetic analysis of the TCF3 gene will lead to definite diagnosis. Regarding LRRC8, its involvement in the pathogenesis of agammaglobulinemia resulted from a chromosomal translocation involving part of the LRRC8 gene in a syndromic patient. The clinical suspicion of LRRC8 should therefore emerge in the case of syndromic patients with agammaglobulinemia and absent B cells. Cytogenetic studies aiming to identify the translocation involving the *LRRC8* gene followed by genetic studies of the gene encoding for LRRC8 will identify the exact genetic alteration.

Good's syndrome is typically diagnosed by means of CT scan showing an anterior mediastinal mass. Surgical removal and histologic analysis confirm the diagnosis. Immunological work-up of affected patients (immunoglobulin serum levels, lymphocyte subset characterization, proliferative responses to mitogens) allow defining the immunological defect in affected patients.

The diagnostic approach for myelodysplasia is based on complete differential blood cell count (CBC), peripheral blood smear and bone marrow aspirate/biopsy. Further investigations include cytogenetic studies on bone marrow aspirates.

3.4.5 Management

The introduction of antibiotics and immunoglobulin replacement therapy has completely changed the prognosis of agammaglobulinemic patients. Nowadays, the prompt use of antibiotics, regular replacement therapy and an early diagnosis can assure a longer life span with less complications. The clinical history of affected patients may include diverse complications such as chronic lung disease and malabsorption due to gastrointestinal infections. However, considered the limited number of patients affected with TCF3 and LRRC8 deficiency, and the limited follow-up period, it is not feasible, at least for the moment, to provide comparative data for known complications in XLA such as incidence of tumours, autoimmune phenomena and similar complications. Regarding Good's syndrome, treatment consists in immunoglobulin replacement therapy, control of infectious episodes, frequently opportunistic ones considering the associated T cell defect, and intense clinical follow-up. According to some reports, affected patients have a worse prognosis when compared with patients affected with

CVID. Myelodysplasia is an incurable disease with non-transplantation therapy, but highly variable in its natural history. Supportive treatments in case for hypogammaglobulinemia, lymphopenia, neutropenia or other cell type alterations follow the general guidelines applicable in such conditions. Treatment options are variable depending on stadiation, clinical features, genetic characterization and other parameters. The only curative approach is represented by stem cell transplantation, with known associated risks for the patients.

3.5 PI3KD Syndrome

3.5.1 Definition

Mutations in class I PI(3)K molecules have now been described to be responsible for primary immunodeficiency with variable clinical presentation ranging from agammaglobulinemia (p85α, p110δ) to hyper-IgM syndrome and combined immunodeficiency with bronchiectasis (p110δ).

3.5.2 Etiology

PI3Ks are a broadly expressed group of enzymes that respond to a variety of extracellular signals to influence cell cycle progression, cell growth and survival, cell migration and metabolic control. Multiple isoforms of PI3K have been described, all of which function as heterodimers. Class I PI(3)K molecules play an important role in cells of the immune system and are composed of a catalytic subunit p100 and a regulatory p85 subunit that regulates stability and activity of p110. The p110 subunit's expression is restricted to leucocytes. Upon cell activation, p85, that normally inhibits p110, releases p110 and allows for p110 to induce the generation of phosphatidylinositol-(3,4,5)-triphosphate (PtdIns(3,4,5)P3), leading to the recruitment of pleckstrin homology domain-containing signaling proteins to the plasma membrane. PtdIns(3,4,5)P3 generation leads also to increased phosphorylation of the AKT kinase and activation of the mTOR complex 1. The first patient reported to be mutated in one of the PI3K subunits carried a heterozygous mutation in p110δ (E1021K) and was affected with primary B cell deficiency [202]. No functional studies aimed to explain the pathogenic role of this mutation were performed at that time [202]. Recently, two independent groups [30, 252] reported on the identification of dominant-activating germline mutations in p110δ leading to combined immunodeficiency with lymphopenia, elevated IgM serum levels (most patients), altered T and B cell distribution, bronchiectasis, lymphoadenopathy and increased predisposition to lymphomagenesis. The most frequently reported mutation in p110δ is the E1021K [30, 252], while one patient was reported to carry the heterozygous mutations N334K, seven patients were reported to carry the heterozygous E525K in p110d [252] and two patients were reported to carry the C416R mutation [105]. While the presence of these heterozygous mutations did not alter the protein expression of p110δ, Akt phosphorylation was increased upon activation when compared to wild type healthy controls. T cell senescence was observed in affected patients with reduction of the naïve T cell subsets and expansion of the later subsets such as T cell effector memory. The reported mutations lead to hyperactivation of the PI(3)K-Akt-mTOR pathway which results in enhanced glycolysis (normally controlled by mTOR), explaining therefore the T cell senescence observed. Increased susceptibility to activation induced cell death (AICD) further explains the T cell lymphopenia observed in affected patients [30]. On the other hand, almost all reported patients share the lack of switched memory B cells and the prevalence of naïve/transitional B cells. Experimental data demonstrated that B cells were able to secrete IgM *in vitro*, but were defective in class switching, confirming the immunological phenotype of affected patients. Inhibition of the PI(3)K-Akt-mTOR cascade either with p110δ inhibitors such as GS-1101 or

mTOR inhibitors (rapamycin) resulted in partial recovery of the observed T cell alterations.

Regarding the regulatory subunit, p85a, the first case of p85α deficiency was recently reported. The single reported patient, identified by whole exome sequencing, harbored a homozygous nonsense mutation leading to the substitution of a tryptophan with a premature stop codon in exon 6 of p85α [101]. This mutation led to the abrogation of p85α expression in patient's T cells, neutrophils or dendritic cells. The amount of p50α (an alternative product of the gene encoding for p85α) was normal/slightly increased in T cells, normal in dendritic cells and reduced in neutrophils. Expression levels of p110δ were decreased in patient's T cells, neutrophils and dendritic cells. A B cell defect similar to that seen in Btk deficient mice was observed in mice that are deficient in the p85α or p110δ subunit of class I PI3K. The reported patient's bone marrow analysis revealed an earlier block in B cell development than that observed in other forms of agammaglobulinemia due to mutations in btk or components of the pre-BCR and the presence of minimal VDJ rearrangement. Surprisingly, although PI3K is widely expressed, the immunological phenotype of the patient is restricted to the B cell compartment with minor additional alterations in PI3K deficient DC responses to LPS stimulation [101]. T cells did not exhibit any alterations in terms of maturation or activation.

3.5.3 Clinical Manifestations

The clinical phenotype of dominant-activating p110δ mutations is complex. Typically, affected patients present an early onset of disease, characterized by recurrent upper and lower respiratory tract infections. Initial immunological work-up shows elevated IgM serum levels while IgG and IgA levels may be normal, elevated or low. Reduction of naïve T cell subsets, expansion of terminally differentiated T cells (such as effector memory CD8 T cells), reduction of switched memory B cells and expansion of naïve and transitional B cells, are immunological hallmarks of the disease [30, 252]. Even upon replacement therapy, affected patients continue to present recurrent respiratory infections leading to the development of bronchiectasis. Affected patients present lymphadenopathy and splenomegaly. Infections by herpes group viruses such as CMV, EBV HASV and VZV, are typical for almost all reported patients. The underlying pathogenic mechanisms render patients' CD8 T cells incapable of eliminating chronic viral infections. Formation of abscesses is also frequent among affected patients, mainly involving skin and glands. A single patient with the E1021K mutation presented with the immunological phenotype of agammaglobulinemia, although clinical details are not available [202]. Finally, patients with p110d mutations present an increased frequency of B cell lymphomas of different types [105, 227]. Regarding p85α deficiency, the single female patient reported, born to consanguineous parents, was evaluated at the age of 3.5 months for neutropenia, interstitial pneumonia and gastroenteritis [101]. Her initial immunological work-up showed lack of peripheral B cells (<1 %) and agammaglobulinemia. She was put on immunoglobulin replacement therapy with progressive resolution of the neutropenia and the clinical manifestations. However, her clinical history resulted rather complicated. At the age of 12 she developed erythema nodosum. At the age of 15, she was treated with TNF antagonists and methotrexate for juvenile idiopathic arthritis. At 17 years of age, the patient was diagnosed with Campylobacter bacteremia and inflammatory bowel disease. No alteration in growth or insulin metabolism was noted, even though the mutated gene is involved in cell growth and metabolic control.

3.5.4 Diagnosis

The laboratory findings for patients affected with p110δ mutations may vary including elevated IgM, variable IgG and IgA serum levels, reduced naïve T cells, expansion of terminally differentiated T cells, reduced switched memory B cells and expansion of naïve and transitional B cells.

Typically affected patients present with lymphopenia. Additional clinical features such as chronic viral infections (CMV, EBV, VZV), lymphadenopathy and bronchiectasis may be of help in the diagnostic process. Definite diagnosis can however only be achieved through genetic analysis of the gene encoding for p110δ.

Regarding p85α deficiency, the typical laboratory findings of AR-Agammaglobulinemia consist in low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells, as defined by CD19 and CD20 expression (<2 %), reflecting the early block in B cell development [22, 101]. When *BTK* mutation analysis results negative and/or when female patients are identified, and sequencing analysis of the other known genes (heavy chain, Igα, Igβ, λ5, BLNK) results negative, p85α genetic analysis should be undertaken.

3.5.5 Management

The limited number of patients affected with p110δ mutations does not offer yet sufficient information on the natural history of this disorder. Clinical management of affected patients may include immunoglobulin replacement therapy, respiratory physiotherapy (due to bronchiectasis) and antibiotic prophylaxis (considering the lymphopenia). The experimental data so far published suggest that specific p110δ inhibitors such as GS-1101 or mTOR inhibitors (rapamycin) may be of help in this disorder since they allow partial T cell recovery in vitro. One patient was treated with rapamycin in vivo with reduction of lymphadenopathy and significant clinical benefits [252]. In addition, one patient underwent HSCT due to severe disease with good clinical response [30, 417]; HSCT may therefore be a long term treatment option for young patients. The high risk of B cell lymphomas in patients with p110δ mutations should always be taken into consideration during clinical management [105, 227].

Regarding p85α deficiency, as in other forms of AR-agammaglobulinemia, treatment consists of immunoglobulin replacement therapy using either the intravenous or the subcutaneous route. Antibiotic treatment is mandatory in case of infectious episodes and frequently prolonged periods of treatment are required. Not enough data on long-term follow-up are available to better define complications.

3.6 Common Variable Immunodeficiency

3.6.1 Definition

Hypogammaglobulinemia with normal or low number of B-cells is the prototype of common variable immunodeficiency (CVID). CVID (OMIM*240500) is a heterogeneous group of disorders characterized by hypogammaglobulinemia, defective specific antibody production and an increased susceptibility to recurrent and chronic infections [12, 110]. Patients with CVID also have an increased incidence of autoimmunity, lymphoproliferative disorders and cancers [116, 220].

CVID affects males and females equally. It has an estimated prevalence ranging from 1:10,000 to 1:50,000 [121, 151, 177] and is the most prevalent human PIDs requiring medical attention. The clinical spectrum of CVID is broad, and it may present at any age, but peaks of presentation is in childhood and early adult life have been noted [253, 292] with an average delay of 4–6 years between the onset of symptoms and diagnosis [12, 109, 110].

In spite of several years of investigation into the nature of this defect since it was first recognized in 1953 [198], the basic molecular defect in CVID is still unknown. As there is no single diagnostic immunological or genetic test for CVID, its diagnosis requires a decrease of immunoglobulins of at least two isotypes (serum IgG, IgA, and/or IgM) reduced by two or more standard deviations from the normal mean and genetic exclusion of other antibody deficiencies associated with well-defined single gene defects [12, 110].

3.6.2 Etiology

Genetics Although the most CVID cases are sporadic, it has been estimated that 10–20 % of the cases are familial presenting in childhood, in which 80 % present with autosomal dominant inheritance presenting in adulthood [34, 177, 288]. In multiple-case families, CVID is often present in one parent, accompanied by IgA deficiency (IgAD) in the descendants [425] and it has been estimated that about 15 % of the patients with CVID have a first degree relative with either IgAD or CVID [80, 426]. Some cases of IgAD, who progress to CVID, have also been reported [370]. All these data support the involvement of hereditary factors and a genetic association between CVID and IgAD, suggesting that the two disorders may represent an allelic condition reflecting a variable expression of a common defect.

In order to identify the genes responsible for CVID, several HLA association studies, as well as linkage analyses, have focused on the HLA region on chromosome 6 [106, 126, 229, 300, 355, 359, 370, 424]. Genetic linkage analysis of families with IgAD and CVID has identified the presence of susceptibility loci near the class II and III MHC regions. The DR/DQ locus has been reported to be the strongest predisposing locus. MHC class II genes play a fundamental role in antigen presentation to T helper cells that in turn provide help to B cells for a proficient Ig production. Therefore, particular MHC class II alleles might contribute to the Ig deficiency and to the associated autoimmune manifestations.

The HLA class III region genes encode components of the complement system and cytokines involved in inflammation, such as tumor necrosis factor (TNF)-α and -β. There is also evidence that IgAD and CVID share susceptibility loci at 4p, 5p, 12p and 14q [67, 229, 424].

Attempts to identify the genes responsible for CVID have resulted in finding new monogenic defects during the past few years, including mutations in Inducible costimulator (*ICOS*, OMIM*604558) causing ICOS deficiency (OMIM*607594) [166, 345], CD19 (OMIM*613493) [353, 413], CD21 (OMIM*120650) [400], CD81 (OMIM*186845) [414], CD20 (OMIM*613495) [231], lipopolysaccharide-responsive, beige-like anchor protein or LRBA (OMIM*606453) [251], TWEAK (OMIM*602695) [429], NFkB (OMIM*615578) [95] and PRKCD (OMIM*615559) [344]; however, these genes account for less than 3 % of patients with CVID [346].

These new monogenic defects which share clinical phenotypes of CVID actually represent a different entity and may occasionally be misdiagnosed as CVID. In addition, alterations in Tumor necrosis factor receptor superfamily member 13b (*TNFRSF13B* or *TACI*, OMIM*604907), Tumor necrosis factor receptor superfamily member 13c (*TNFRSF13C* or *BAFFR*, OMIM*606269) and MutS, the *E. coli*, homolog of, 5 (MSH5*603382) sequences may represent disease-modifying alterations [160].

B cell development and differentiation is critically dependent upon signal transduction through the B cell antigen receptor (BCR). Co-receptors associated with the BCR can modulate BCR signal transduction positively or negatively. Mutations in CD19 lead to relatively normal B cell development but the lack of CD19 signal transduction results in a poor response to antigenic stimuli and an inability to mount an effective humoral response.

There are also other diseases which may present with hypogammaglobulinemia: X-Linked Lymphoproliferative syndrome 1 (OMIM*308240), which is characterized by fulminant infectious mononucleosis, dysgammaglobulinemia and lymphoma, and is caused by mutations in SH2 domain protein 1A *SH2D1A* gene (OMIM*300490). *(See* Sect. 5.4 *for more details)*

Hepatic veno-oclussive disease with immunodeficiency syndrome (OMIM*235550), which is characterized by severe hypogammaglobulinemia, combined T- and B-cell immunodeficiency, absent lymph node germinal centers and tissue plasma cells and hepatic veno-occlusive disease, is caused by mutations in the Nuclear body protein sp110 (*SP110*, OMIM*604457) gene. *(See* Sect. 9.19 *for more details)*

Disturbances in B-cells There is no definite explanation for the molecular basis of CVID. Based on current knowledge, the core defect is in late B cell differentiation, although the nature is unknown. Other components of the immune system such as T cells or dendritic cells could also be involved.

Although most CVID patients have normal numbers of B cells, their B cells fail to differentiate into immunoglobulin-secreting plasma cells. Consequently, CVID patients have reduced levels of serum immunoglobulin, isohemagglutinins and respond abnormally to immunization with protein and polysaccharide antigens.

The level of IgG at time of diagnosis shows a direct association with switched memory B cell, and autoimmune cytopenia and a reverse association with chronic lung disease and efficiency of therapy [94, 330]. Patients with decreased level of antibodies also suffer from pulmonary complications especially bronchiectasis, whereas those with an increased level of serum IgA mainly suffer from infections only [205, 324]. Lymphoproliferation, reduced survival, and lymphoid malignancy are also observed a higher frequency in patients with increased IgM. Elevated serum levels of BAFFR and APRIL have been documented in CVID cases with Polyclonal lymphocytic infiltration and autoimmunity [220].

Moreover, evaluation of the total count of B cells (correlating with increased pulmonary morbidity and mortality), IgD-IgM-CD27+ switched memory B cells, $Tr^{hi}CD38^{hi}IgM^{hi}$ transitional B cells and CD21 low B cells (linked to lymphoproliferative disorders) are in line with the clinical manifestation of CVID patients [94, 438].

However, some CVID patients can produce normal post-vaccination titers of antibodies [334, 335]. B cell activation and differentiation depend on the interaction between populations of T cells and B cells. Inadequate help from HLA class-II-restricted CD4+ T cells in T cell- dependent B cell responses can be the reason for the low serum immunoglobulin concentration of switched immunoglobulin isotypes and impaired specific-antibody production in patients with CVID [50].

The reduced number of switched CD27+ memory B cells in CVID patients has been considered as a basis for sub classification of CVID [9, 69, 317, 420, 434]. Based on this classification, CVID patients with more than 0.4 % of class switched memory B cells (group II) are potentially able to respond to immunization with a polyvalent pneumococcal polysaccharide vaccine [221]. Furthermore, the severe reduction of class switched memory B cells in the peripheral blood is an indicator of a disturbed germinal center reaction in CVID [165].

Ig CSR deficiencies seem to be closely related to CVID, as they also lack switched isotypes, which is one of the clinical hallmarks of CVID. Many patients diagnosed with Ig CSR deficiencies have serum IgM levels in the normal range for their age, making it difficult to distinguish them from patients with CVID. For a diagnosis of CVID, selected molecular genetic defects should be ruled out in patients who meet the diagnostic criteria for CVID, whenever possible [5, 343].

The severe decline in the production of high affinity antibodies, due to a failure in somatic hypermutation (SHM), is another sign of impaired terminal B cell differentiation in CVID patients [58]. Impaired SHM has been detected in 77 % of patients with CVID who are susceptible to frequent severe respiratory-tract infections [29]. In addition, light-chain mutation levels are directly related to the percentage of memory B cells in CVID patients [49, 165] and may be considered as a prognostic factor for respiratory complications.

Recently, two TNF family members, B-cell activating factor of the TNF family (BAFF) and a proliferation inducing ligand (APRIL), were identified on the surface of antigen presenting cells (APC). APRIL and BAFF both bind to receptors of the TNF-R family, called B-cell maturation antigen (BCMA) and TACI [254]. Interaction between APRIL and BAFF with their receptors induces isotope switching in naive human B cells which is a mechanism independent of formal T cell regulated isotype switching [91]. A third receptor, BAFF-R, unique for BAFF, is expressed on B cells but also on resting T cells [255]. Although BAFF enhances B-cell survival [167, 356], APRIL has no detectable effect on

B-cell survival and is known mainly as an oncogenic factor, with expression in different tumor lines [130].

Disturbances in T-cells Approximately half of the patients with CVID may have reduced T-cell numbers and diminished lymphocyte proliferative responses to mitogens and antigens. Several defects have been demonstrated in the T-cell function of CVID patients. Of all patients with CVID, 25–30% have increased numbers of CD8+ T cells and a reduced CD4/CD8 ratio (<1). This subtype of patients often has splenomegaly and autoimmune manifestation [188]. Two studies evaluating thymopoiesis have yielded different results [129, 193]. One group found a significantly increased level of T-cell receptor excision circles (TRECs) as a marker for increased thymopoiesis [129], while the other group showed a decrease in thymopoiesis, subsequent to a reduction of CD31+ recent thymic emigrants [193]. Over 70% of CVID patients have decreased numbers of CD4+ T cells, suggesting a decreased thymopoiesis and the difference between the above studies could potentially be explained by the heterogeneous character of the patient populations [165].

Alteration in the production of IL-7 has been investigated in different studies [188, 193]. Isgro et al. demonstrated that a possible pro-inflammatory cytokine state (low level of IL-7) impairs growth and differentiation of several CFC progenitors in the bone marrow of the patients [193]. In contrast, Holm et al. showed an elevated plasma level of circulating IL-7 in a subgroup of CVID [188]. These patients show increased numbers of circulating CD8+ T cells with decreased rate of apoptosis and a predominance of (CCR7−) effector-memory T cells [49, 189]. It was also suggested that a relative deficiency of transforming growth factor (TGF)-1, as a regulator of IL-7 secretion by bone-marrow stromal cells, could be a reason for the high IL-7 level in this subgroup of patients [49]. Defects in IL-7 synthesis in a subgroup of patients with CVID suffering from splenomegaly, autoimmune disorders and an increase in circulating CD8+lymphocytes have also been described [188].

In addition, based on an in vitro study, increased expression of interleukin-12R and interleukin-18R was noted in a subset of patients with CVID [268]. Collectively, these findings favor the hypothesis of a Th1 immune response polarization in CVID patients [49]. Decreased expression of the co-stimulatory molecules and defects in IL-12 production, result in reduction of T-cell activation and proliferation and this may be due to the association of CVID with specific HLA alleles [49]. Although in some cases of CVID, alterations in the production of IL-12 [114, 259] have been reported, no notable Th2>Th1 shift has been verified [165].

Considering the T cell receptor signaling pathways, failure to recruit ZAP70 [57] and/or reduced Vav expression [169] have been demonstrated in a subgroup of patients with impaired proliferative T cell responses. However, as no mutation in the Vav gene or its promoter has been shown, it remains obscure whether the defective expression of Vav results in an impaired recruitment of ZAP70 or whether both are subsequent to another defect upstream [165].

Cellular immunity biomarkers also correlate with clinical consequence of CVID including naive CD4+ T cells (diminished in cases with autoimmune cytopenia and lymphoproliferation) [163, 302] and regulatory T cells (reduced in autoimmunity and granulomas) [31, 271].

Disturbances in NK-cells The NK gene complex, essential for NK-cell function is located on the short arm of chromosome 12. According to linkage studies, this locus may be one of the major non-HLA susceptibility loci for CVID [67]. This finding may be interesting, as decreased absolute numbers of peripheral blood NK cells have been observed in a subgroup of CVID patients [35].

Disturbances in the innate immune system Some studies have demonstrated abnormalities in the innate immune system including dendritic cells (DC), in CVID [28, 50, 82, 114, 293, 294, 362]. However, these abnormalities may involve some, but not all, CVID patients. Most of the described abnormalities in dendritic cells are related to the

monocyte derived DC [50, 362]. DCs have a well-known role in both innate and adaptive immunity in initiation and persistence of the primary immune response. Thus, a failure of DCs to mature into fully stimulatory cells might be an explanation for the failure to support antigen-specific immune responses in CVID [49].

Recently, it has been realized that CVID patients have broad TLR9 activation defects, which would prevent CpG-DNA-initiated innate immune responses. These defects may lead to impaired responses of plasmacytoid dendritic cells and loss of B cell function [115]. Involvement of Toll-like receptor pathways in the pathogenesis of CVID is supported by the fact that genetic defects in TLR signaling are associated with impaired antibody responses and an increased susceptibility to bacterial infections [123, 316].

3.6.3 Clinical Manifestations

The main clinical symptoms associated with CVID patients are recurrent infections, autoimmune manifestations, lymphoproliferation, lymphoma and other selected cancers. The age at onset of symptoms is variable, ranging from childhood to late adult life, with some evidence of a bimodal distribution [12, 110]. In contrast to patients with XLA, patients with CVID have normal sized or enlarged tonsils and lymph nodes and approximately 25 % of patients have splenomegaly [188].

Four distinct clinical phenotypes have been described for categorizing patients which can assist the prognosis of disorder including infections only, cytopenias, lymphoproliferation, and enteropathy [47, 93].

Acute sino-pulmonary infections Almost all patients with CVID have a history of acute, chronic, or recurrent infections; particularly pneumonia, sinusitis, and otitis mainly by encapsulated bacteria [12, 110, 184]. Approximately 89 % of patients with CVID have had at least one episode of chronic sinusitis and 70 % have had recurrent otitis media before diagnosis [14, 260]. Between 75 and 84 % of CVID patients have experienced at least one episode of pneumonia before diagnosis and many have suffered multiple episodes [81, 320, 388].

Chronic pulmonary disease Bronchiectasis, an irreversible lung complication, has been reported in 37.5–73 % of CVID patients [204, 310, 398]. It has been documented that a subgroup of CVID patients who have low numbers of IgM memory B cells and reduced levels of anti-pneumococcal polysaccharide IgM antibodies are at an increased risk of developing recurrent bacterial pneumonia and bronchiectasis [85, 420]. Measurement of these parameters may guide the physician and result in a more aggressive treatment in patients susceptible to infections and lung disease.

Asthma is an obstructive lung complication, which has been observed in 9–15 % of patients with CVID [284]. The etiology of asthma in patients with CVID is unknown.

Non-caseating, granulomatous infiltrations have been reported in 5.4–22 % of patients with CVID [150, 269]. These lesions are not clearly distinguishable from sarcoidosis. Non-caseating granulomas are occasionally also found in lymphoid tissues or the liver [269].

Lymphoid interstitial pneumonitis (LIP) may also develop in the airways of patients with CVID [76, 122]. LIP can be suspected based on findings on high resolution CT (HRCT) scans. Presence of granulomatous lung disease and lymphoid interstitial pneumonia are associated with a worse prognosis and a higher rate of lymphoproliferative disease [48, 225].

Gastrointestinal disease There is a high prevalence of inflammatory and infectious gastrointestinal disorders in patients with CVID [436]. Mild, watery diarrhea is common and occurs periodically in about 20 % of patients, with 10 % having a more severe enteropathy resulting in malabsorption and weight loss [392]. Gastrointestinal pathology in these patients includes nodular lymphoid hyperplasia, inflammatory bowel disease (ulcerative colitis, ulcerative proctitis, or Crohn's disease), sprue-like illness with flat villi, giardiasis and nonspecific malabsorption. Defects in cellular immunity, rather than antibody deficiency

alone, appear to predispose patients to such symptoms [436]. *Helicobacter pylori* is an important pathogen in CVID resulting in chronic active gastritis involving both the antrum and corpus [455].

Approximately 10 % of CVID patients have significant liver dysfunction, with hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous disease.

Autoimmune diseases Approximately 20–25 % of subjects with CVID have, at the time of diagnosis or later, developed one or more autoimmune conditions such as autoimmune cytopenia, rheumatoid arthritis, or pernicious anemia [38, 113, 184].

The mechanism underlying the increased susceptibility to autoimmunity in CVID patients is unknown. Most CVID patients with idiopathic thrombocytopenia purpura (ITP) or autoimmune hemolytic anemia (AIHA) have been successfully treated with infusions of high doses of intravenous immunoglobulin (IVIG), coupled with a short course of corticosteroids. However, due to a higher incidence of medical complications associated with use of immunosuppressive treatment in patients with CVID, this type of therapy should be used with caution [110].

Lymphoma and cancers Individuals with CVID are susceptible to malignancy, particularly lymphoma. The incidence of malignancy is increased (11–13 %) in CVID patients during the fifth and sixth decades of life [184]. The majority of these malignancies involve the gastrointestinal tract and the lymphoid tissues [113, 156, 217, 222, 270, 347]. Patients with lymphoma usually have a childhood onset, while those with gastric cancer were in their fourth decade of life when the cancer was diagnosed [4].

An association between Non-Hodgkin Lymphoma (NHL) and congenital immunodeficiency is well established and most of the NHL cases associated with immunodeficiency appear in patients with T cell defects. In a survey of malignancy in CVID patients, a 438-fold increased likelihood of developing NHL was reported for females compared to the age-adjusted expected incidence [116]. A 1.8 to 5-fold increase in all types of cancers has also been described in CVID patients [217, 270] including a 47-fold increase for stomach cancer and a 30-fold increase for lymphoma [217]. Benign manifestations, including nodular lymphoid hyperplasia, splenomegaly and generalized lymphadenopathy, have also been reported [217, 222].

Mucosa-associated lymphoid tissue (MALT) lymphoma, which represents a subset of low-grade B-cell non-Hodgkin lymphomas, is a rare lung complication in CVID patients [19, 329].

Selected CVID patients show evidence of radiosensitivity [18]. Unnecessary radiographic diagnostic tests should thus be avoided or replaced by alternative tests, and minimum radiation doses should be ensured in all cases. There is also controversy surrounding the use of radiotherapy in CVID patients with cancer. The toxic effects of radiation in CVID patients, however, are dose-dependent and it would be interesting to establish a threshold for radiation-induced aberrations in CVID patients as this would help to ensure the use of safe doses for diagnostic and therapeutic procedures [4].

3.6.4 Diagnosis

The most important laboratory criterion for establishing the diagnosis of CVID (International Classification of Diseases 10: D83) is a low serum IgG concentration, ranging from profoundly reduced (<100 mg/dL) to just 2 SDs below the normal values for age [2, 103]. Most patients have low levels of IgA, and approximately half show reduced IgM levels.

Isohemagglutinins are naturally occurring IgM antibodies against the ABO blood group antigens. By 1 year of age, 70 % of infants have positive isohemagglutinin titers, depending, on their blood group. The measurement of specific antibodies after immunization with protein (tetanus, diphtheria) and polysaccharide (pneumococcal vaccines) antigens is important to evaluate the ability of patients to produce specific antibodies. Documenting impaired production of specific

antibodies (isohemagglutinins and/or poor responses to one or more vaccines) is thus potentially valuable for the diagnosis of CVID.

Flow cytometry is important in evaluating numbers of peripheral B cells in patients with profound hypogammaglobulinemia. Numbers of B cells in the peripheral blood may be normal or reduced and approximately 13 % of patients will have a B-cell count of less than 3 % in peripheral blood [110].

Patients with a definite diagnosis of CVID should be more than 4 years of age (excluding transient hypogammaglobulinemia of infancy) and should present clinical symptoms directly attributable to immune dysfunction [363].

Many disorders with hypogammaglobulinemia present with recurrent bacterial infections. As there is no single diagnostic immunological or genetic test for CVID, it is important that patients are investigated to exclude other well-defined causes of hypogammaglobulinemia. Secondary causes of hypogammaglobulinemia should be ruled out including medication, protein loss, B cell lymphomas and bone marrow failure.

In male CVID patients, X-linked agammaglobulinemia (XLA), X-linked lymphoproliferative (XLP) syndrome and X-linked immunoglobulin class switch recombination (CSR) deficiency should be excluded [13, 209]. The onset of XLA and XLP is usually shortly after birth, whereas CVID is most often manifested after the age of 2. XLA can be distinguished from CVID by agammaglobulinemia and the nearly complete lack of B cells (<1 % of lymphocytes). Patients with less than 2 % B cells (CD19+) will need further molecular evaluation for XLA, or abnormalities in the pre-B-cell receptor complex (resulting in autosomal recessive agammaglobulinemia). XLP can be distinguished from CVID by a very low number of natural killer T-cells [311] and a history of EBV infections.

Although there is no screening test for CVID, evaluation of calculated globulin during liver function testing using the bromocresol green methodology (a cutoff value of <18 g/L) were explained recently[201].

3.6.5 Management

The mainstay of treatment for CVID is immunoglobulin replacement therapy [79, 297, 303]. Intravenous (IVIG) [303] or subcutaneous (SCIG) [152, 298] immunoglobulin prophylaxis can be used on a regular basis to maintain a trough level of at least 400–500 mg/dL. A dose of 400–600 mg/kg every 3–4 weeks is usually required. It has been shown that doses of 600 mg/kg every 4 weeks achieved serum IgG trough levels of greater than 500 mg/dL [338]. In patients with lung damage, a trough level of 700–800 mg/dL is required. Higher doses of immunoglobulin may be necessary for patients with severe chronic sino-pulmonary infections and to prevent bronchiectasis [322]. Trough levels should be measured periodically and the dose adjusted, as endogenous production or clearance of immunoglobulin in individuals may change over time.

Adverse reactions to immunoglobulin administration should be monitored during therapy. The most common reactions include backache, nausea, vomiting, chills, low-grade fever, myalgias and fatigue. Adverse effects occur within 30 min of the infusion and usually last for several hours. Slowing the rate of infusion or interrupting the infusion for a few minutes helps in preventing symptoms. These reactions may be minimized by pre-medication with anti-inflammatory drugs including corticosteroids.

In addition to use of the IVIG or SCIG, other forms of supportive care, such use of prophylactic antibiotics are important as bacterial infections may become chronic even with appropriate immunoglobulin replacement [81, 110].

Long-term antibiotic therapy may be added to immunoglobulin replacement therapy. There are no controlled studies that compare the effectiveness of any regimen of antibiotic prophylaxis in patients with established immunodeficiency. Regimens derived from studies of preventing otitis media in children include: sulfisoxazole 50 mg/kg daily; amoxicillin 20 mg/kg daily or divided bid; trimethoprim-sulfamethoxazole 3–5 mg/kg as trimethoprim once daily or divided into twice-daily dosages; and azithromycin, 10 mg/kg weekly [119, 124, 396].

Table 3.1 Abstracted guideline for management of common variable immunodeficiency complications

Type of clinical Complication	Prevention	Screening	Treatment
Infectious	Ig replacement; prophylactic antibiotics; vaccination	Patients' awareness; sputum monitoring; routine visits	High dose Ig; therapeutic antibiotics
Pulmonary	Control of infection; high dose Ig	Spirometry; HRCT; routine visits	Endoscopic sinus surgery; inhaled corticosteroids; anti-inflammatory antibiotics; IL-2 therapy; B2 agonists; leukotriene receptor antagonists; lung transplantation
Lymphoproliferative		Lymph nodes biopsy; spirometry; imaging; routine visits	Systemic corticosteroids; hydroxychloroquine; immunosuppressive agents
Autoimmune	Ig replacement?	CBC, diff, PBS; thyroid examination and thyroid function; routine visits	Corticosteroids; anti-CD20 monoclonal antibodies; TNF-α Inhibitors
Gastrointestinal	Control of infection, autoimmunity and lymphoproliferative complications	Upper and/or lower endoscopy and yearly ultrasonography; routine visits	Immunomodulators; TNF-α inhibitors
Neoplasia	*Helicobacter pylori* eradication; decreasing unnecessary irradiation	Routine cancer screening; screening by endoscopy; bone marrow examinations	Routine chemotherapy; rituximab protocols; surgical modalities; allogeneic stem cell transplantation

Adapted from Salehi Sadaghiani et al. [342]
CBC complete blood count, diff differentiation of cell blood count, HRCT high-resolution computed tomography, Ig immunoglobulin, *PBS* peripheral blood smear

The prognosis for patients with CVID depends on the frequency of infections, structural lung damage and concomitant presence of autoimmune disease. Other major factors in determining the prognosis is the extent of end-organ damage and the success of prophylaxis against infections. Patients and their families should thus be educated about early signs of infection in order not to delay treatment. Prevention, screening and treatment of different CVID complications were given in Table 3.1 [342].

3.7 LRBA Deficiency

3.7.1 Definition

Childhood onset hypogammaglobulinemia, caused by homozygous mutations in *LRBA* gene (OMIM*606453) (lipopolysaccharide-responsive, beige-like anchor protein) with autosomal recessive inheritance have recently been described. LRBA deficiency (OMIM*614700) is characterized by impaired antibody production, infections, autoimmunity and immune dysregulation. Affected patients show an early-childhood onset of recurrent infections, particularly respiratory infections, variable autoimmune disorders, including ITP, AIHA as well as gastrointestinal symptoms, including IBD.

3.7.2 Etiology

The *LRBA* gene is located on the long arm of chromosome 4 at 4q31.3. In humans, it encodes the lipopolysaccharide-responsive and beige-like anchor protein, which is a protein involved in autophagy or self-digestion, leading to deficient antigen presentation [3]. *LRBA* interacts with the

signaling enzymes (PKA and PKC) with an A-kinase anchoring protein (AKAP) motif to compartmentalize these signaling molecules in organelles and membranes [3]. It has been suggested that *LRBA* plays a role in apoptosis, and increased apoptosis has been observed in LRBA-deficient EBV-immortalized B-cell lines [139]. Phosphorylation of BAD, a key apoptosis regulator, is diminished in LRBA-deficient cells [3]. Reduced areas of autophagy in the Golgi apparatus and accumulation of autophagosomes have been observed in response to cellular stress, raising the hypothesis that antibody producing plasma cells are undergoing apoptosis in LRBA deficient patients [312].

Moreover, it has been proposed that there is an autophagy-dependent regulation of the mucosal tissues which could explain the gastrointestinal manifestations in LRBA deficient patients [243].

3.7.3 Clinical Manifestations

The clinical manifestations are not well known but recently 13 autosomal recessive LRBA-deficient patients with childhood-onset humoral immune deficiency (ranging from IgA deficiency to total hypogammaglobulinemia) have been diagnosed [3, 23].

Autoimmunity (especially ITP), bronchiectasis due to lymphoid interstitial pneumonia, chronic inflammatory bowel disease, growth retardation, and CNS granuloma formation are other associated complications in this disease and all patients with LRBA deficiency have shown reduced counts of switched memory B cells.

3.7.4 Diagnosis

The laboratory findings of LRBA deficiency include hypogammaglobulinemia (low serum IgG and IgA and normal or reduced IgM level) and normal number of B cells in peripheral blood.

Flow cytometry has shown reduced counts of switched memory B cells. Once the clinical suspicion is supported by laboratory findings, molecular analysis of the *LRBA* gene should be performed in order to identify the mutation.

3.7.5 Management

Similar to CVID, the mainstay of treatment for patients with LRBA deficiency is immunoglobulin replacement therapy. Intravenous or subcutaneous immunoglobulin prophylaxis can be used on a regular basis to maintain plasma levels at trough level of at least 500–600 mg/dL.

3.8 CD19 Complex Deficiencies

(CD19 deficiency, CD21 deficiency, CD81 deficiency)

3.8.1 Definition

During last two decades, multiple genetic defects have been found, resulting in different antibody deficiency syndromes [6]. One group encompassed genes of the CD19 complex, which encode B cell surface proteins, including CD19, CD21, CD81 (TAPA-1), and CD225 [66, 261]. This complex functions as a B cell co-receptor to reduce threshold for B cell antigen receptor (BCR) activation following antigen binding [86, 262]. Different components of this complex are involved in B cell development and differentiation as well as in innate and adaptive immune responses [153]. To date, humoral immunodeficiencies due to genetic defects in 3 out of the 4 components of CD19 complex have been reported in humans [33, 207, 400, 412–415]. Whereas CD19 and CD21 are specifically expressed on B cells, CD81 and CD225 are widely expressed on immune cells (T, B, and NK lymphocytes, monocytes, and eosinophils), hepatocytes and most stromal and epithelial cells [419].

3.8.2 Etiology

CD19, a member of the Ig family, is encoded by the *CD19* gene (OMIM*107265), which is located on 16p11.2 [128]. This B cell surface protein is involved in B cell development, differentiation and activation. As a part of the CD19 complex, it functions in reducing the activation

threshold of the B cell receptor as well as in immune responses [128, 153]. Furthermore, CD19 appears to influence the differentiation of the B1 B-cell subset. CD19-deficient mice have decreased numbers of natural antibody-producing B1 B cells and are susceptible to infections with *Streptococcus pneumoniae* [173].

Different types of CD19 mutation are found to be responsible for CD19 deficiency. All of these deletions or insertions with subsequent frame shifting, create premature stop codons, leading to a truncated CD19 protein. Presumably, early degradation of the truncated CD19 protein leads to lack of CD19 expression, though the remaining truncated protein is likely to be non-functional.

CD21 is encoded by the *CD21* gene (OMIM*120650), located on 1q32 [6]. Heterozygous mutation in the *CD21* gene is responsible for a form of specific antibody deficiency. Substitution at the splice donor site of exon 6 in one allele (c.122511G>C) causes in-frame skipping of the exon. Whereas mutations at exon 13 (c.2297G>A) causes a frame shift, leading to a premature stop codon. These mutations lead to lack of CD21 expression which, together with a low frequency of memory B cells, is responsible for the hypogammaglobulinemia [400].

CD81, another component of the CD19 complex, is encoded by the *CD81* gene (OMIM*186845), located on 11p15.5 [6]. Studies using animal models have identified the role of CD81 in regulating CD19 expression [256, 279, 403]. In humans, a homozygous substitution mutation (c.561+1G>A), directly downstream of exon 6, disrupts the normal splice donor site with subsequent activation of a cryptic splice site. Alternative splicing of CD81 transcript creates a premature stop codon, presumably leading to truncated protein product. In the absence of the CD81 protein and in the context of normal CD19 alleles, CD19 protein products are sequestered within the ER/pre-Golgi and prevented from translocation to the cell membrane. The resulting $CD81^{-}CD19^{-}$ B cells fail to respond to BCR stimulation by antigens, leading to hypogammaglobulinemia [414]. The genetic pattern in CD19 complex deficiency is thus autosomal recessive.

3.8.3 Clinical Manifestations

The increased threshold of BCR activation and the decreased count of memory B cells lead to diminished antibody responses by B cells. The resulting hypogammaglobulinemia and defective vaccine-driven antibody production predisposes affected individuals to recurrent infections, mostly involving the upper respiratory tract, and gastrointestinal systems [33, 207, 413, 419]. Therefore, mutations in the CD19 complex cause CVID [413].

Patients with CD19 deficiency experience a late onset immunodeficiency, usually in the second decade of life, with autoimmune nephritis, marked decrement in CD19+ B lymphocytes, selective IgG1 deficiency, decreased IgM levels, autoimmune cytopenia, increased IgD-CD27- naïve B cells and a decreased frequency of CD5+ B and CD27+ memory B cells 1.

The only CD21 deficient patient described to date was a 6 year old boy, born to non-consanguineous parents, who was tonsillectomized due to episodic infections in the upper respiratory tract. Protected from infections up to 26 years of age, he subsequently developed persistent myalgias, fevers, sore throat, chronic diarrhea with weight loss, frequent infections in the respiratory tract and splenomegaly, leading to continuous administration of IVIG. Hypogammaglobulinemia, lack of IgG4, lower than normal levels of IgG1, and a very low frequency of $IgD^{-}CD27^{+}$ memory B cells was demonstrated. The patient was devoid of CD21 expression both on the B cell surface and intracellularly which was shown to be due to compound heterozygous mutations in *CD21* [400].

The CD81 deficiency patient showed progressive glomerulonephritis, a normal absolute B cell count and a lack of CD19+ B cells, decreased frequency of memory and transitional B lymphocytes and normal transcriptional levels of *CD19* [414].

3.8.4 Diagnosis

The clinical symptoms resemble CVID and include an increased susceptibility to recurrent infections, especially those caused by bacteria in

the respiratory and gastrointestinal tracts. In some cases, patients develop nephritis. Characteristic laboratory findings include hypogammaglobulinemia accompanied by decreased levels of IgA and/or IgM, and an absence of B cell responses to antigens. Flow-cytometric analyses show a decline in $CD19^+$ B cells as well as in $CD27^+$ memory and $CD5^+$ B lymphocytes. Following affirmative laboratory findings, *CD19* sequencing confirms the diagnosis. In the case of chromosomal deletions, fluorescence *in situ* hybridization analysis may verify this [33, 207, 413, 419].

The flow-cytometric analyses of the patient with CD21 deficiency revealed a lack of $CD21^+$ B cells and a reduced frequency of IgD^-CD27^+ class-switched memory B lymphocytes and the disease was confirmed by DNA sequencing of the *CD21* gene. Furthermore, the high levels of in-frame skipped CD21 transcripts lacking exon 6 and the lack of the transcripts containing the mutated exon 13 sequence were affirmative [400].

Lack of normally spliced CD81 transcripts and increased levels of alternatively spliced transcripts is characteristic for CD81 deficient patients. Sequencing of the *CD81* gene confirms the diagnosis [414].

3.8.5 Management

Antibiotic management of infections as well as prophylactic antibiotics is administered similar to other CVID patients. Treatment of choice for hypogammaglobulinemia is usually immunoglobulin replacement therapy [342].

3.9 CD20 Deficiency

3.9.1 Definition

CD20 has been identified as one of the first B cell–specific discrimination antigens [378] and is related to the MS4A (membrane-spanning 4-domains, subfamily A, member 1) family of molecules with several membrane spanning domains [244, 245]. Despite being expressed on pre-B and mature B cells, it is lost during differentiation into plasma cells [394]. It has been shown that CD20 can regulate B cell activation and proliferation [393, 395] as well as regulating of Ca^{2+} transport across the cell membrane [73, 211]. It has recently been reported that CD20 deficiency causes a new type of humoral immunodeficiency with a normal development of antigen independent B cells, along with a reduced capacity to develop proper antibody responses and production of class-switched memory B cells [231].

3.9.2 Etiology

A homozygous mutation of the *CD20* gene (OMIM*112210), located at 11q12.2 leading to CD20 deficiency has previously been described [231]. CD20 is involved in B cell signaling associated with B cell survival, proliferation, activation, differentiation, development and immunoglobulin secretion [96]. Absence of CD20 expressing B cells with a diminished formation of germinal centers leads to a reduced frequency of memory B cells and subsequent decrease in IgG levels. Lack of B cells "counter selection for long V_H-CDR3" explains the defective antibody responses against polysaccharide vaccines [231]. Despite that the majority of lymphocyte subpopulations was normal, there was either reduced or nearly absent numbers of marginal zone and class switched memory B cells. Ca^{2+} responses elicited by triggering IgG or IgM and B-cell proliferation were normal while somatic hypermutation was affected. There were a small number of memory B cells in the presented patient.

3.9.3 Clinical Manifestation

The immunological and clinical findings in CD20 deficiency are early onset, but mild, perhaps reflecting more an IgG subclass deficiency than a CVID-like antibody deficiency. However, a history of frequently respiratory infections and recurrent bronchopneumonia has been

reported. During 5 years observation IgG levels were persistently low in this patient whereas IgA and IgM serum levels were normal. This patient has diminished frequency of somatic hypermutation in IgG heavy chain genes, and very low number of memory B cells. T-dependent responses against tetanus toxoid were normal, whereas T-independent responses after vaccination with pneumococcal polysaccharides were reduced [231].

3.9.4 Diagnosis

With clinical symptoms somewhat resembling a mild form of CVID, the patient shows recurrent respiratory infections, hypogammaglobulinemia and defective antibody responses to polysaccharide vaccine. CD20 deficiency is defined as consistently low IgG levels but normal IgM and IgA levels. Also, the number of CD19+ B cells was normal, but CD20 expression was noticeably absent. Therefore, patients suspected of having CD20 deficiency should be evaluated for expression of CD20 on B cells and investigation genomic and transcript sequences of CD20 verify the diagnosis.

3.9.5 Management

The primary treatment of CD20 should be replacement of antibody [231], achieved by either the intravenous or subcutaneous route of Ig, usually in doses same as CVID patients for treatment of hypogammaglobulinemia [109]. Antibiotic prophylaxis, including co-trimoxazole, may be considered [231].

3.10 Other Monogenic Defects Associated with Hypogammaglobulinemia

(ICOS deficiency, TACI deficiency, BAFF receptor deficiency, TWEAK deficiency, NFKB2 deficiency, MOGS deficiency, TRNT1 deficiency, TTC37 deficiency)

3.10.1 Definition

There are several new monogenic defects leading to partial antibody deficiency, presenting with recurrent respiratory infections, lack of antibody responses to vaccines, hypogammaglobulinemia or IgG subclasses deficiency, thus resembling CVID [6].

3.10.2 Etiology

Defects in the following genes *ICOS* (OMIM*604558), *TACI* (*TNFRSF13B*; OMIM*604907), *BAFF receptor* (*TNFRSF13C*; OMIM*), *TWEAK* (*TNFSF12*; OMIM*602695), *NFKB2* (OMIM*164012), *MOGS* (OMIM*601336), *TRNT1* (OMIM*612907), and *TTC37* (OMIM*614589) have recently been described to be associated with hypogammaglobulinemia.

The ICOS gene is located at 2q33.2 and the product of this gene is the inducible T-cell costimulator, which belongs to the CD28 and CTLA-4 Ig-like costimulatory receptor family [368]. This molecule is constitutively expressed on naive B cells and involved in signaling pathways related to T-dependent antibody responses [233, 449]. Experimental studies have shown that the ICOS protein is involved both in the regulation of T-cell proliferation (secretion of IL-2, TNF-α, and IFN-γ) and humoral immune responses (secretion of IL-4, IL-5, IL-6) and it is pivotal for super-induction of IL-10 [166, 345]. The former mechanism may lead to dysregulation of terminal B-cell differentiation into memory and plasma cells. Selective impairment of IL-17 production has also been observed in ICOS deficient helper T cells stimulated by anti-CD3/anti-ICOS, which play a key role in the regulation of inflammatory processes in the tissues [233].

TACI is a highly polymorphic gene, located at position 17p11.2. This gene produces the transmembrane activator and calcium-modulator and cyclophilin ligand interactor, which is known as the lymphocyte-specific member 13B from the tumor necrosis factor receptor superfamily with a

high degree of amino acid substitutions [357]. TACI interacts with the calcium-modulator and cyclophilin ligand (CAML), B-cell activating factor (BAFF), a proliferation-inducing ligand (APRIL) and TWEPRIL [182]. Signaling through this protein activates several transcription factors in B cells via binding to TRAFs, including calcineurin NFAT, AP-1 and NF-kappa-B [42]. Together with BAFF-R and the B-cell maturation antigen (BCMA), TACI constitutes a complex signaling network that modulates CSR, plasma cell formation, and negatively regulates B-cell homeostasis [421]. This network shows partly overlapping expression patterns and redundant functions [88]. TACI is also found on a subset of T cells, is highly expressed by human marginal zone B cells and switched memory B cells, but low to absent on mature naive and transitional B cells [89]. Additional molecular studies will be required to determine exactly how *TACI* mutations influence the clinical phenotype of antibody deficiency [325].

The *BAFF-R* gene, which is located on the long arm of chromosome 22 (22q13.2) encodes a homotrimeric protein that serves as a receptor for the tumor necrosis factor receptor family [337, 445]. As described above, this receptor forms a complex receptor network of TACI/BCMA/BAFF-R together with the BCR and is required for BAFF-mediated proliferation and differentiation of transitional and mature B cells [265, 404]. By activation of BAFF-R, a survival signal is followed by BclXL and Mcl1 (via NF-kappa-B induced by NIK and TRAF 3) and mTOR (via AKT induced by PI3K) which is necessary for terminal B cell development [178, 444]. BAFF-R expression increases when transitional B cells differentiate into MZ and follicular B cells. However, BAFF-R is not found on long-lived plasma cells in the BM, which rather express BCMA, whereas TACI is expressed by B cells of the MZ and switched memory B cells [435].

TWEAK (TNF-like weak inducer of apoptosis), a cytokine belonging to tumor necrosis factor (TNF) superfamily, is encoded by the *TWEAK* gene located on 17p13 [429]. Upon binding to its receptor, Fn14 in immune cells, it induces apoptosis, possibly via the MAPK and NF-kB pathways, and promotes immune functions [52, 212, 213, 287]. A heterozygous loss of function mutation in exon 6 of *TWEAK* was previously reported in the conserved TNF-homology domain and when introduced into selected cell lines, the mutant TWEAK failed to elicit apoptosis. Defective TWEAK, via the formation of TWAEK-BAFF complexes, also reduces BAFF-induced B cell proliferation, survival, and immunoglobulin isotype switching. These dysfunctions explain the abnormalities observed in lymphocyte survival and immune function in TWEAK deficiency [429].

The role for PKCδ in promoting apoptosis and subsequent regulation of B-cell survival and tolerance was previously documented [389]. Analyses revealed that a homozygous mutation in *PRKCD* with a recessive inheritance impaired expression of PKCδ at the protein level and diminished its nuclear translocation which otherwise is required for its pre-apoptotic function, especially in B cells [45, 309] PMA (phorbol-12-myristate-13-acetate) induces apoptosis in normal B-cells, whereas, PKCδ deficient B lymphocytes showed inhibition of cell death. This inhibition was observed in the case of PMA induction but not recorded in FAS and thapsigargin treated cells [290, 309]. The aberrant survival of immature B cells leads to hyperproliferation. Increased secretion of IL-10 by the affected B cells and may be responsible for observed autoimmunity [281]. Defects in caspase-3 activation may also be involved in the etiology of the disease. The observed failure in NK cell function possibly involves chronic EBV infection [45].

NF-kB2 is a member of NF-kB transcription factor family encoded by the *NFKB2* gene located on 10q24 with roles in immune system development and function [60]. Different members of the TNFR superfamily, including BAFF-R, RANKL, CD40, and LTβR are involved in NF-kB2 activation [328]. Following stimulating signals upon binding of the cognate ligands to these receptors, inactive NF-kB2 (p100) is phosphorylated by IKKα dimers at specific serine residues in the C terminus (Ser866, Ser870), which allows for ubiquitination of Lys855. The subsequent proteasomal processing leaves a p52 subunit which is

translocated to the cell nucleus as a p52/RelB dimer that initiates transcription of target genes involved in lymphoid organ development, B and T cell maturation and adaptive immune responses [60, 170, 386]. NF-kB2 also prevents hyper-responsiveness of naïve $CD4^+$ T cells, thus avoiding autoimmune responses [194].

3.10.3 Clinical Manifestations

ICOS deficiency was first reported in 2003 [242] in a CVID patient with an autosomal recessive pattern with a late onset. This case was followed by reports on 8 patients living along the River Danube who had a common ancestry owing to a founder mutation [336, 345, 391, 433, 435]. Major clinical features of ICOS deficiency include diminished Ig levels, autoimmunity, lymphocyte infiltration, malignancy, reduced class-switched and memory B-cell counts and defective IgG1 and IgE antibody production in response to immunization, suggesting a reduced germinal center formation [336, 451]. Histopathology revealed severely aberrant and vestigial germinal centers in the patients' lymph nodes [104, 450].

In the TACI-mutated patient cohort, autoimmunity was present in 40 % and signs of lymphoproliferation were present in 60 % of the patients and the frequency of malignant B-cell lymphomas was higher than in patients with other monogenic defects associated with a partial antibody deficiency. From 2005 to now, TACI deficiency has been described in up to 10 % of CVID patients and also in individuals with a diagnosis of IgG subclass and IgAD deficiency in CVID/IgAD families with marked differences both in the type of immunodeficiency and immunodysregulation [137]. Complex pattern of heritage (homozygous, heterozygous, and compound heterozygous), mostly in the hotspot extracellular portion (C104R and A181E) of the molecule, and phenotypic diversity/incomplete penetrance in clinical manifestations of these cases suggest that modifying factors may play a role in these cases. Screening for mutations for *TACI* to predict prognosis or help in genetic counseling has not as yet proven to be useful [127].

Mutations in the *BAFFR* gene have been reported to cause lymphopenia and a late onset antibody deficiency (CVID) in humans leading to respiratory and gut infections, and autoimmunity, cancer and granuloma are prevalent in patients [137]. BAFFR deficient patients suffer from a defect of the long-term humoral memory (except of IgA+ memory), short-lived plasma cells (except IgA secreting plasma cells from mucosal tissues), a relative increase of transitional B cells and reduced specific antibody responses, especially to polysaccharide antigens [127].

Patients with TWEAK deficiency show an autosomal dominant pattern of inheritance and patients manifest with numerous warts, B cell lymphopenia, chronic thrombocytopenia and intermittent neutropenia, decreased IgA and IgM levels, increased frequencies of double-negative and CD8+ T cells, with a majority of B cells having a naïve phenotype and lack of antibody production in response to T cell-dependent and T cell-independent vaccines [429].

To date, two different heterozygous mutations in the *NFKB2* gene were reported to cause antibody deficiency. Both of these mutations are heterozygous alterations with a dominant pattern of inheritance. Regarding the role of NF-kB2 in development and function of lymphoid organs and of T and B cells, lack of this transcription factor leads to decreased frequency of memory B cells, reduced immunoglobulin levels, defective responses to vaccination, atopy or asthma and autoimmunity.

In PKCδ deficiency, in addition to common bacterial infections including sinusitis and episodes of otitis, the patients suffer from intermittent fever and chronic EBV infection. Autoimmune-driven hepatosplenomegaly as well as persistent generalized lymphadenopathy have been observed without any microbial deposits in lymph node biopsies. Progression of autoimmunity with elevated levels of different autoantibodies with subsequent "intermittent lupus-like rash" and confluent erythematosus macules over the trunk and extremities has also been noted.

3.10.4 Diagnosis

The patients affected by all above novel monogenic defects, manifest CVID-like symptoms. Serum immunoglobulin analysis reveals diminished IgA and IgM levels as well as IgG deficiency or IgG subclass deficiency. Affected individuals are unable to respond to both T-dependent and T-independent vaccinations. However, special features may provide important clues as to the diagnosis including: Increment in double-negative and CD8+ T cell subsets (in CD19 deficiency), B cell lymphopenia with normal IgA serum levels and IgA1 plasma cells (BAFF-R deficiency), severe autoimmune adrenal insufficiency (NF-kB2 deficiency), lymphoproliferative disorders (TACI deficiency) and increased levels of inflammatory markers, defective FAS activity and proliferation of double-negative T cells reminiscent of ALPS (PKCδ deficiency). Next generation sequencing of patients with CVID presentation may help identification of the mutation, leading to a correct diagnosis. Western blot analysis, looking for truncated proteins, also may lead to a timely diagnosis.

3.10.5 Management

Antibiotic prophylaxis as well as antimicrobial management of infections is recommended. Immunoglobulin replacement therapy, either by the intravenous or subcutaneous route, is used to correct the antibody deficiency. For management of autoimmunity, lymphoproliferation and endocrinopathy of these patients, specific therapy should be considered by consultation of specialists [342].

3.11 Immunoglobulin Class Switch Recombination Deficiencies Affecting B Cells

(AICDA deficiency, UNG deficiency, MMR deficiency, INO80 deficiency)

3.11.1 Definition

Immunoglobulin class switch recombination deficiencies (CSR-Ds) are a consequence of various defects impairing the CSR machinery. They selectively result from an intrinsic B-cell defect, and are caused by mutations in genes encoding molecules essential for CSR, such as Activation-Induced Cytidine Deaminase (*AICDA* or *AID*; OMIM*605257), Uracyl-DNA Glycosylase (*UNG*; OMIM*191525), Post meiotic segregation 2 (*PMS2*; OMIM*600259), INO80 complex subunit (*INO80*; OMIM*610169), MutS E. coli homolog of 6 (*MSH6*; OMIM*600678), and others still undefined genes [137, 191, 313, 331]. They are defined by the presence of elevated or normal serum IgM levels contrasting with low or null serum levels of the so-called "switched isotypes" (IgG, IgA and IgE), hence this condition's former name "hyper-IgM syndrome" They are clinically characterized by recurrent and chronic bacterial infections (not opportunistic infections), lymphoid hyperplasia and autoimmune disorders. As compared to CSR-D due to defects in the CD40-mediated signaling, they have a much better prognosis since most of bacterial infections can be controlled by IgG substitution. However, some of them could be associated with malignancies [137].

3.11.2 Etiology

CSR-Ds caused by an intrinsic B cell defect result from a defective maturation of the antibody repertoire, a process required for production of diverse antibody isotypes with high affinity for antigen. Antibody maturation takes place within the secondary lymphoid organs (the spleen, lymph nodes and tonsils) in an antigen- and T-cell-dependent manner. When mature but naive B cells emigrating from the bone-marrow (or fetal liver) encounter antigens that they specifically recognize through their BCR of the IgM isotype and through a close interaction with the T follicular helper T cells (T_{FH}), they proliferate vigorously and give rise to a peculiar lymphoid

formation, the germinal center (GC), in which B cells undergo the two major events required for antibody maturation, CSR and generation of somatic hypermutation (SHM) (Fig. 3.3).

CSR is achieved through a recombination process between two different switch (S) regions (each of which located upstream of a constant (C) region in the Ig locus), with deletion of the intervening DNA [197, 263, 422]. Replacement of the Cμ region by a downstream Cx region (Cα, Cγ or Cε region, coding respectively for IgA, IgG or IgE) results in the production of switched isotypes with the same variable (V) region and thus the same antigen specificity and affinity. The first step of this process is the transcription of S-regions' DNA, which is induced by cytokines. Interestingly, each cytokine targets a specific S region, leading to the production of the corresponding isotype (as an example, IL4 targets the Sε region and induces CSR towards the IgE isotype). As a result of this transcription step, RNA/DNA hybrids are formed on the template DNA strand, leaving DNA strands accessible to the activity of a B cell specific molecule, the Activation-induced cytidine deaminase (AID) [286]. This enzyme introduces a lesion on DNA by selectively changing cytosine (C) residues into uracil (U) residues [46, 68, 315]. The U:G mismatch lesion is subsequently recognized and processed by the uracil N-glycosylase (UNG), which removes the U residues and produces an abasic site that is eventually cleaved by apurinic/apyrimidinic endonucleases (APE) [168, 326]. The single strand DNA breaks are then processed into DNA double strand breaks (DSBs) required for the inter-switch regions' recombination process. DSBs can also be generated through the endonuclease activity of the postmeiotic segregation 2 (PMS2) enzyme (a component of the mismatch repair (MMR) machinery in a PMS2/MLH1 complex) [411]. CSR-induced DSBs are sensed by different components such as Ataxia-telangiectasia mutated (ATM), the MRE11/RAD50/NBS1 complex, phosphorylated histone γH2AX and the repair protein p53 binding protein 1 (53BP1) and repaired mostly through the Non Homologous End Joining (NHEJ) pathway.

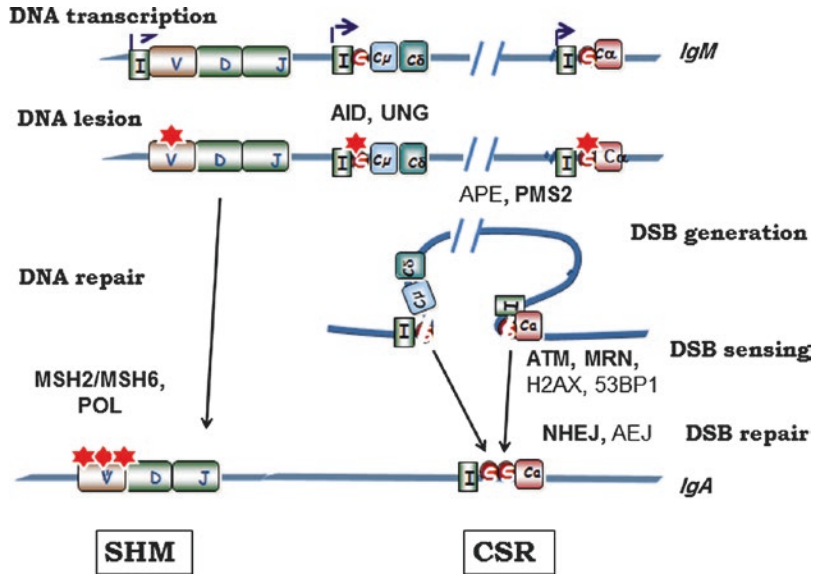

Fig. 3.3 Schematic representation of class switch recombination and somatic hypermutation. *CSR* class switch recombination, *SHM* somatic hypermutation, *DSB* double strand DNA breaks, *AID* activation induced cytidine deaminase, *UNG* Uracil N glycosylase, *APE* endonuclease, *PMS2* post meiotic segregation 2, *ATM* Ataxia Telangiectasia mutated, *MRN* MRE11/RAD50/NBS1 complex, *NHEJ* non homologous end joining, *AEJ* alternative end joining, *MSH2/6* MutS homologous 2/6, *POL* error prone polymerases. In *bold* known human defects (Defect in POLɧ leads to Xeroderma Pigmentosum variant, but not to antibody deficiency)

Somatic hypermutation stochastically introduces missense mutations (or, much more rarely, deletions or insertions) into Ig V regions and their proximal flanking regions at a very high rate (around 1 mutation for 1×10^{-3} bases), without changing the C region, thus the Ig isotype [384]. This process leads to the selection and proliferation of B cells expressing a BCR with high affinity for antigen, through an interaction with follicular dendritic cells in the GC. As in CSR, the first step in SHM is the introduction of uracil residues by AID during the transcription of V region's DNA, followed by the UNG's activity and creation of an abasic site [315]. However, this lesion's repair differs from that of CSR since no DSBs are needed. The UNG-induced abasic sites are repaired by several error prone polymerases. AID-induced U:G mismatches, not processed by UNG, can also be repaired during DNA replication or by the MutS homologous 2/6 (MSH2/MSH6) complex, another component of the MMR machinery and the error prone polymerase η [384].

Although CSR and SHM occur simultaneously in B cells in GCs following CD40/BCR activation, each is not a prerequisite for the other; since IgM may be mutated and IgG or IgA unmutated. Although SHM defects have never yet been reported as being causative of an immunodeficiency, CSR defects always cause a pathological condition characterized by a susceptibility to recurrent and severe bacterial infections.

Autosomal recessive AID deficiency It is the most frequent of CSR-D caused by an intrinsic B cell defect (around 40 % of these conditions). It is characterized by a drastic defect in both CSR and SHM since AID is absolutely required for both processes [138, 285, 331]. Mutations are scattered all along the gene, with no peculiar hotspot; most of them (but not all) lead to an absence of protein expression. However, few mutations located in the C terminal part of AID (AID C^{ter}), that do not affect protein expression, lead to defective CSR but normal SHM [138]. This observation strongly suggests that AID is not only a cytidine deaminase but plays a further role in CSR, likely by recruiting CSR-specific cofactors, still unknown [390].

Autosomal dominant AID deficiency Interestingly, two different nonsense mutations located in the nuclear export signal located in the C terminal part of AID lead to a CSR-D transmitted as an AD disease, an observation likely related to the fact that AID acts in CSR as a multimeric component [192].

Autosomal recessive UNG deficiency This condition is very rare (<1 % of CSR-Ds) and characterized by a profound impairment in CSR but normal frequency of SHM. However in the absence of UNG, SHM which are introduced only during replication or through MMR repair present a strikingly abnormal pattern of nucleotide substitution with an excess of transitions. The four mutations reported in the three patients lead to lack of protein expression [191].

Autosomal recessive PMS2 deficiency Although the main symptom of AR PMS2 deficiency is the early onset occurrence of cancers, as others defects in the MMR pathway, some patients can firstly present with a CSR-D with normal SHM, pinpointing the role of this molecule in human CSR [313]. In the 13 patients observed, all present drastic mutations in PMS2 gene, leading to lack of protein expression.

Autosomal recessive INO80 deficiency This appears as a very rare CSR6D, while only two patients have been reported so far. The three observed mutations are missense mutations that led to normal expression of protein [228].

Other CSR-D As much as 60 % of patients affected by a CSR-D caused by an intrinsic B cell defect remain not molecularly defined. In these conditions, the clinical and biological phenotype can be very close to that caused by AID C^{ter} mutations with drastic CSR defect and normal SHM. A possible defect in the putative cofactor(s) of AID is suspected. Other patients are likely sufferings from a DNA repair defect with occurrence of malignancies [314].

3.11.3 Clinical Manifestations

Most of clinical manifestations are shared these different forms of CSR-Ds caused by an intrinsic B cell defect. Patients present recurrent bacterial infections that predominantly affect the respiratory tracts (leading to the severe complications of sinusitis and bronchiectasis, if left untreated). *Streptococcus pneumonia* is the most prevalent microorganisms causing these infections. Gastrointestinal infections may occur. They are vulnerable to intestinal tract infections (sometimes in relation to persistent *Giardia* infections) leading to malabsorption and failure to thrive, especially in cases of inadequate treatment. Symptom onset generally occurs during early childhood, although some patients are only diagnosed in adulthood. In contrast to patients with CD40L or CD40 deficiency, susceptibility to opportunistic infections (which is characteristic of abnormal T cell responses) and neutropenia are not observed in these patients. Unlike agammaglobulinemic patients, these CSR deficient patients do not appear to develop severe enteroviral infections – suggesting that IgM (even when lacking mutations) acts as an initial barrier against enteroviruses and perhaps other viruses. Interestingly, IgM has been shown to protect efficiently against some bacteria, such as non typable *Haemophilus influenzae* [273]. Other complications are frequent such as lymphadenopathies and auto-immune/inflammatory disorders. The clinical features characteristic of the different molecular defects is described below:

Autosomal recessive AID-deficiency In all of the 72 patients we observed, the CSR-defect appears dramatic, with a very high susceptibility to bacterial infections, most of them being diagnosed in childhood [321, 331]. Besides the high susceptibility to infections, a hallmark of the disease is the occurrence of impressive lymphadenopathies affecting as much as 75 % of patients, and often requiring tonsillectomy or lymph node biopsy/resection. They affect cervical, mediastinal and mesenteric lymph nodes. Histological examination reveals the presence of characteristic giant GCs, (between 5 and 10 times larger than normal), which leads to reduction/disappearance of mantle zone and inter-follicular areas (Fig. 3.4). The GCs are filled with proliferating B cells that express CD38, surface IgM and surface IgD – all markers of GC founder cells [321]. One possible explanation is that, in the absence of functional AID, antigens continuously induce B cells' proliferation, since no successful antibody maturation and selection can occur or that AID plays a direct role in GC B cells' apoptosis [240] Lymphadenopathies are not obviously linked to infections since they can occur in patients receiving adequate Ig substitution [321].

Autoimmunity is a frequent complication (affecting 31 % of patients) with the presence of IgM auto-antibodies against blood cells (causing hemolytic anemia, thrombocytopenia and (more rarely) neutropenia) or other tissue types (causing hepatitis and systemic lupus erythematous, for example). Auto-inflammatory manifestations are also described, as uveitis, non-infectious arthritis or Crohn's disease [135, 321]. There is no correlation between the presence of autoimmunity/auto-inflammatory diseases and the occurrence of infections, since AID-deficient patients receiving optimal Ig replacement therapy may still develop these complications. A defect in central and peripheral tolerance has been described with surprisingly, a defect in the T reg cells' counts [272].

Interestingly, the very few patients carrying AID C^{ter} mutations that allow normal SHM generation present with the very same susceptibility to infections as other AR AID-deficient patients. However, auto-immune manifestations have not been reported in these four patients and, more strikingly, lymphadenopathies occur but are much less impressive. In the one patient who had two successive biopsies of an enlarged cervical lymph node, a feature of follicular hyperplasia without the presence of giant GCs was noted.

Autosomal dominant AID deficiency Patients with AD AID deficiency present with a milder phenotype as compared with the AR condition and most of them are diagnosed at adulthood [192]. The phenotype is very close to that observed in common variable immunodeficiency

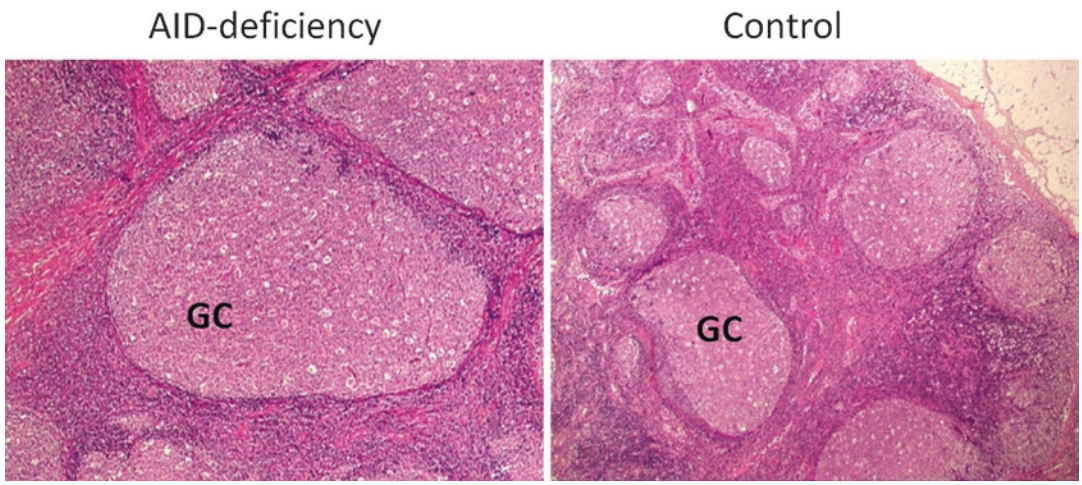

Fig. 3.4 Biopsy of a cervical lymph node from an AID-deficient patient and a control. *GC* germinal center

(CVID), characterized by recurrent bacterial infections affecting mainly the respiratory tract. In contrast to the AR form of AID-deficiency, .no lymphadenopathies, no auto-immune manifestations have been reported (but only 15 patients have been observed so far).

Autosomal recessive UNG deficiency Uracil-N glycosylase deficiency is a very rare AR disease and only three patients have been described to date. All three patients had a history of frequent bacterial respiratory infections from early childhood onwards. One patient developed chronic epididymitis in adulthood [191]. Neither opportunistic infections nor abnormally severe viral infections are reported. Two of the three patients presented with lymphadenopathy, with enlargement of mediastinal or cervical lymph nodes. The only one performed biopsy revealed lymphoid hyperplasia but with no giant GC typical of AID deficiency. In adulthood, the eldest of the patients developed autoimmune manifestations, hemolytic anemia and Sjögren syndrome. Clinically UNG deficiency is indistinguishable from AID deficiency. As UNG belongs to the base excision repair pathway involved in the repair of spontaneously occurring DNA lesions, it appears as an important anti-mutagenesis mechanism. Although not observed in patients, UNG defect could however predispose to tumourigenesis as reported in elderly UNG-deficient mice [289]. Although UNG is expressed in mitochondria, no mitochondrial abnormalities have been observed in patients, suggesting the presence of efficient compensatory mechanisms. However, in UNG-deficient mice, post-ischemic brain injury is more severe than in control animals likely because of defective mitochondrial DNA repair [143]. Hence, this type of complication might also occur in patients.

Autosomal recessive PMS2 deficiency The hallmark of this disease is the early onset of malignancies (mean: 9 years of age), especially colorectal cancers, supratentorial primitive neuro-ectodermal tumors, medulloblastoma and hematological malignancies, which strongly worsens the prognosis [443]. However, before occurrence of cancers, patients can present during years with symptoms evocative of a CSR-D, with recurrent and severe sino-pulmonary bacterial infections, that require IgG replacement therapy [313]. A frequent (11/13 patients observed) characteristic (but not specific) feature is the presence of *café au lait* skin spots or hypopigmented skin areas.

Autosomal recessive INO80 deficiency The two described patients present with a CVID-like phenotype with recurrent bacterial pulmonary infections from childhood [228].

Other CSR-D These pathological conditions, which are not molecularly defined, are certainly a

heterogeneous entity. Some patients present with a phenotype very close to that of AR AID deficiency, although the CSR-D can be milder with residual IgG and/or IgA levels. Recurrent bacterial infections affecting mostly the respiratory tract are the main symptom of the disease. Lymphadenopathies can occur with features of follicular hyperplasia (with no giant GC) at histological examination. Auto-immunity is also reported in 25 % of patients. Some of these forms are associated to a higher frequency of hematopoietic malignancies [190, 314].

3.11.4 Diagnosis

The most important laboratory criteria for establishing the diagnosis of CSR-D is a low serum IgG, IgA, and IgE concentration and normal or elevated serum IgM levels. Antibody responses are restricted to the IgM isotype with the presence of antibodies to isohemagglutinins and polysaccharide antigens and non-typable *Haemophilus influenzae* [273, 321]. In contrast, the IgG response to protein infectious or vaccinal antigens is impaired. Although circulating B cell counts are found normal, analysis of subpopulations reveals an absence of switched B cells (IgM(−), IgD(−)). B cells, although normally able to proliferate upon *in vitro* activation, cannot undergo CSR, pinpointing to a defect in the CSR machinery [136]. In all cases, a T cell immunodeficiency has to be excluded since T cell functions' impairment leads to a secondary CSR defect (4). Phenotyping of T cells and T cell subsets and study of T cell functions, including expression of CD40L on activated T cells, are required before making the diagnosis of CSR-D caused by an intrinsic B cell defect.

Some signs are essential to orientate properly the genetic study which remains, however, the only way for a definitive diagnosis (Table 3.2).

Autosomal recessive AID deficiency Consanguinity (which is reported in 70 % of cases) and/or episodes of massive lymphadenopathies/and or autoimmune manifestations are evocative of AID-deficiency. The diagnosis is confirmed by the Ig dosages since the CSR-D is drastic, with neither IgG nor IgA produced. Very high IgM levels (up to tenfold above normal values) are not uncommon. Although there is no switched B cells as in other CSR-Ds, the proportion of B cells expressing CD27 is normal, suggesting that CD27 is a marker of proliferation in GC rather than a marker of mutated B cells.

Autosomal dominant AID deficiency There is no peculiar sign evocative of this disease but this diagnosis should be checked for in adult patients with a phenotype of CVID, especially, in familial cases.

Autosomal recessive UNG deficiency UNG-deficiency appears as very rare and two out of the three reported patients were born from a consanguineous family. The CSR–D is drastic although very low residual levels of IgG and IgA can be detected. The proportion of B cells expressing the CD27 marker is variable, observed in low range in the youngest of the three patients.

Autosomal recessive PMS2 deficiency Although the main symptom is the occurrence of early onset cancers, some of the patients present firstly with a CSR-D for years. The CSR-D is mild, affecting especially IgG2 and IgA production and tending to ameliorate with age, likely by accumulation of long-lived plasma cells. CD27+ B cell counts are always found decreased. Diagnosis can be suspected when anamnesis reports familial history of non polyposis colic carcinoma, a frequent complication in adult heterozygous subjects (Lynch syndrome). Moreover, detection of café-au-lait skin spots or depigmentated skin areas (highly suggesting of an MMR defect) can orientate the gene investigation. As *PMS2* gene is difficult to sequence because of the presence of a pseudogene, a biochemical approach studying PMS2 protein expression in EBV B cell lines appears as an easier tool for diagnosis.

Of note, defect in MSH6, a component of the MSH2/MSH6 complex of the MMR pathway, leads to subtle CSR-D defect with decreased serum IgG2 levels, decreased numbers of CD27+ cells, and a strong bias in nucleotide substitution

Table 3.2 Diagnosis of CSR-Ds caused by an intrinsic B cell defect

Gene defect	transmission	Main clinical features[a]	Main biological features	Differential diagnosis
AID	AR	Massive lymphadenopathies Auto-immunity	Drastic CSR-D Normal counts of CD27+ B cells	
AID C^{ter}	AR	Lymphadenopathies	Drastic CSR-D Normal counts of CD27 + B cells	
AID ^{NES}	AD		Mild CSR-D Normal counts of CD27 + B cells	CVID
UNG	AR	Lymphadenopathies Auto-immunity	Drastic CSR-D Variable counts of CD27+ B cells	AID deficiency
PMS2	AR	Café au lait skin spots cancers	IgG (especially IgG2) and IgA mild defect Decreased counts of CD27+ B cells	
INO80	AR		Decreased counts of CD27+ B cells	CVID
unknown	? ?	Lymphadenopathies Auto-immunity Susceptibility to malignancies	Variable CSR-D Normal counts of CD27+ B cells Variable CSR-D Decreased counts of CD27+ B cells	Ataxia Telangiectasia DNA repair defects

AR autosomal recessive, *AD* autosomal dominant, C^{ter} C terminal part of AID, *NES* nuclear export signal of AID, *CVID* common variable immunodeficiency

[a]Besides the susceptibility to bacterial infections shared by all CSR-Ds

of SHM, but without obvious clinical consequences [159]. This observation pinpoints to the peculiar role of PMS2 in human CSR, likely through its endonucleasic activity [411].

Autosomal recessive INO80 deficiency Both described patients present with decreased IgG and IgA serum levels with normal IgM. Interestingly, in the youngest patient, switched Ig levels tend to increase with age, likely by accumulation of long lived plasma cells. SHM are found normal, however on a reduced CD27+ B cell population [228].

Other CSR-D This condition characterized by a variable CSR-D with normal SHM, lymphadenopathies and auto-immune manifestations is not easily diagnosed. The CSR-D is variable as well as the numbers of CD27+ B cells. Some of these patients present with a drastic CSR, normal SHM, a phenotype very similar to that induced by AID C^{ter} mutations. Strikingly, physicians should be aware that Ataxia Telangiectasia patients can present with the very same phenotype [148]. Therefore, this disease, which is much more frequent than CSR-D, has to be excluded by simple tests such as careful clinical examination looking for specific signs, even still discrete (telangiectasia, neurological disabilities) and/or by dosage of α-fetoprotein in serum.

3.11.5 Management

The mainstay of treatment for CSR-Ds is immunoglobulin replacement therapy that effectively reduces the incidence and severity of complications in this group of patients. IVIG can be used

on a regular basis to maintain a trough level of 400–500 mg/dL in patients. Subcutaneous Ig replacement is certainly a treatment for the future. However, Ig substitution does not prevent lymphoid hyperplasia, which can require surgical resection in case of impressive enlargement, as observed in AR AID deficiency. IgG substitution does not prevent either auto-immunity which can be life threatening and require treatments with steroids, anti-CD20 antibodies or immunosuppressive therapies. Antibiotics are generally administrated during infectious episodes rather than a prophylactic treatment.

An accurate diagnosis based on clinical, biological and especially genetic data is essential to set-up an adequate follow-up and prevent complications. Moreover, it allows a prenatal diagnosis in severe forms of CSR-Ds (especially PMS2-deficiency). New genetic approaches, such as whole exome/genome sequencing, will very likely allow the delineation of the molecularly undefined CSR-Ds in the near future.

3.12 Selective IgA Deficiency

3.12.1 Definition

Selective IgA deficiency (IgAD, OMIM*137100) is the most common primary antibody deficiency [2, 177]. It is defined as a serum IgA level of less than 0.07 g/l and normal serum IgG and IgM levels in a patient older than 4 years [27, 59, 77, 80]. Partial IgA deficiency is defined as a decreased IgA levels that are more than two standard deviations below the normal age-adjusted means [118].

IgA deficiency was first described in patients with ataxia-telangiectasia in 1961 [399]. IgAD affects both males and females equally. Based on different ethnic groups, the frequency of IgAD varies, ranging from 1:142 to 1:18,000 [21, 210, 354].

The defect is presumed to result from impaired switching to IgA or a maturational failure of IgA-producing lymphocytes, but the nature of basic defect is unknown. Many affected individuals are asymptomatic whereas selected patients suffer from recurrent mucosal infections, allergies, and autoimmune diseases [80, 179].

3.12.2 Etiology

IgAD and CVID often coexist in members of the same family, and some individuals initially present with IgAD subsequently then develop CVID [87, 146, 172, 177, 195, 200, 248, 370, 372, 373].

These data support the involvement of hereditary factors and a genetic association between IgAD and CVID. Genetic linkage analysis of families with IgAD and CVID had identified susceptibility loci on chromosome 6 within the MHC locus near the class I, II, and III regions [358–360]. The DR/DQ locus has been reported to be the strongest predisposing locus. Studies on multiply-affected families with IgAD and CVID have shown an increased allele sharing in the proximal region of the MHC at chromosome 6p21 [425]. A more detailed genetic analysis in 101 multiple-case families and 110 single-case families also localized the defect to the HLA-DQ and HLA-DR loci [229].

Although it has been found that a fundamental defect in IgAD is the failure of IgA-bearing B lymphocytes to mature into IgA secreting plasma cells, the reason of this defect is still not understood. Isotype switching and terminal differentiation into IgA-secreting plasma cells using transforming growth factor beta (TGF-ß) [380] or IL21 [62] may indicate a key role of cytokine in this process.

Genetic defects of a tumor-necrosis factor receptor family member termed TACI have been identified in a few patients with IgAD and CVID, possibly causing defects in isotype switching [90]. Although the former point has been questioned, molecular studies have demonstrated impaired mu switch (S) to S alpha rearrangements in peripheral B cells in some IgA deficient subjects [196, 432]. IgAD can be a component of other forms of PIDs, such as ataxia-telangiectasia, mucocutaneous candidiasis [206, 399] and IgG2 subclass deficiency [306].

Transient or permanent IgAD may develop after therapy with certain drugs including phenytoin, carbamazepine, valproic acid, zonisamide, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs [206, 304]. IgAD has also been reported in

patients with chromosome 18 abnormalities [423]. In addition, congenital rubella and Epstein-Barr virus infections have been implicated in a few cases of acquired IgAD [108].

A subgroup of patients with IgAD exhibit IgG subclass deficiency and defective specific antibody production and have higher rates of recurrent infections and bronchiectasis, which require more effective monitoring [11]. Moreover, severe clinical manifestation, including infectious complications and autoimmune diseases may be present in IgAD patients with a low count of switched memory B cells [10, 249] . Diminished number of regulatory T cells in the former group has been demonstrated and correlates with autoimmunity.

Selected IgAD patients may develop into CVID and familial aggregation of these two disorders suggesting a common genetic background (associated with the HLA A1-B8- DR3-DQ2 haplotype) and a similarity of the underlying B cell defect. In line with this reasoning IgAD patients with autoimmune disorders (defective switched memory B cells or regulatory T cells) and severe infections (IgG subclass deficiency or specific antibody deficiency) are at higher risk for development of CVID [16, 87, 146, 305, 360]

3.12.3 Clinical Manifestations

Approximately two thirds of patients with IgAD remain asymptomatic [107]. Association of concomitant defects in individuals with IgA deficiency may predispose affected individuals to recurrent infections. These concomitant immune defects may include deficiency of IgG subclasses, defects in specific antibody production against protein and polysaccharide antigens and defects in mannan-binding lectin (MBL) [20, 63, 142, 157].

In symptomatic IgA deficient patients, infections include recurrent viral infections, recurrent otitis media, frequent sinopulmonary infections, and gastrointestinal infections [142, 177].

Invasive infections such as septicemia and meningitis are not generally features of IgAD. Patients with IgA deficiency are also have a higher frequency of autoimmune diseases [430], and, potentially, malignancy [270].

Lack of severe infection in patients with IgAD may, in some cases, be attributed to a compensatory increase in secretory IgM [2, 177].

Sinopulmonary infections Recurrent sinopulmonary infections are the most frequent symptom associated with IgAD. These are caused by extracellular encapsulated bacteria (e.g. *Haemophilus influenza* and *Streptococcus pneumoniae*). Frequent, recurrent episodes of otitis media and sinopulmonary infections are most commonly observed in patients with IgAD and decreased IgG subclass levels (especially IgG2 in children) [376, 440].

Patients with IgAD who have a combination of IgA deficiency and a deficiency of one or more IgG subclasses or impaired antibody responses to protein and polysaccharide antigens are at risk for chronic lung complication such as impaired lung function and bronchiectasis [55, 381, 416].

In our unpublished study, among 40 patients with bronchiectasis of unknown etiology, we found 3 (7.5 %) patients with IgAD with an associated IgG subclass deficiency and/or defects in specific antibody production against polysaccharide antigens. This finding is similar to previous studies in which the rate of IgAD among patients with bronchiectasis varied between 5.3 and 14 % [381, 416].

Some authors have indicated a need to assess antibody responses to polysaccharide vaccines in patients with bronchiectasis of unknown etiology [410]. This is may be indicated for patients with IgAD and a history of recurrent or chronic otitis media and/or sinusitis, IgG2 subclass deficiency, or low levels of baseline specific antibodies [416]. Therefore, a search for IgAD should be performed in patients with bronchiectasis of unknown etiology and in patients with a history of recurrent otitis media and sinopulmonary infections.

Gastrointestinal diseases Patients with IgAD are more susceptible to gastrointestinal diseases including giardiasis, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel disease [183]. Up to 50 % of IgA deficient individuals have precipitins to cow's milk [111, 112] and

most of IgA deficient patients develop circulating immune complexes in their serum 15–60 min after drinking milk [112].

Autoimmune disorders A variety of autoimmune diseases including immune thrombocytopenic purpura, autoimmune hemolytic anemia, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, celiac disease and vitiligo are associated with IgAD [108].

It has been postulated that absence of IgA in the serum permits cross reactive antigens to enter the circulation and subsequently initiate autoimmune reactions.

Patients with IgAD often have autoantibodies against thyroglobulin, red blood cells, thyroid microsomal antigens, basement membrane, smooth muscle cells, pancreatic cells, nuclear proteins, cardiolipin, human collagen, and adrenal cells [236, 348]. A significant number of patients with IgAD have anti-IgA antibodies that may result in transfusion reactions [236, 348]. Anti-IgA antibodies occur in some IgA deficient individuals with undetectable IgA but may occasionally be seen in patients lacking in one of the two IgA subclasses [387]. Thus, blood products should be carefully considered before use in patients with IgAD.

Allergy IgA deficiency may be associated with allergy and the most common allergic disorders reported in IgA deficient individuals are asthma, allergic rhinitis, allergic conjunctivitis, urticaria, atopic eczema and food allergy [177, 354, 369, 385].

Malignancies IgA deficient patients have been reported to be at a higher risk for gastrointestinal and lymphoid malignancies [117, 246]. However, more recent studies suggest no marked over representation of tumors in IgA deficient patients [270].

3.12.4 Diagnosis

IgAD is defined as serum IgA level (less than 7 mg/dL) in a patient older than 4 years with normal serum levels of IgG and IgM and exclusion of other causes of hypogammaglobulinemia. Low serum IgA levels in children aged 6 months to 4 years should be confirmed to be persistently low at age 4 years before making a diagnosis of IgAD. Patients with IgAD, especially patients with absent secretory IgA, which is associated with one or more IgG subclass deficiencies or an impaired polysaccharide responsiveness, may develop recurrent sinopulmonary infections and GI tract infections. Therefore, IgA deficient patients may be evaluated for specific antibody production against protein and polysaccharide antigens. Measurement of IgG subclass and secretory IgA should also be performed to determine if there is a concomitant functional antibody deficiency and if these patients would benefit from administration of immunoglobulin.

Some patients with IgAD may progress to CVID. Therefore, long-term follow-up and repeat immunoglobulins determinations at regular intervals (bi-annually) is indicated, especially in symptomatic IgA deficient patients.

The presence of auto-antibodies such as ANA and thyroid antibodies should be investigated in patients with IgA deficiency. Allergy tests and measurement of anti-gluten antibodies of the IgG class should be performed, if there is evidence of food intolerance or malabsorption. IgA deficient patients with concomitant functional antibody deficiency, who are selected for IVIG therapy, should be assessed for the presence of anti-IgA antibodies.

3.12.5 Management

For individuals with asymptomatic IgAD, no therapy is recommended. The use of prophylactic antibiotics can be considered in IgA deficient patients with a history of infections and some patients may benefit from long-term prophylactic antibiotics [246]. Aggressive antimicrobial therapy is indicated in all IgA deficient patients at the time of infections. Routine active immunization is not contraindicated in patients with IgAD. The use of immunoglobulin replacement therapy for patients without a

demonstrable impairment of specific antibody formation is controversial [142, 171, 246]. If there is inadequate response to antimicrobial therapy and patients have a concomitant specific antibody defect, a trial of gammaglobulin should be considered [27]. Gammaglobulin should be given with a product low in IgA and with caution and potentially providing premedication. The anti-IgA antibodies are not a contraindication, if the gammaglobulin is given subcutaneously [171, 387].

If patient with IgAD who are on a medication known to cause IgA deficiency, the drugs should be changed or discontinued. The prognosis of patients with IgA deficiency depends on the presence of a concomitant specific antibody defect, allergy and autoimmune diseases.

3.13 Other Immunoglobulin Isotypes or Light Chain Deficiencies

(Isolated IgG subclass deficiency, IgA with IgG subclass deficiency, Ig heavy chain mutations/deletions, k light chain deficiency)

3.13.1 Definition

IgG subclass deficiency was first reported in 1970 [361]. It is defined as a deficiency of one or more IgG subclasses, (less than 2SD below the mean normal level for their age) in the presence of a normal level of total IgG [257]. Most such patients show a normal IgM level. In some patients, abnormal IgG subclasses are associated with a low level of IgA [157]. Therefore, IgG subclass deficiency could be seen with or without IgA deficiency. The clinical significance of IgG subclass deficiency in patients with recurrent infections remains unclear because approximately 2 % of normal individuals have an IgG subclass deficiency of one or more IgG subclasses [75, 257]. A low level of one or more IgG subclasses without clinical manifestations is generally not considered sufficient for a diagnosis of immunodeficiency.

3.13.2 Etiology

Human IgG is subdivided into four subclasses, IgG1, IgG2, IgG3 and IgG4. IgG1 is the major component of total IgG (66 %), followed by IgG2 (24 %), IgG3 (7 %) and IgG4 (3 %). IgG1 and IgG3 appear early in ontogeny [257, 361], are efficient activators of the classical complement pathway [70, 120] and are directed mainly against protein antigens. IgG2 includes a preponderance of antibodies to polysaccharide antigens of encapsulated bacteria. The IgG2 subclass reaches the adult level at 5–10 years of age.

The basic pathogenesis of IgG subclass deficiencies remains unknown. In a few cases, lack of expression of Ig isotypes has been shown to be due to homozygous deletions of corresponding constant region genes [64, 274, 301, 308, 371]. Most IgG subclass deficiencies are due to dysregulation of the expression of the γ genes.

The most common type of IgG subclass deficiency is IgG4 deficiency (40 %), followed by those of IgG2 (28 %), IgG3 (17 %) and IgG1 (14 %). Isolated IgG1 deficiency is rare because it usually results in a major deficiency of total IgG.

IgG subclass deficiency is sometimes associated with IgA deficiency. IgG subclass deficiency is also observed in association with other primary immunodeficiency diseases including ataxia telangiectasia [37], Wiskott-Aldrich syndrome [296] and secondary immunodeficiencies such as HIV infection or AIDS [44], as well as following hematopoietic stem cell transplantation [230].

Immunoglobulin heavy chain deletion is an autosomal recessive disease, which is caused by chromosomal deletion of a cluster of genes, the IgG heavy chain locus at 14q32.32 (*IGHG1*, OMIM *147100). One or more IgG and/or IgA subclasses as well as IgE may be absent, but the affected cases may be asymptomatic [71].

klight chain deficiency is an autosomal recessive disease, which is caused by mutations in the immunoglobulin kappa constant region gene located on chromosome 2p11.2 (*IGKC*, OMIM*147200). Although this disease can be associated with other conditions, it can also be asymptomatic. The pathogenesis of the disease involves a failure to express kappa chains, but

the reason for this remains unknown [51, 250, 379, 452].

3.13.3 Clinical Manifestations

The most frequent symptom observed in patients with IgG subclass deficiencies is recurrent respiratory infections such as otitis media, sinusitis and bronchitis caused predominantly by encapsulated organisms [318, 365, 366, 407]. Severe systemic infections including sepsis, pneumonia, meningitis and cellulitis are less common. Some patients also present frequent viral infections. Allergic disease is also frequently encountered in patients with IgG subclass deficiency [234] and many patients are atopic; asthmatic bronchitis is also associated with the respiratory infections.

IgG2 deficiency is the most common subclass deficiency associated with recurrent infection, and may be accompanied by IgA and/or IgG4 deficiencies. Most of these patients have impaired polysaccharide responsiveness. IgG4 deficiency is the most common form of IgG subclass deficiency, but is not usually of clinical significance. However, recurrent pneumonia and bronchiectasis have been described in IgG4 deficiency.

3.13.4 Diagnosis

In patients with recurrent respiratory infections and normal IgG levels, IgG subclass should be evaluated. IgG subclass levels must be compared with those of age-matched controls. In some cases, the total IgG level may be low, and care should be taken to determine whether a diagnosis of common variable immunodeficiency (CVID) might be more appropriate.

Impaired responses to polysaccharide are observed commonly in young patients with IgG2 subclass deficiency [407]. A clinically significant IgG subclass deficiency must be established by measuring the antibody response to vaccine antigen, especially pneumococcal polysaccharide vaccine. In individuals 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 [75]. Susceptibility to infection may wane over time, although immunologic abnormalities may persist [185].

Tests for cellular immunity, complement activity and phagocytic function should be performed to rule out other primary immunodeficiency diseases. Chest X-ray, sinus imaging and pulmonary function tests should be considered. A search for associated illnesses should be undertaken.

3.13.5 Management

Asymptomatic patients with IgG subclass deficiency and normal antibody responses to polysaccharide antigens require no therapy. Many patients do well with prompt medical management and immediate use of antibiotics in the course of an infectious episode.

Some patients with recurrent infections or chronic respiratory infections need to be treated with prophylactic antibiotics, especially in winter. Immunoglobulin replacement therapy is occasionally required in cases with a failure of prolonged antibiotics, severe symptoms and persistent radiographic abnormalities. IgG subclass deficiency without symptoms are not an indication for immunoglobulin replacement therapy.

Some children may recover from IgG subclass deficiency spontaneously, particularly if there is not a complete absence of a subclass. In contrast, symptomatic patients may progress to CVID. Therefore, a repeat of subclass determination yearly or half-yearly is required in patients with IgG subclass deficiency.

3.14 Specific Antibody Deficiency with Normal Immunoglobulin Concentrations

3.14.1 Definition

Specific antibody deficiency (SAD) is characterized by abnormal IgG antibody responses to a majority of polysaccharide antigens and increased

susceptibility to recurrent bacterial infections in subjects over the age of 2 years, but who show normal concentrations of immunoglobulins and IgG subclasses [376, 377, 437]. SAD may be the most common immunodeficiency observed among children with increased susceptibility to infection [145, 186, 199].

3.14.2 Etiology

Although the basic origin of SAD remains unclear, there is some evidence of genetic involvement in certain families and an association with certain Gm and Km IgG allotypes [125]. Studies also suggested a defect in the B-cell repertoire[25] and marginal zone of the spleen [402]. A strong association between SAD and allergic disease suggests that this disorder may be caused by immune dysregulation, with impaired response to polysaccharide antigens [65]. This may help in defining the molecular basis of SAD.

3.14.3 Clinical Manifestations

Patients with SAD usually develop recurrent bacterial respiratory infections such as sinusitis, otitis media and bronchitis. Systemic infections such as pneumonia, sepsis or meningitis are less common. Affected individuals frequently show asthma-like symptoms caused by chronic sinusitis. Almost all children with SAD have at least one form of allergic disease, most commonly allergic rhinitis [65]. Patients usually exhibit normal growth and development.

3.14.4 Diagnosis

The diagnosis of SAD should be considered in patients older than 2 years with recurrent upper and/or lower respiratory tract infections. SAD with normal immunoglobulin levels is a primary immunodeficiency of unknown origin [25, 26, 158, 352, 374, 375]. The prevalence of this disorder is unknown, but it may be a frequent finding in patients evaluated for recurrent respiratory tract infections [145, 186, 199].

Methods that measure IgG and IgM antibodies simultaneously may give falsely normal antibody concentrations due to short-lived increases in IgM antibodies. IgG specific for serotypes included in currently used pneumococcal vaccines may be determined by a standardized ELISA method and expressed in micrograms per milliliter [374].

The most accurate type-specific determinations are made using a reference standard serum (Food and Drug Administration SF89) and preadsorption with C polysaccharide common to all types and the 22 F polysaccharide, which is cross-reactive [98]. (Laboratories that meet these standards include Louisiana State University Children's Hospital, New Orleans, LA; ARUP Laboratories, University of Utah, Salt Lake City, UT; and IBT Reference Laboratory, Progene Biomedical Inc, Lenexa, KS.)

Protection against infection and colonization is associated with antibody concentrations of 1.3 μg/mL or higher or 200–300 ng of antibody nitrogen per milliliter (N/mL) per serotype. The conversion factor is 160 ng of antibody N/mL to 1 μg/mL [235, 238].

The interpretation of antipneumococcal antibody concentration results is based on antibody increases over preimmunization concentrations (immune response) and on final concentrations following immunization. High pre-immunization antibody concentrations to a specific serotype are less likely to rise after immunization [375].

Adequate responses to individual pneumococcal serotypes are defined as a postimmunization antibody concentration of 1.3 μg/mL or higher or at least fourfold over baseline [26, 375]. In patients immunized with heptavalent pneumococcal conjugate vaccine, it is important to measure antibody responses against at least 6 serotypes present only in the polysaccharide vaccine.

Age also plays a significant role in the interpretation of responses to polysaccharide immunization. Well-validated age-adjusted criteria that define normal responsiveness to pure polysaccharides are yet to be developed. In general, responses to pure polysaccharide antigens are

unreliable in patients younger than 2 years [375]. Between the ages of 2 and 5 years, individuals should respond to approximately half or more of the pneumococcal type-specific polysaccharides.

Although controversy exists regarding the actual number of pneumococcal serotypes needed to determine a normal response, the consensus recommends that for patients older than 5 years, individuals should respond to at least approximately 70% of pneumococcal serotypes. Pneumococcal conjugate vaccines stimulate antibody responses as would other protein immunogens. Criteria regarding the magnitude and number of serotypes in response to conjugate pneumococcal vaccines with respect to the diagnosis of primary immunodeficiency have not been established.

3.14.5 Management

Patients with SAD may benefit from additional immunization with conjugate pneumococcal vaccines. Patients who fail to respond to the polysaccharide vaccine when immunized after 2 years of age usually respond to the conjugate vaccine [374]. If there are no responses to vaccines and the patient remains symptomatic, immunoglobulin therapy should be considered to control and prevent infections.

3.15 Transient Hypogammaglobulinemia of Infancy

3.15.1 Definition

Transient hypogammaglobulinemia of infancy (THI) was first reported in 1956 [164]. It is defined as hypogammaglobulinemia due to abnormal and prolonged delay in IgG production by infants that extends to the 2 or 3 years of age [133, 266]. THI is defined as a low level of IgG (less than 2SD below the mean for their age), with or without reduction of IgA and/or IgM, in an infant beyond 6 months of age in whom other primary immunodeficiencies have been ruled out. Despite the low level of IgG, most infants can respond to vaccine antigens. The true incidence of THI has not been estimated because it is rarely associated with severe infection and cases are not referred to immunologists.

3.15.2 Etiology

There is no known genetic basis for THI, although an increased incidence is reported in families with other immunodeficient individuals. Twelve patients with THI were described to have an increased incidence of atopic diseases [428]. Transiently elevated $CD4^+$ $CD25^{high}$ $FOXP3^+$ T-cell numbers, reduced CD19 expression and decreased memory B-cell numbers were also observed in patients with THI [32, 341]. Some studies suggested that THI was caused by T-helper deficiency [367] or a cytokine imbalance [226].

3.15.3 Clinical Manifestations

Some infants with THI are asymptomatic, have a normal response to vaccine antigen and grow out of their hypogammaglobulinemia. However, clinical manifestations of THI include bacterial sinopulmonary infections and other respiratory tract infections [74]. THI is rarely associated with sepsis, meningitis, or invasive infections [74, 216]. Case reports have documented these more severe infections [74, 224], but studies of larger cohorts indicate that they are uncommon [216]. Sixty percent of patients are male. Some children may have asymptomatic hypogammaglobulinemia, and others may have allergies or autoimmune diseases [283]. Patients may be associated with hematologic abnormalities, most commonly mild neutropenia and less commonly thrombocytopenia. Infants with THI have normal growth and development.

3.15.4 Diagnosis

The clinical presentation of transient hypogammaglobulinemia of infancy (THI) occurs in infants and young children with recurrent

bacterial sinopulmonary infections and frequent viral illnesses. Infants are normally protected by transplacentally acquired maternal IgG for the first 3–6 months of life, until the natural degradation of the maternal antibodies (half-life of approximately 21 days). In some infants, production of IgG (and in some cases IgA and IgM) does not reach normal levels until early childhood (as late as 36 months). This delay in antibody production may be associated with recurrent infections. In THI, IgG levels spontaneously correct to normal at a mean age of 27 months, with all patients reaching normal levels by 59 months [134].

The definitive diagnosis of THI can only be made after IgG (and in some cases IgA and/or IgM) levels have corrected; before that, infants with a decreased IgG concentration have hypogammaglobulinemia of infancy that may become THI. Although most children with THI spontaneously recover their IgG values and have a benign clinical course, some of them do not recover and develop selective IgA deficiency, common variable immunodeficiency or other forms of dysgammaglobulinemia [266].

In THI, IgG concentrations were repeatedly below the age-specific normal range for a period of time during infancy and early childhood. IgM and or IgA may also be transiently low. Specific antibody production is usually preserved, and cellular immunity is intact. Isolated, transient deficiencies of IgA, IgG2 [36] and specific antibody deficiencies are sometimes associated with THI.

Laboratory evaluation in THI reveals IgG levels below the fifth percentile for their age [447]. Some authors stipulate that measurements be repeated to eliminate misdiagnosis due to laboratory error [401]; however, this is not universally applied. A decreased IgG level is sometimes associated with a decreased IgA level and, less often, with a decreased IgM level [216]. Evaluation also includes measurement of specific antibody production to protein and polysaccharide antigens and enumeration of lymphocyte subsets by flow cytometry. Most children have normal booster responses to protein vaccines and normal isohemagglutinin concentrations. Transient impairment of antibody responses to viral infections was noted in one report, but measurement of antiviral antibody titers is not usually part of the evaluation [84]. Rare individuals have transient suppression of vaccine responses, which recovers by the age of 3–4 years [118]. Decreased numbers of circulating T cells were noted in some patients with THI, but this is also not a prominent feature in most patients [367].

3.15.5 Management

Prediction of the eventual outcome of hypogammaglobulinemia towards THI as opposed to a persistent form of immunodeficiency is based on the clinical severity [439] and the ability to respond to specific antigens despite low IgG concentrations. Recently, evaluation of memory B cells has been used to predict the evolution of hypogammaglobulinemia of infancy with patients with low IgM and/or class-switched memory B cells being more likely to have a permanent form of immunodeficiency [283].

THI is a self-limited disease, with recovery by 3 years of age. Therefore, asymptomatic patients with THI require no treatment, and immunoglobulin levels should be monitored at least every 12 months if infections begin to occur, to document their therapy.

Preventive antibiotic therapy may be indicated for some patients with THI. A period of IVIG replacement may be considered. Antibiotic prophylaxis should be the initial mode of preventive therapy. If this fails or is not tolerated, some patients may benefit from immunoglobulin administration, particularly during seasons when respiratory illnesses are more frequent. An increase in the patient's own IgG production can be monitored by keeping the IgG dose and infusion intervals constant; IgG production is clearly reflected by increasing IgG trough levels. When IgA and/or IgM are also low at the start of IgG replacement, their levels should also be monitored regularly. An increase into the normal range is a clear sign of improvement and may allow discontinuation

of IgG replacement therapy based on objective data. Immunoglobulin replacement therapy should be stopped after 3–6 months to reassess the status of the patient's humoral immune function [118].

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