Agammaglobulinemias: Basic Pathogenesis and Clinical Spectrum

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2.1 X-Linked Agammaglobulinemia (XLA)

2.1.1 Definition

X-linked agammaglobulinemia (XLA) is a rare form of primary immunodeficiency characterized by absence of circulating B cells with severe reduction in all serum immunoglobulin levels due to mutations in the gene encoding BTK (Bruton's tyrosine kinase). The incidence of the disease varies from 1:100.000 to 1:200.000 depending on ethnicity.

2.1.2 Etiology

The first patient affected with agammaglobulinemia was described by Colonel Bruton in 1952 [1]; however, it was only after four decades that the underlying genetic defect was identified [2, 3]. The gene responsible for XLA maps on the X chromosome and encodes for a member of the Tec family of kinases, i.e., Bruton's tyrosine kinase (BTK). BTK was found to be mutated in the majority of male patients [4–7]. B cells express an important receptor complex on their cell surface: the B-cell receptor (BCR) or pre-BCR in the bone marrow [8]; BTK is an important downstream kinase of the BCR-signaling cascade. The knockout mouse model for XLA (xid mouse) was particularly helpful in studying the role of BTK [9]. Normally, early B-cell development takes place in the bone marrow, where, starting from the pluripotent stem cells, B cells undergo several steps of differentiation: from pro-B

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to pre-B to immature B cells to mature B cells, ready to enter the periphery [10–12]. Bone marrow analysis of patients mutated in BTK showed a consistent block at the pro-B to pre-B stage of B-cell development, underlying the important role for BTK in early B-cell development [13]. In fact, affected patients typically have less than 1–2 % of B cell in the periphery, confirming the almost complete block of early B-cell development in this disorder [14, 15]. Consequently, immunoglobulin serum levels are severely reduced, and there is no humoral response to vaccinations. The lack of B cells results in a significant reduction in size of tissues such as lymph nodes and tonsils, normally highly populated by B cells.

Mutations in BTK are transmitted in an X-linked manner and may be familiar (in this case, mothers of affected patients are healthy carriers) or de novo ones.

2.1.3 Clinical Manifestations

Maternal IgGs, transferred through the placenta, play a protective role against infections in infants for the first 6–12 months of life. In XLA patients, clinical manifestations become evident around this period, when maternal IgGs are catabolized and their protective effect is not present anymore. The hallmarks of the disease are recurrent bacterial respiratory and/or gastrointestinal infections, although some patients may remain asymptomatic for the first years of life. In rare cases, diagnosis of XLA is made in adolescence or even in adulthood due to lack of symptoms until that age. The typical range of infections in XLA patients includes recurrent otitis media, sinusitis, bronchitis, pneumonia, and gastrointestinal infections. Although the incidence of these types of infections varies among the different cohorts so far reported, it appears that the main type of infections involves the upper and lower respiratory tract [4, 6, 16, 17].

Encapsulated pyogenic bacteria are the main infectious agents in XLA, both at diagnosis and upon immunoglobulin replacement treatment. Bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and others are most frequently identified as causative in these patients (Table 2.1). In the case of invasive bacterial infections, such as septicemia, the main infectious agents are *Pseudomonas species*, followed by *H. influenzae*, *S. pneumoniae*, and *S. aureus*. Bacterial meningitis on the other hand may complicate the clinical history of these patients, especially before diagnosis, and is caused by the same infectious agents mentioned before. Before diagnosis, septic arthritis may complicate the clinical history of affected patients and is mainly caused by *H. influenzae* and *S. pneumoniae*, while once immunoglobulin replacement treatment is initiated, viral agents are frequently responsible.

Recurrent infections of the upper and lower respiratory tract are an important clinical problem for patients with XLA, both before and after diagnosis [4, 6, 16]. Chronic sinusitis is reported to be a consistent clinical finding in almost two thirds of affected patients, even upon Ig treatment. Similarly, recurrent infections of the lower respiratory tract, even under Ig replacement treatment, lead to the development of bronchiectasis compromising severely the clinical course of the disease (Fig. 2.1).

Table 2.1 Most frequently isolated bacterial infectious agents in X-linked agammaglobulinemia according to the site of infections

Etiology of pneumonia in XLA	
Haemophilus influenzae type b	58 %
Streptococcus pneumoniae	17 %
Staphylococcus aureus	17 %
Pseudomonas aeruginosa	8 %
Etiology of sinusitis in XLA	
Haemophilus influenzae type b	67 %
Streptococcus pneumoniae	14 %
Staphylococcus aureus	10 %
Klebsiella	3 %
Moraxella	3 %
Pseudomonas aeruginosa	2 %
Etiology of GI infections in XLA	
Giardia	60 %
Salmonella	20 %
Campylobacter	8 %
Escherichia coli	8 %
Blastocystis	4 %

Data based on long-term follow-up of 125 XLA patients, courtesy of the IPINET registry, Italy

Infections of the gastrointestinal tract represent an important clinical burden in XLA (Table 2.1). One of the most frequently isolated infectious agents is *Giardia lamblia*, and unfortunately, its eradication is not always successful, leading to protracted and/or recurrent diarrhea and malabsorption (Fig. 2.2). A similar clinical picture may be caused by *Campylobacter jejuni*, and several cases of gastrointestinal infections caused by *Salmonella* have also been reported in XLA. *Helicobacter-like* organisms may cause invasive infections with fever and lower limb cellulitis that may progress to a "woody-appearing" skin lesion (Fig. 2.3) and require long period of intravenous antibiotics. Finally, *Helicobacter cinaedi* bacteremia was recently reported in an adult XLA patient presenting with macules but without fever [18].

Besides the infectious agents mentioned so far, *Mycoplasma species* may cause infections in XLA patients, especially of the respiratory and urogenital tract and in rare cases the joints. It is not always easy to isolate the infectious agent, and therefore, the clinical course may be prolonged and severe. *Mycoplasma* may coexist with other bacterial agents during infections rendering the disease more severe. Bacterial conjunctivitis is relatively frequent in agammaglobulinemia, affecting almost 6–8 % of patients.

Besides bacteria, also virus may complicate the clinical history of patients affected with XLA. The most frequently isolated virus in XLA is enteroviruses, namely, poliovirus, echovirus, and coxsackievirus. Patients with XLA have been reported to develop vaccine-associated poliomyelitis in the case of vaccination with the live attenuated oral vaccine (Sabin) associated with a high mortality rate.

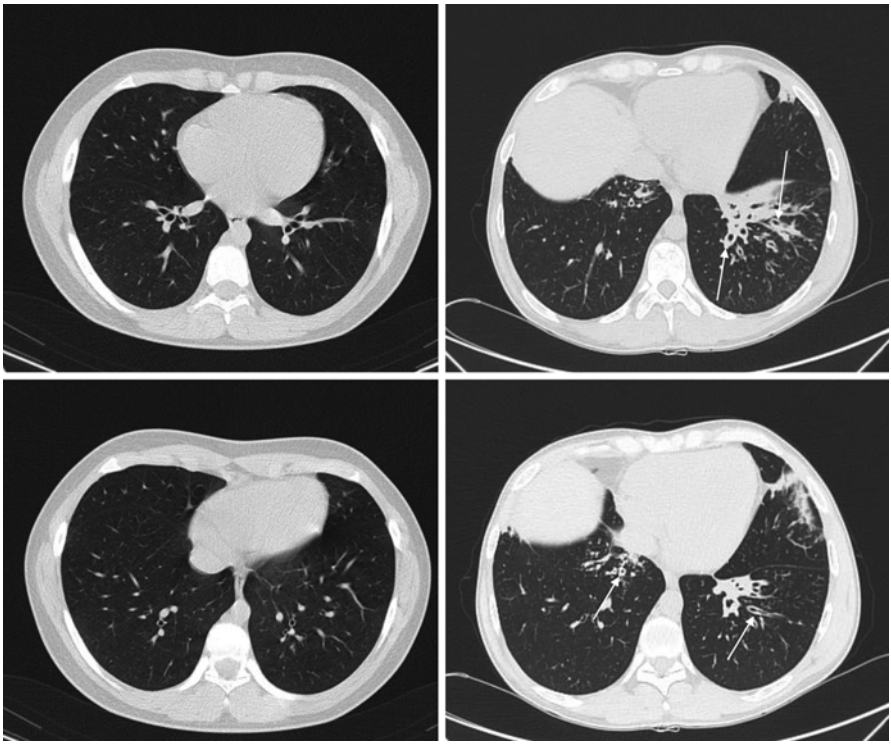

Fig. 2.1 Lung CT scans from XLA patients. While some patients do not develop bronchiectasis (*left panels*), many XLA patients tend to develop bronchiectasis (*right panels*, *white arrows*) even when under regular immunoglobulin replacement treatment (Courtesy of Dr. MP Bondioni, Pediatric Radiology Unit, University of Brescia, Spedali Civili di Brescia, Italy)

Besides the classical manifestations associated with the onset of the enteroviral infection, XLA patients may also develop subacute progressive neurological symptoms such as ataxia, loss of cognitive skills, paresthesias, and sensorineural hearing loss; these symptoms should always raise the suspicion of an infection caused by enterovirus. In fact, XLA patients may develop enteroviral meningoencephalitis mainly with a slow, chronic, and progressive pattern, although acute onset with fever and seizures has also been reported in a limited number of cases. It is not always easy to isolate the enterovirus from the CSF. In recent years, the application of molecular biology techniques such PCR was initially thought to be able to overcome this problem; however, despite this technical improvement, enteroviral detection is not always successful. Typical findings in the CSF of these patients may include pleocytosis, elevated protein content, and in some cases hypoglycorrhachia, suggestive of a viral infection, although most frequently the CSF characteristics in XLA patients may be almost normal. IVIG treatment radically reduced the incidence of chronic enteroviral infections in XLA patients, although they are not completely eradicated yet. In some cases, the protective effect of IVIG against enteroviral

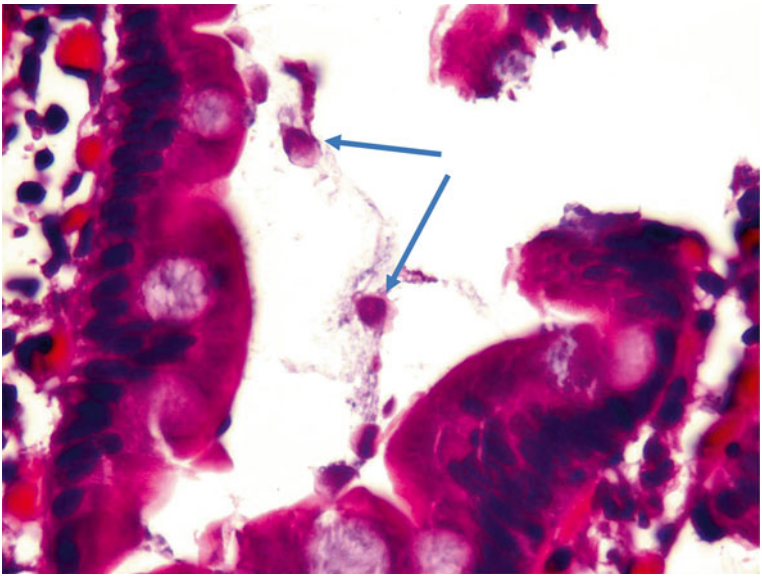

Fig. 2.2 Giardia lamblia gastrointestinal infection in XLA. Histological examination of gastric biopsy specimen from an XLA patient showing the presence of Giardia lamblia (*blue arrows*) (Courtesy of Dr. V. Villanacci, Institute of Pathology, Spedali Civili, Brescia, Italy)

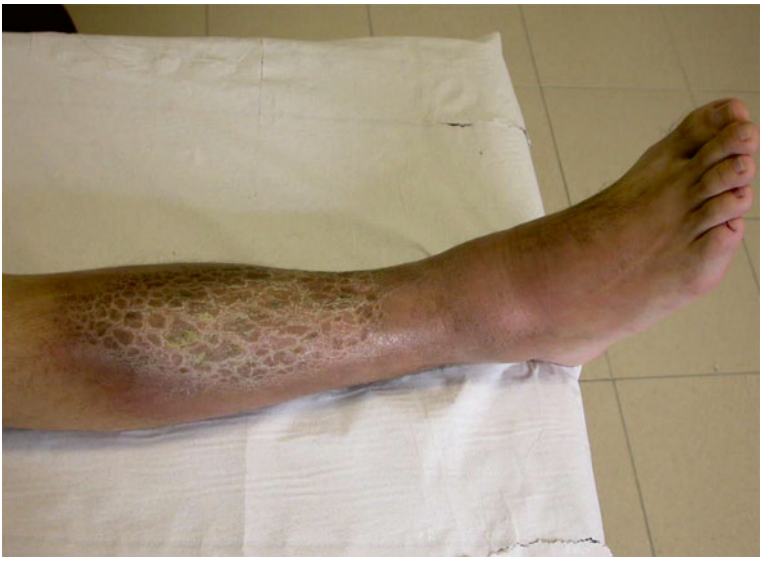

Fig. 2.3 Skin manifestations during Helicobacter-like organism infection in an XLA patient. Erythemato-squamous lesions of the lower right art during a systemic infection sustained by Helicobacter-like species

infections in XLA has been associated to high-dose treatment (and not the usual dosage applied in replacement treatment), although the limited number of patients reported does not allow definitive conclusions. The mechanism proposed is based on the anti-inflammatory effect of high-dose immunoglobulins, although further data are needed to validate the effective mechanism. Combined treatment with high-dose immunoglobulins and pleconaril has been reported to be effective in controlling enteroviral infection in patients affected with XLA [19–21]. Although reported data have shown certain efficacy of pleconaril in this type of infection, this drug is no longer available for compassionate use. Brain imaging such as MRI or CT scans is almost always normal at the onset of the disease, while chronic enteroviral infections are progressively characterized by the development of cerebral edema, diffuse inflammation, and progressive cerebral atrophy [22–25]. Rare cases of leptomeningitis in XLA patients (instead of the classical form of encephalitis) have also been reported.

Besides neurological involvement, CNS enteroviral infection may also present with other symptoms such as peripheral edema and erythematosus rash that may resemble a dermatomyositis-like syndrome [26]. When biopsies are performed from the skin or the muscle, they evidence inflammation as main feature. Enteroviral infection may also present with liver involvement including ALT increase and hepatomegaly, with or without fever or rash. The peripheral involvement described here is characteristic of disseminated enteroviral infection, which is not always characterized by a favorable prognosis.

Immunoglobulin preparations are quite safe nowadays; however, in the early 1990s, hepatitis C contamination was reported in XLA patients. Interestingly, it seems that XLA patients tolerate better this infection when compared to patients affected with CVID. Among reported XLA patients with hepatitis C, more than one third of infected patients cleared the infection or remained asymptomatic, and only one patient developed hepatic failure, but he was also coinfected with hepatitis B. Rare manifestations in XLA patients include pneumonia caused by *Pneumocystis jiroveci* (Fig. 2.4) [27–29], recurrent pyoderma (being the only clinical finding in an XLA patient) [30], and chronic gingivitis (being the only clinical finding in an XLA patient) [31].

Joint involvement may be present in XLA patients in almost 20 % of cases [4, 6, 16, 17]. The typical clinical presentation resembles that of rheumatoid arthritis (RA) with pain, motion limitation, effusion, and destructive pannus formation. Although in most cases no isolates are found, a pyogenic cause may be identified in a limited number of cases. Empirical treatment consists of IVIG treatment, with frequently beneficial effect, in addition with antibiotic treatment, suggesting a possible infectious cause. Among the reported isolates, enterovirus and *Mycoplasma species* are the most frequent ones. Although B cells have been reported to be associated with the pathogenesis of RA, no B-cell infiltrates were found in the synovium of XLA patients with RA.

The hematologic manifestation that has been mainly reported in XLA is neutropenia. The percentage of XLA patients with neutropenia, mainly of secondary nature, before IVIG treatment is variable, depending on the cohort of patients

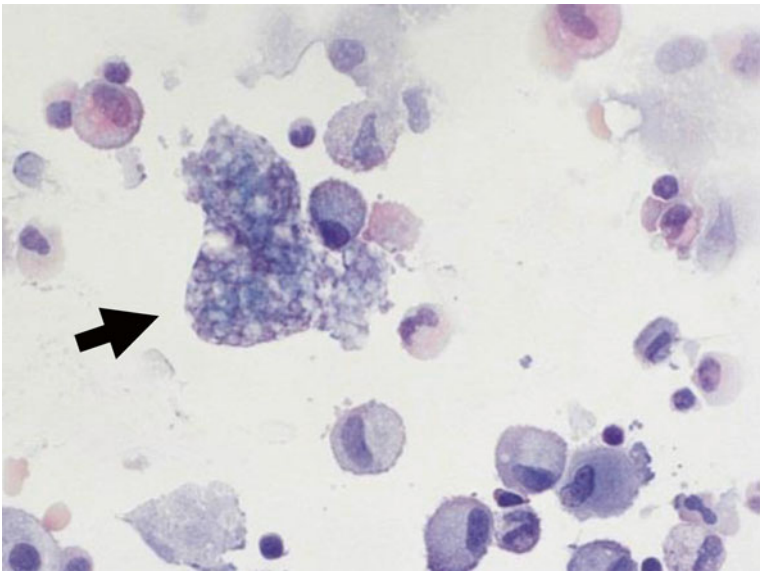

Fig. 2.4 Bronchoalveolar lavage from an XLA patient showing *Pneumocystis jiroveci*. A patient affected with XLA and respiratory symptoms nonresponsive to classical antibiotic treatment underwent bronchoalveolar lavage revealing the presence of *Pneumocystis jiroveci* (*black arrow*). This patient was under steroid therapy

reported, ranging from 10 to 25 % [32–36]. However, to date, the precise role of BTK in neutrophil development/homeostasis is not completely clear yet. XLA patients have also been reported to develop acute lymphoblastic leukemia [37].

Finally, other manifestations that have been reported in XLA patients include glomerulonephritis [38], alopecia, amyloidosis, and von Recklinghausen disease [39].

2.1.4 Diagnosis

The hallmark of XLA is the absence of peripheral B cells (<2 %) in the presence of very low to absent immunoglobulin serum levels of all classes [40, 41]. In rare cases, B cells may be detected in the periphery, but additional immunological workup such as recall antibody responses to specific antigens may be of additional help. Once the clinical suspicion is confirmed from the immunological examination, BTK protein expression in cells other than B cells such as monocytes can be a rapid and economic diagnostic tool allowing both for early diagnosis of affected patients and identification of healthy carriers (Fig. 2.5). The genetic analysis should always follow BTK expression testing, being the former considered the gold standard for a definite diagnosis of XLA. In the case a mutation in BTK is found in the affected patient, the mother's carrier status should be examined. Finally, prenatal diagnosis can also be performed once the mutation in BTK is identified.

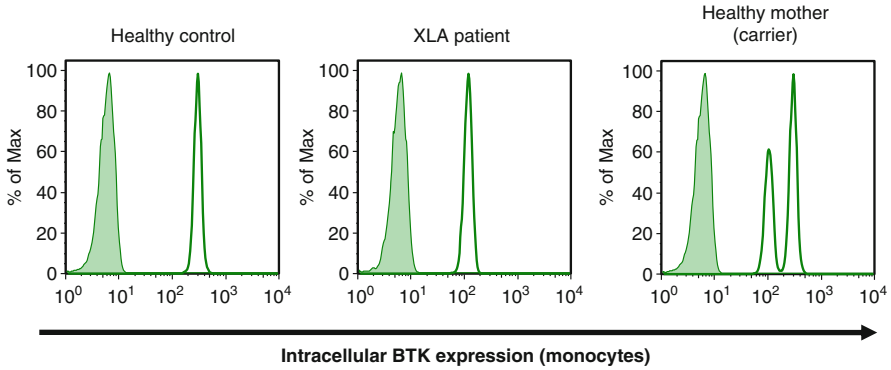

Fig. 2.5 Flow cytometric analysis of BTK intracellular expression in monocytes. BTK expression in human monocytes shown as histogram in a healthy control (*left panel*), an affected patient (*mid panel*), and his mother who is a healthy carrier (*right panel*) (Courtesy of Dr. D. Moratto, Institute for Molecular Medicine "A. Nocivelli," Spedali Civili di Brescia, University of Brescia, Brescia, Italy)

Table 2.2 List of genes associated with autosomal recessive agammaglobulinemia (ARA)

Gene	Protein	Chromosome	OMIM
IGHM	Mu HC	14q32.33	147020
CD79A	Igα	19q13.2	112205
CD79B	Igβ	17q23.3	147245
BLNK	BLNK	10q24.1	604515
IGLL1	λ5	22q11.23	146770
PIK3R1	p85α	5q13.1	171833

2.2 AR-Agammaglobulinemia (MUHC, IGA, IGB, L5, BLNK, and p85α)

2.2.1 Definition

Autosomal recessive agammaglobulinemia (ARA) affects both males (in the absence of BTK mutations) and females and is a rare form of primary immunodeficiency characterized by severe reduction of all immunoglobulin classes and absence of peripheral B cells [40, 41]. The underlying genetic defect is currently known only in a limited number of patients (Table 2.2).

2.2.2 Etiology

Early B-cell development takes place in the bone marrow through a highly orchestrated process with the sequential and highly regulated expression of specific gene products that regulate the maturation from pro-B to pre-B to immature B cells to

mature B cells that can entry the periphery [42–47]. An important step in this differentiation process is the formation of the pre-B cell that expresses on the cell surface the pre-BCR (pre-B-cell receptor) complex formed by the mu heavy chain, Igα, Igβ, VpreB, and λ5 [8]. Pre-BCR is essential for the signaling events that promote further differentiation of B cells trough kinases such as BTK, BLNK, and others. Furthermore, kinases dependent on other signaling cascades, such as PI3K (e.g., downstream of the CD19-CD21-CD81 complex), have a positive effect on the BCR-signaling cascade [48, 49]. The important role of these molecules in early B-cell development was demonstrated through both animal models and in vitro models, rendering therefore the genes encoding for these proteins' candidate genes for agammaglobulinemia of unknown genetic origin.

In 1996, the first patients mutated in mu heavy chain with autosomal recessive agammaglobulinemia (ARA) were described [50]. Two parallel studies in the USA and in Italy studied the prevalence of mu heavy chain deficiency among patients affected with ARA which reached around 40–50 % among the studied patients [51].

The surrogate light chains λ5/14.1 and VpreB are part of the pre-BCR complex and are important of the early B-cell development. A single patient with mutations in the λ5/14.1 gene has been reported so far [52].

The two signaling transducing molecules Igα and Igβ associate with the pre-BCR and the BCR and are essential for B-cell development [8, 10, 11]. So far, five patients have been reported to be affected with Igα deficiency. The mutation in Igα in the first patient identified resulted in alternative exon splicing of the gene product which abolishes the expression of the protein on the cell surface [53]. The second reported patient, of Turkish origin, carried a homozygous alteration at an invariant splice donor site of intron 2 [54]. Two additional patients with defects in the extracellular domain were also reported [15]. Finally, the fifth reported patient, of Iranian origin, carried a novel homozygous nonsense mutation in the gene encoding Igα [55].

To date, only three patients with biallelic mutations in Igβ have been reported. The first one is a female patient carrying a hypomorphic mutation in Igβ and a leaky defect in B-cell development [56]. The second patient, a male of 20 years of age, presented a homozygous nonsense mutation resulting in a stop codon, resulting in a complete block of B-cell development at the pro-B- to pre-B-cell transition in the bone marrow, similarly to what observed in the animal model [57]. Finally, the third patient is a female child that carries a novel homozygous nonsense mutation in the gene encoding for Igβ [58].

Upon BCR cross-linking, various kinases are involved in the downstream signaling cascade. One of these, BLNK (also called SLP-65), was initially found to be mutated in a single patient with a specific block at the pro-B to pre-B stage in the bone marrow [59]. Recent experimental data have underlined the important role of BLNK for B-cell homeostasis and differentiation upon BCR expression on the cell surface [60]. Other two siblings with deleterious frameshift mutations in BLNK and agammaglobulinemia were recently reported [61].

PI3K comprises a family of kinases expressed in various cell types that play important roles in various biological processes such as cell cycle, metabolism cell

growth, migration, and others. Regarding B cells, a novel homozygous nonsense mutation in p85α was recently identified in a single female patient with agammaglobulinemia, leading to an earlier block in B-cell development in the bone marrow, before the expression of CD19 on the surface of B cells [62]. Interestingly, although expressed in other cell types such as T cells, dendritic cells, and others, these appear functionally unaffected from the presence of this mutation.

2.2.3 Clinical Manifestations

Clinical findings in patients affected with ARA resemble those of XLA, although apparently in a more severe manner. Frequently, the onset of the disease is also earlier.

Regarding mu heavy chain deficiency, the infectious spectrum at onset is rather similar to that observed in XLA: recurrent otitis media, bronchitis, sinusitis, pneumonia, chronic enteroviral encephalitis, and sepsis (frequently caused by *Pseudomonas aeruginosa*) [50, 51]. As observed in XLA, the clinical picture ameliorated upon Ig replacement treatment is initiated on a regular basis. Chronic intestinal infection sustained by *Giardia lamblia*, resistant to treatment, has been observed in one female patient (Plebani, personal communication). Neutropenia is a rather frequent hematological finding in this disorder, since it may be observed in almost one third of patients and usually normalizes upon immunoglobulin replacement therapy.

The limited number of patients affected with the other reported autosomal recessive defects leading to agammaglobulinemia does not allow for conclusive remarks. The only patient reported so far to be affected with λ5/14.1 deficiency presented an episode of *Haemophilus* meningitis and recurrent otitis media and was found to be hypogammaglobulinemic at the age of 5 years. Peripheral B cells were almost undetectable (<0.06 %). Bone marrow analysis confirmed the early block in B-cell development at the pro-B to pre-B stage.

The clinical spectrum of patients affected with Igα deficiency is variable, even though a limited number of patients (five) have been reported so far. The first reported patient presented an early onset with diarrhea and failure to thrive in the first month of life [53]. She was admitted at the age of 12 months for bronchitis and neutropenia. Immunological workup showed absence of peripheral B cells and undetectable serum immunoglobulins; the patients did not have detectable lymph nodes. Bone marrow analysis showed a pro-B to pre-B block in the early steps of B-cell development. The second reported patient (male) presented a clinical history of diarrhea and respiratory infections; he also developed a dermatomyositis-like phenotype. Unfortunately, the patient died of a pulmonary infection [54]. The female patient carrying the early stop codon in Igα presented a severe neurological manifestation resembling initially a febrile seizure that was however not responsive to classical therapeutic approaches [55]. The continuous worsening of the clinical status of the patient led to the immunological workup showing agammaglobulinemia and absence of peripheral B cells. Clinical data on the other two patients affected with Igα deficiency are not available.

Three patients affected with Igβ deficiency have been reported so far. The patient carrying the hypomorphic mutation had a history of recurrent lower respiratory infections starting from 5 months of age, while diagnosis was made at the age of 15 months [56]. Immunoglobulin replacement treatment ameliorated the patient's clinical condition. The patient with the first nonsense mutation reported in Igβ was admitted at the age of 8 months for pneumonia and salmonella enteritis [57]. During this admission, his immunological workup showed indosable immunoglobulin serum levels for all classes and absence of peripheral B cells (<1 %). Although the patient was started on IVIG, his clinical history was complicated by recurrent respiratory infections both of the upper and the lower respiratory tract and bacterial conjunctivitis. The third patient carrying a novel homozygous mutation in Igβ presented a history of respiratory infections; at the age of 15 months, she was admitted due to echthyma of the left gluteus and neutropenia [58]. Immunological workup showed lack of serum immunoglobulins of all classes and absence of peripheral B cells. IVIG treatment was started and the neutropenia resolved within three months.

The clinical presentation of the first patient affected with BLNK deficiency included, by the age of 8 months, two episodes of pneumonia and recurrent otitis [59]. Once the diagnosis of agammaglobulinemia was made due to low immunoglobulin serum levels and absence of peripheral B cells, he was started on IVIG; however, he continued presenting recurrent otitis media and sinusitis and developed protein-losing enteropathy during adolescence. Unfortunately, he also developed hepatitis C related to the immunoglobulin preparations. Another two patients (siblings) affected with BLNK deficiency were recently reported [61]. The male patient was diagnosed at the age of 6 months with a clinical history of recurrent otitis and diarrhea [61]. During follow-up he developed arthritis and diffuse dermatitis. PCR revealed the presence of enteroviral infection in peripheral blood, although the skin biopsy did not evidence the presence of the virus. The female sister of the above-mentioned patient was diagnosed at the age of 12 months with a clinical history of recurrent otitis and sinopulmonary infections. Her clinical history was complicated by diarrhea, obstructive lung disease, and arthralgia [61].

The female patient affected with p85a deficiency presented an early onset of symptoms: at the age of 3.5 months, she was admitted for neutropenia, gastroenteritis, and interstitial pneumonia. Immunological workup showed agammaglobulinemia in the absence of peripheral B cells [62]. During follow-up and into her adolescent years, the patient developed erythema nodosum, arthritis, *Campylobacter* bacteremia, and inflammatory bowel disease. No metabolic alteration was reported.

2.2.4 Diagnosis

The presentation of ARA is similar to that of XLA: low to undetectable immunoglobulin serum levels in the almost complete absence of peripheral B cells, as defined by CD19 and CD20 expression (<2 %). Male patients, once BTK deficiency is excluded, and affected female patients should undertake sequencing analysis for mu heavy chain, Igα, Igβ, λ5, BLNK, and p85α for a definite diagnosis.

2.3 Autosomal Dominant Agammaglobulinemia (E47/TCF3)

Until recently, X-linked (the more frequent) or autosomal recessive forms of agammaglobulinemia were known. However, autosomal dominant E47/TCF3 deficiency was recently described in four patients with agammaglobulinemia and reduced peripheral B cells that expressed CD19 but lacked BCR expression on the cell surface [63].

The broadly expressed transcription factor E47 resulted mutated in the four patients with TCF3 deficiency. The role of E47 in B-cell development had been previously highlighted in the animal model [64]. All reported patients harbored the heterozygous E555K mutation and showed an unusual peripheral B-cell phenotype: enhanced CD19 expression with absent expression of BCR. B-cell development in the bone marrow was performed in two out of four affected patients and showed a block of B-cell development earlier than that observed in XLA or ARA. Affected patients presented a complicated clinical history compatible with agammaglobulinemia: pneumococcal meningitis, recurrent otitis, vaccine-associated poliomyelitis, and arthritis. Associated clinical features included eosinophilic dermatitis and hepatomegaly [63].

2.4 Management of Agammaglobulinemia (X-Linked, Autosomal Recessive, and Autosomal Dominant Forms)

Agammaglobulinemia is a humoral immunodeficiency, and as such, patients' management is based on immunoglobulin replacement treatment. The introduction of immunoglobulin replacement treatment has radically changed the prognosis of affected patients. In the past, the intramuscular route of administration was applied with the major pitfall of not reaching protective IgG trough serum levels. Current routes of administration are two: intravenous or subcutaneous. While intravenous preparations are administered every 21–28 days at a dose of 400 mg/kg/dose, the subcutaneous ones are administered weekly at a dose of 100 mg/kg/dose. The main objective of the replacement treatment has been to maintain pre-infusion IgG levels >500 mg/dl. However, in recent years, it is becoming more and more evident that the dose should be more patient oriented in order to obtain the maximum benefit.

Considering the rarity of autosomal recessive and even more autosomal dominant forms of agammaglobulinemia, the majority of available data in the literature is based on XLA. In fact, long-term follow-up studies in patients affected with XLA have demonstrated that they tend to develop lung complications (chronic lung disease, CLD), even if Ig replacement treatment is performed regularly. This may depend on different factors: delayed diagnosis, previous intramuscular route of administration (reduced IgG availability and therefore lower trough levels), secreted antibodies cannot be substituted (Ig preparations contain only IgG), and Ig preparations contain pools of poly-specific IgGs, nonselected on antigen specificity. One of the major factors affecting XLA patients' prognosis is the development of CLD [6].

Since Ig replacement treatment alone is not always sufficient to prevent the development of bronchiectasis and consequently CLD, respiratory physiotherapy may have a beneficial effect on long-term outcome in XLA patients in terms of maintenance and even improvement of lung function.

Infectious episodes in patients affected with agammaglobulinemia should always be treated with antibiotics. In some cases, affected patients under Ig replacement treatment may require brief or long periods of antibiotic prophylaxis, depending on their clinical conditions. Considering the monogenic defect in XLA, novel therapeutic approaches have been proposed in recent years. Gene therapy is one of them and has been applied in murine models with encouraging results [65], although clinical application is not under consideration yet. Another recent therapeutic approach used antisense oligonucleotides (ASOs), compounds that have the ability to modulate pre-mRNA splicing and alter gene expression, in BTK mutations that affect normal mRNA splicing [66]. Further experiments are required before considering this option in patients' management.

As mentioned before, and although regular Ig replacement treatment and correct antibiotic therapy have radically modified patients' clinical history, their prognosis is still conditioned by the occurrence of complications. In particular, pulmonary complications such as development of bronchiectasis and CLD still occur, and so far, it appears that the right therapeutic approach is still to be defined [6].

Regarding ARA, the clinical data regarding follow-up and clinical complications is rather limited, due to the small number of reported cases. Nonetheless, so far, the prognosis for ARA appears similar to that of XLA.

Finally, XLA patients are reported to have an increased incidence of malignancies, including colorectal cancer, gastric adenocarcinoma, and lymphoid malignancies [4, 6, 16, 17, 37, 67–69].

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