Chapter 10

Bruton's Disease

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Additional information is available at the end of the chapter

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Abstract

Bruton's disease, in other terms X-linked agammaglobulinemia (XLA), is the first reported primary immunodeficiency in 1952, caused by a single genetic defect. The development of B cell is under control of signals transmitted by the B-cell antigen receptor (BCR) complex. Lyn, Syk, and Bruton's tyrosine kinase (BTK) are cytoplasmic protein tyrosine kinases. XLA is caused by mutations in the Btk gene, and Btk mutations are responsible for 85% of all antibody deficiencies. Btk mutation interrupts the B-cell development at the pre-B-cell stage, resulting in the absence of B lymphocytes and plasma cells in peripheral blood and peripheral lymphoid tissues. Up till now, 380 unique mutations have been identified. Autosomal recessive forms of agammaglobulinemia also result in B-cell defects, but more severe bacterial infections are seen in XLA patients due to absolute block in early B-cell development. All serum immunoglobulin isotypes are decreased, and antibody production especially against vaccine antigens is impaired.

Most of the XLA patients have clinical signs and symptoms after 6 to 9 months of age due to diminished protective maternal antibodies transmitted through placenta. The most frequent symptoms are recurrent upper and lower respiratory tract infections, some of them may suffer from neutropenia.

These patients are susceptible to enteroviral infection, which causes chronic meningoencephalitis and dermatomyositis-like syndrome. Recurrent respiratory tract infections lead to chronic lung disease and bronchiectasis. These infections may disable the patient and result in death. B-cell dysfunction may also cause autoimmunity and B-cell malignancies.

Patients with recurrent infections have to be evaluated for the primary immunodeficiency. X-linked agammaglobulinemia has to be considered with low serum IgG, IgA, and IgM levels and severely decreased B-cell number in the peripheral blood by

lymphocyte subset analysis. A definitive diagnosis can be made by genetic studies. The majority of patients are diagnosed at the age of 5 years.

Immunoglobulin replacement therapy and antibiotic for infections are current choice of treatment to prevent life-threatening infections and organ damage. Hematopoietic stem cell (HSC)-based gene therapy can be curative.

Neonatal screening assays (KRECs) have been developed to determine the absence of B cells, seen in XLA.

Keywords: Absence of B cells, Bruton's disease, X-linked agammaglobulinemia, agammaglobulinemia, *Btk* gene mutation, Bruton's tyrosine kinase defect

1. Introduction

Bruton's disease is an X-linked agammaglobulinemia (XLA OMIM No. 300300) that was first described as primary immunodeficiency in 1952 by Dr. Bruton. It is the best-known antibody deficiency [1–5]. More than half of the patients with Bruton's diseases characterized by recurrent bacterial infections such as otitis, sinusitis, and sinopulmonary infections are developing after 7 to 9 months of age when transplacental maternal immunoglobulin G (IgG) levels decrease below protective levels in infants. In this disorder, genetic abnormalities lead to blockage in the maturation of B cells in the bone marrow and only confined to the B-cell lineage. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common responsible encapsulated pathogens for recurrence of otitis and sinusitis. Pneumonia, empyema, meningitis, septicemia, and septic arthritis are severe infections, which may be the first warning signs of disease for physician to suspect immunodeficiency. The distinctive clinical features of the disease are early onset bacterial infections, absent mature B cells or remarkably reduced circulating B cells, severe reduction in the basal serum immunoglobulins, inability to produce antibodies against antigens, and occurrence of autoimmune diseases paradoxically. Based on these principal findings, approximately 90% of male patients presumed with XLA are likely to have mutation in *Btk* [6–9].

2. History

In 1952, an American pediatrician, Dr. Ogden Carr Bruton, described the clinical case of an 8-year-old boy who had recurrent episodes of pneumococcal sepsis [1, 2]. Dr. Bruton vaccinated the patient to prevent infections, but the boy did not produce antibodies to *Pneumococcus.* Electophoretic analysis revealed a lack of gammaglobulins in the patient's serum. Dr. Bruton treated this patient with monthly injections of exogenous gamma globulin. The patient remained free of sepsis episodes for 14 months during which he received injections. The disorder was observed only in male patients. Based on the observation of five additional male

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patients similar to Bruton's disease by Janeway and colleagues, the disorder later became known as X-linked agammaglobulinemia [9, 10, 11]. This disease was named Bruton's X-linked agammaglobulinemia after having discovered the first immunodeficient patient [12].

3. Prevalence

The frequency of Bruton's disease has been estimated as 1 per 200,000 live births. Prevalence is approximately 1 per 10,000. The prevalence of XLA varies in different countries obtained from published reports. Based on national registries, the prevalence was ranging between 0.09 and 11.25 per 100,000 population [13–17]. The minimum prevalence has been reported as 0.09 (minimum) from Germany [14], while it has been reported as 11.25 (maximum) in the USA [16]. The prevalence of XLA in Eastern and Central European (ECE) countries (total population, 145,530,870) was found to be 1 per 1,399,000 individuals.

4. *Btk* genes and function

X-linked agammaglobulinemia is caused by mutations in the gene encoding a cytoplasmic protein tyrosine kinase, called Bruton's tyrosine kinase (Btk), in honor of the discoverer of the disorder, Colonel Ogden Bruton, MD. Btk is signal transduction molecule downstream of pre-B-cell receptor (PreBCR) and the B-cell receptor (BCR). It is a key regulator for B-lymphocyte precursors to differentiate into B cells in bone marrow. Mutation in Btk results in the defective production and function of the enzyme. In a healthy person, the enzyme is activated by the pre-B-cell receptor, and it delivers biochemical signals that prompt the B cells to divide or mature and survive. Therefore, patients with defective Btk have almost complete absence of B cells and plasma cells due to arrest in maturation beyond pre-B cell [5–9].

The gene for this enzyme was identified in 1993 by two independent groups [18, 19]. It is located on the Xq21.3-Xq22, the long arm of the X chromosome [18–24]. Btk belongs to a distinct family of protein kinases. Tec, Itk, Bmx, and Txk are other members of this family. The protein contains five regions, PH, TH, SH3, SH2, and kinase domains, and any of these domains may be affected by mutations causing XLA [23, 24]

Since 1993, the number of genetic studies has increased. XLA is a variable disease in certain patients [25, 26]. The types of mutations causing XLA include missense, nonsense, point, frameshift, slice site, deletion, insertion, and premature stop codon mutations [27]. In general, missense mutations account for 40% of all mutations, whereas nonsense mutations account for 17%, deletions account for 20%, insertions account for 7%, and slice site accounts for 16%. This distribution is similar to those listed in Immunodeficiency mutation database [28].

In a study conducted on 56 patients, mutations affecting the *Btk* gene were demonstrated in 51 patients. It was shown that 22 mutations were missense [29]. In another study, the number of missense mutations was found to be higher [30]. In the study by Chan et al., 12 patients were

evaluated, and 3 deletion mutations, 8 nucleotide substitution mutations, and 1 insertion–deletion mutation were detected [31]. In the study carried out in Central European patients with agammaglobulinemia, the point mutations were observed to be more frequent [32]. The first study in 16 Turkish XLA patients was done by Wang et al. [33], seven novel mutations were identified: 2 missense and 4 deletions resulting in frameshift and premature stop codon, novel mutations were determined in 7 cases; 2 missense, 1 nonsense, and 4 deletion mutations were detected. In the last update, lists of the online BTKbase, 1155 entries have been compiled from 974 unrelated families with 602 unique molecular events [32]. The genetic profile of XLA has been studied in 122 patients from 109 families in Eastern and Central European (ECE) countries in 2009 [17]. BTK sequence analysis revealed 98 different mutations, in which 46 of them were reported for the first time. The mutations included single nucleotide changes in the coding exons (35 missense and 17 nonsense), 23 splicing defects, 13 small deletions, 7 large deletions, and 3 insertions.

We conducted a study in Istanbul University, Cerrahpaşa Medical School, Children's Hospital, to determine the BTK mutation in a total of 19 Turkish boy from 18 unrelated families with recurrent infections, almost no CD19(+) B cells and agammaglobulinemia (Table 1) [34].

Patient no.	Age at diagnosis	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	$CD19^+$ B cells	Family history	Consanguinity
P 1	4	<166	0	<128	3	(–)	(–)
P 2	1.5	29	0	<29	0	(–)	(+)
P 3	3	0	0	32	-	(–)	(+)
P 4	3.5	250	0	31	0	(–)	(–)
P 5a	3.5	-	-	-	0	(+)	(–)
P 5b	3 months	21	3	<18	0	(+)	(–)
P 6	1.5	611	179	55	2	(–)	(+)
P 7	1.5	157	<25	<18	0	(–)	(–)
P 8	8	307	28	121	0	(–)	(+)
P 9	6	<145	0	28	0	(–)	(–)
P 10	5	83	4	12	0	(–)	(–)
P 11	4	447	6	4	0	(–)	(+)
P 12	2	<140	<6	<16	0	(–)	(–)
P 13	9	<153	0	<2	0	(–)	(+)
P 14	5	<143	<23	70	0	(+)	(–)
P 15	7	681	188	25	2	(+)	(–)
P 16	3	180	<28	<29	0	(–)	(–)
P 17	8	302	152	8	0	(–)	(–)
P 18	1	315	60	33	2	(–)	(–)

Table 1. Clinical data of 18 male patients with agammaglobulinemia

BTK gene mutations were determined within 10 patients. The types of the mutations were 3 missense, 4 frameshift and premature stop codon; 2 splice site; and 1 point. Missense mutations were determined in the three patients (patients 2, 4, and 17). In one patient (patient 17), a novel amino acid substitution was determined within the TH domain in exon 6 (c. 491G > A) (p.G164D), which was not included previously in the ESID database. A novel point mutation within the PH domain in exon 2 (c. 49A > T) (p.K17X) was detected in Patient 7. This mutation as well has not been defined previously in the ESID database. The frameshift and premature stop codon mutations were observed to be frequent, followed by missense mutations (Table 2). Although four of the patients have features relevant with a clinical and immunological diagnosis of XLA, a BTK gene mutation could not be determined. In such cases, other autosomal recessive gene defects (μ heavy chain, surrogate light chain λ5, Igα and Igβ signaling molecules, and B-cell linker adaptor protein (BLNK)) should be investigated [35–40]. These genes map proteins involved in maturation of pro-B cells into pre-B cells. These defects have also been shown to result in agammaglobulinemia and an absence of circulating B cells, which cannot be clinically distinguished from XLA.

Patient no.	Localization	Nucleotide aberration	Amino acid aberration	Protein domain
P 2	Exon 18	c.1762T>G	p.W588G	TK
P 4	Exon 2	c.40T>C	p.S14P	PH
P 5a	Exon 13	c.1157_1161delCCACT	p.S386fsX10	TK
P 5b	Exon 13	c.1157_1161delCCACT	p.S386fsX10	TK
P 7	Exon 2	c.49A>T	p.K17X	PH
P 10	Exon 9	c.839+4_+7delAGTA		
P 12	Exon 15	c.1461_1465delGA	p.E488fsX19	TK
P 14	Exon 8	c.713delG	p.G238fsX39	SH3
P 16	Exon 12	c.1102+1G>A		
P 17	Exon 6	c.491G>A	p.G164D	TH

Table 2. *Btk* mutations identified in 10 XLA patients

In the light of these studies, gene defect has to be defined for the accurate diagnosis of XLA, carrier detection, and prenatal diagnosis.

5. Genetic counseling

XLA is inherited in sex-linked diseases (x-linked). As the defects are connected with the X-chromosome and the inheritance is recessive, only male infants are affected. If a boy inherits a defective gene, since he does not have a healthy gene from his father, the boy may have the

disease. Women who carry a mutant allele of the *Btk* gene on one of their chromosomes are carrier of the disease. Therefore, mothers, sisters, and maternal aunts should be investigated for carrier status because they are obligate carriers. Brothers, uncles, or nephews of the mother must be questioned for this disorder. The family history of XLA is nonexistent in approximately 50% of patients. Some of these patients (15–20%) with XLA may have a de novo mutation in *Btk* gene, and their mothers are not carriers. If the mutant *Btk* allele is known previously in the family, carrier testing for at-risk female relatives or prenatal diagnosis is possible [41–43].

6. Immunology of XLA

B cells arise from hematopoietic stem cells in the bone marrow. B cells begin to generate and express B-cell receptors (BCRs) (Fig. 1). The entire developmental process of B cells occurs within the bone marrow. A common lymphoid progenitor (CLP) gives rise to pro-B lymphocytes, which next develop into pre-B lymphocytes and then to B lymphocytes. Stimulated B cells may further differentiate into plasma cells that synthesize and secrete immunoglobulins. Mutation in Bruton tyrosine kinase causes arrest in the development of B lymphocyte at the early stage of large pre-B-cell ($CD19^+$ cytoplasmic μ^+) stage in the bone marrow (Fig. 2). This defect is leaky, resulting in a few immature B cell. B-cell developmental defects in bone marrow lead to a marked decrease or absence of fully mature B lymphocytes in peripheral blood, absent or few follicles, and germinal centers in lymphoid organs. Plasmocytes are absent, and reticuloendothelial tissue and lymphoid organs (tonsils, spleen, Peyer plaques, and lymph nodes) are poorly developed. Therefore, secondary lymphoid organs such as lymph nodes and tonsils are reduced in size. The consequence of decreased immunoglobulin-producing B cell is diminished in all serum immunoglobulin isotypes, resulting in inability to produce antibodies against protein and polysaccharide antigens. The percentage of T cell is increased, and T cell functions are intact. These patients have the ability to control viral and fungal infections because of intact cell-mediated immunity. The thymus is in normal size and architecture.

Antibodies are produced by plasma cells that are terminally differentiated B cells. When B lymphocytes identify and interact with a specific antigen in the body, it is triggered to mature into a plasma cell that is able to produce specific antibodies. Plasmocytes produce nine antibody isotypes: immunoglobulins G (IgG1, IgG2, IgG3, and IgG4), immunoglobulins M (IgM), immunoglobulins A (IgA1 and IgA2), immunoglobulins D (IGD), and immunoglobulins E (IgE). Antibodies are soluble molecules that bind to antigens to render them harmless by agglutination and neutralization or "tag" the antigens to facilitate destruction and removal by phagocytes and via activating complement components. Antibodies are an important component of humoral immune responses and integral part of body's defense mechanism against bacteria. During the first 6–9 months of life, infants with XLA are protected from infections by transferred maternal IgG antibodies. Reduced maternal antibodies by 6–9 months of age and failures in humoral immunity leave the affected XLA patient with a reduced ability to resist infections and increased susceptibili-

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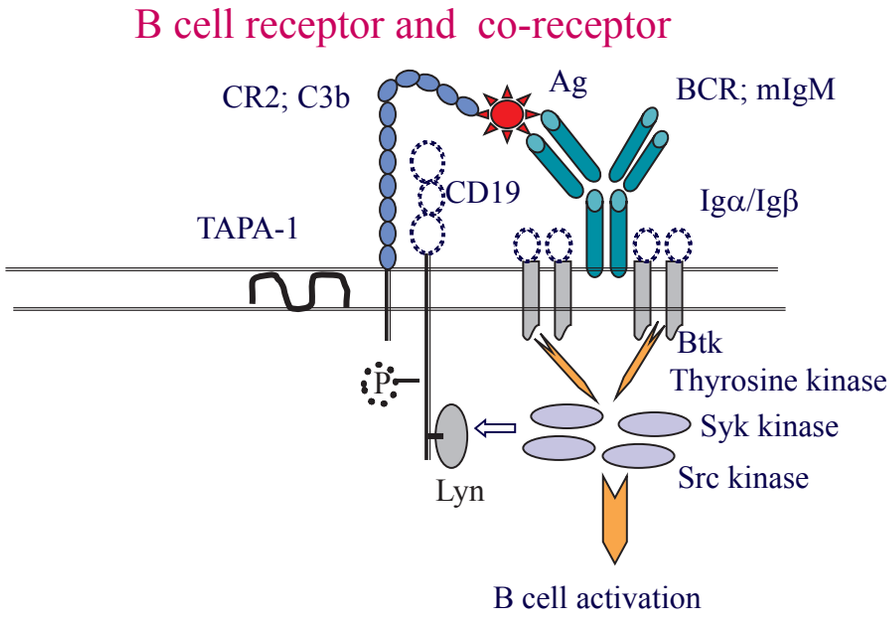

Figure 1. Btk, delivering signals for maturation of B cell.

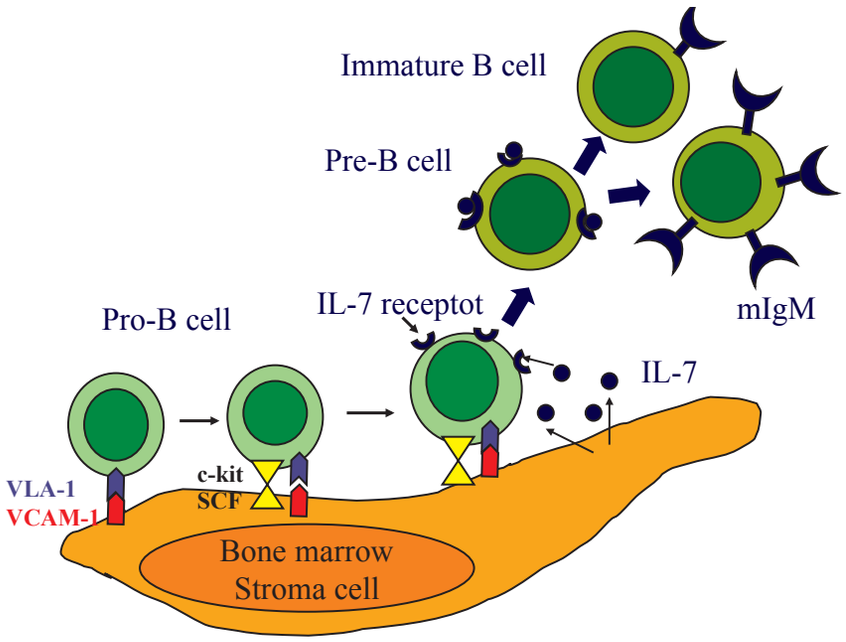

Figure 2. Development of B cells in bone marrow.

ty to encapsulated bacteria and enteroviruses as well. As a consequence, there is a virtual absence of humoral response to recall antigens [9, 12, 44–47].

7. Clinical presentation

Symptoms of patients with XLA most often begin at about 6 to 9 months of age, when the transferred maternal immunoglobulin has been catabolized and the infant becomes dependent on his own immune system. Widespread use of antibiotics may often mask the presentation of disease and despite recurrent sinopulmonary infections diagnosis of XLA may delay until 3–5 years of age or adolescence in some cases [8]. In a small subpopulation of cases with XLA, about 10% to 15%, who are not recognized to have immunodeficiency until 5 years of age, serum immunoglobulin levels may be high [46]. Patients with XLA are clinically characterized by an onset of recurrent bacterial infections due to remarkable decrease in immunoglobulin levels [5–9, 47–50].

The clinical findings leading to the diagnosis of XLA were determined in 82 patients with proven mutations in Bruton's tyrosine kinase. The authors reported that the majority of patients with XLA had a history of recurrent otitis at the time of diagnosis. The physical findings of decreased or absent tonsils and cervical lymph nodes could have alerted physicians to the diagnosis of XLA [51].

Clinical presentations of X-linked agammaglobulinemia have been defined by a multicenter retrospective survey of 96 patients. The onset of infections was in the first 4 months of life (25% of cases), 8 months of life (50% of cases), 12 months of life (75% of cases), and 18 months of life (90% of cases). The most frequent infections involved the upper respiratory tract (75%), the lower respiratory tract (65%), the gastrointestinal tract (35%), the skin (28%), and the central nervous system (16%) [52].

Infection usually develops at the surface of mucous membranes, namely, middle ear, sinuses, and lungs. Pneumonia, otitis media, sinusitis, conjunctivitis, and diarrhea are the hallmark of XLA patients. In some cases, infection can spread through the bloodstream, and septicemia, meningitis, septic arthritis, cellulitis, and osteomyelitis may occur. *S. pneumoniae* and *H. influenzae* are the most common responsible encapsulated pathogens of infections. These microorganisms also affect all patients with antibody deficiency, such as common variable immunodeficiency (CVID); however, patients with XLA have susceptibility to enteroviral infection in contrast to other antibody deficiencies.

There are many published data about the clinical presentation of XLA. They are reflecting the results of different population of XLA patients. The frequency of clinical presentations is variable due to different cohorts of XLA patients assessed.

Infection was the most common initial clinical presentation (85%), followed by a positive family history (41%) and neutropenia (11%) in 201 XLA patients included in the United States Registry. The average age of diagnosis was significantly younger in patients with a positive family history (2.59 years) than in patients with a negative family history (5.37 years) ($p < 0.001$). Seventy percent of patients had at least 1 episode of otitis, 62% at least 1 episode of pneumonia, 60% at least 1 episode of sinusitis, 23% at least 1 episode of chronic/recurrent diarrhea, 21% at least 1 episode of conjunctivitis, 18% at least 1 episode of pyoderma and/or cellulitis, 11% at least 1 episode of meningitis/encephalitis, 10% at least 1 episode of sepsis, 8% at least 1 episode

of septic arthritis, 6% at least 1 episode of hepatitis, and 3% at least 1 episode of osteomyelitis. Of 201 patients, 14 (6.9%) were dead at the time they were entered in the registry. Causes of death were disseminated enterovirus infection (n = 6), pulmonary insufficiency (n = 5), adenovirus infection (n = 1), sepsis (n = 1), acquired immunodeficiency disease syndrome (AIDS) (n = 1), myocarditis (n = 1), hepatitis (n = 2), and stem cell transplantation (n = 1) [53].

The median age at the onset of the disease was 8 months, and the median age of diagnosis was 48 months based on the records of 33 Iranian XLA patients. The most frequent infections were seen in the respiratory tract (93.9%), gastrointestinal tract (75.8%), central nervous system (33.3%), and musculoskeletal system (21.2%). Chronic otitis media, chronic sinusitis, chronic diarrhea, and bronchiectasis were developed complications in 75.8% of cases [54].

The mean age of onset was 2.5 years, and the mean age at diagnosis was 7.3 years in six patients with XLA from northern Thailand. Patients had a history of otitis media, pneumonia, arthritis, and sinusitis (5/6); pericarditis (1/6), meningitis (1/6), and pyoderma (1/6) were other experienced infections. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were isolated on multiple occasions in five patients. Five cases had developed bronchiectasis and three patients septicemia [55].

Recurrent pulmonary infections and an unusual course of common pulmonary infection should alert physician for underlying immunodeficiency. Lung infections were evaluated in 39 Iranian patients with XLA. The authors reported that 82% (32/39) of patients with XLA experienced at least one episode of pneumonia, and 84% (27/32) of those patients had more than one episode. An average rate of pneumonia episode per patient per year was 1.67 for XLA patients [56].

A patient with XLA presenting with respiratory distress, was reported to have *Pneumocystis jirovecii* pneumonia. This patient is a reminder that the potential consequences of BTK deficiency in cells other than B-cells should be considered [57].

Mycoplasma infections may involve the respiratory tract, the urogenital tract, and joints, leading to prolonged than severe course or asymptomatic in some cases [58, 59].

Skin infections such as impetigo, abscesses, and furuncles due to group A streptococcus or staphylococcus had been also reported.

Although patients with XLA experience childhood viral infections uneventful, they have susceptibility to certain viruses. Enteroviral infections (echovirus, coxsackievirus, and polio virus) frequently run a severe course and often resist therapy in affected patients. Enterovirus may cause severe and, eventually, fatal progressive encephalitis [5–9, 52, 60, 61].

Clinical manifestations of enteroviral meningoencephalitis demonstrate great variation changing from severe infection to chronic enteroviral infection. Illness may be overt as acute infection with fever, headache, and seizures or tend to progress slowly throughout the years with loss of cognitive skills, ataxia, paresthesia, neurosensory hearing loss, and lethargy [60, 61]. The laboratory assessment of cerebrospinal fluid (CSF) may reveal clear fluid, pleocytosis (<1000/mm^3), elevated protein level (0.5–5 g/dL), and in a few cases hypoglycorrhachia or normal CSF results. Polymerase chain reaction (PCR) techniques may detect virus in CSF.

Initial magnetic resonance imaging (MRI) or computed tomography (CT) scan reveal no abnormality; however, cortical or subcortical atrophy, ventricular dilatation, periventricular changes, and hydrocephaly may be observed later in life. There are no typical histopathology findings at brain biopsy. Illness is progressive and mortality is very high. As a result of disseminated enteroviral infection, dermatomyositis-like syndrome may develop with erythematous rash and peripheral edema. Hepatitis with increased alanine aminotransferase (ALT) may accompany [60–63].

Gastrointestinal disorders are common problems of XLA patients. Patients may have infections, autoimmunity, or rarely malignancy. *Campylobacter jejuni* is the most frequent pathogen causing gastrointestinal tract infection. Typically, affected patients suffer from fever, skin rash, and persistent diarrhea [64–66]. Parasitic infection especially *Giardia lamblia* infection may cause abdominal pain, diarrhea, poor growth, or loss of serum proteins. *Giardia* can be isolated from stool samples of patients and too hard to eradicate.

Inflammatory disorders in XLA patients unexpectedly occur. A web-based patient survey was conducted in patients with XLA. Based on 128 patient responses, the majority of respondents (69%) reported having at least one inflammatory symptom. Just 28% of them had been diagnosed with an inflammatory condition. Arthritis had been diagnosed only in 7% XLA patients, despite 20% reported painful joints and 11% reported swelling of the joints. Similarly, 21% reported symptoms of chronic diarrhea and 17% reported abdominal pain. However, only 4% had been diagnosed with Crohn's disease. Data from the United States Immune Deficiency Network (USIDNET) Registry on 149 patients with XLA revealed that 12% had pain, swelling, or arthralgia, while 18% had been diagnosed with arthritis [67]. Kawasaki disease is also reported in an XLA patient, providing opportunity to understand the relationship between autoimmunity and XLA [68].

Noninfectious or infectious arthritis may occur in patients with X-linked agammaglobulinemia. Juvenile rheumatoid is relatively common in patients with XLA. The mechanisms are not clear of noninfectious arthritis. *H. influenzae*, *S. pneumoniae*, and mycoplasma are pathogens causing septic arthritis. Pain and swelling of joints are presenting symptoms. Erythrocyte sedimentation rate increase, rheumatoid factor (RF), and antinuclear antibody (ANA) tests are negative. Arthritis may be the first presenting symptom of X-linked agammaglobulinemia. That is the reason why physicians must be aware of immunodeficiencies [69, 70].

Growth hormone deficiency associated with XLA patient has been reported [71].

Although the relationship between the Bruton kinase mutation and the development of malignant tumors is unknown, XLA patients seem to be at risk for colorectal cancer and lymphoid malignancies. B-cell precursor acute lymphoblastic leukemia (BCP-ALL) has been reported in a case with XLA. It has been reported that somatic mutation found in MLL2 suggests that the alterations of BTK and MLL2 synergistically function as leukemogenesis [72, 73].

Cases with vaccine-associated paralytic poliovirus infection as a consequence of attenuated oral polio (Sabin) have been reported in XLA patients [74]. The incubation period of the infection is more than 30 days, and chronic encephalomyelitis develops eventually [75].

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8. Physical Examination

Remarkable physical findings of XLA patients are the absence or hypoplasia of tonsils and lymph nodes. Chronic otitis, sinusitis, mastoiditis, or bronchiectasis are consequences of recurrent infections.

9. Diagnosis

Significant progress in the field has been achieved in the light of collaborative studies. Guidelines for screening primary immunodeficiencies have been published by experts, non-immunologists and immunologists [51, 76–78]. The classification of primary immunodeficiency diseases had been updated by the *ad hoc* Expert Committee of the International Union of Immunological Societies [79]. The hallmark of clinical features and laboratory evidences were provided for each immunodeficiency, which help physicians to recognize and diagnose patients with immunodeficiency timely.

9.1. Clinical clues

X-linked agammaglobulinemia (XLA) should always be considered in children with recurrent, persistent, unusual sinopulmonary infections or a life-threatening severe bacterial infection below 5 years of age. Small tonsils and lymph nodes on physical examination are warning signs of disorder. Patients with strong family history of immunodeficiency relevant with X-linked inheritance should be investigated further.

9.2. Laboratory approach

Based on studies, detailed family and medical history combined with careful physical examination further guide specific blood tests of the immune system, which will be performed step by step to confirm the diagnosis of XLA. Severe defects of immune systems should be ruled out at the first steps of diagnostic protocol for suspected immunodeficiency. Infection with human immunodeficiency virus (HIV) has to be excluded rapidly. Tests have to be performed and interpreted by a specialist immunologist. The use of age-matched reference values for lymphocyte subsets and immunoglobulin levels are highly recommended to avoid misinterpretation.

Baseline blood tests give useful information. The complete blood test (CBC) is a crucial test to reveal anemia, neutropenia, lymphopenia, thrombocytopenia, or eosinophilia, which may give a clue to which type of PID is present. Neutropenia is associated with a small subpopulation of patients with XLA (11%), which can be misdiagnosis as congenital neutropenia [8, 80, 81]. Severe neutropenia is usually in association with pseudomonas or staphylococcal sepsis. A CBC and a manual leukocyte differential can aid in the identification of striking lymphopenia, which is a very important clue for severe combined immunodeficiencies (SCID) accepted as medical emergency.

Screening tests for antibody deficiencies as recommended by experts are presented as follows [8, 50, 76–78, 82]:

- Serum total protein level
- Serum immunoglobulin assay: IgG, IgA, IgM
- Isohemagglutinins (IgM antibodies to A and B blood group antigens)
- Specific antibody responses
- Tetanus, diphtheria (IgG1)
- Pneumococcal and meningococcal polysaccharides (IgG2)
- Viral respiratory pathogens (IgG1 and IgG3)
- Other vaccines: hepatitis B, influenza, MMR, and polio (killed vaccine)
- Lymphocyte subpopulation by flow cytometry (B-cell quantitation)
- Lymphocyte proliferation tests
- B-cell maturation analysis in bone marrow
- Genetic determinations of defect

Serum immunoglobulin concentration should be measured by quantitative techniques, and IgG, IgA, and IgM are routinely measured in serum. Values of determined immunoglobulin levels have to be compared with normal-for-age values. The majority of patients with XLA have less than 200 mg/dL serum IgG level. However, serum IgG concentration is more than 200 mg/dL in 10% of children with XLA. Serum IgM and IgA are classically less than 20 mg/dL. Low serum IgG concentration may also be determined in patients who have protein-losing enteropathy and nephrosis. The concomitant serum protein levels of these patients are low; hence, they produce antibodies normally. Under certain conditions, the determination of IgE and IgD levels may be required.

Isohemagglutinins are natural IgM-class antibodies against A and B blood group antigens. Therefore, they are not found in patients who have type AB blood group. In addition, the measurement of isohemagglutinin titers in the serum is not reliable below 6 months of age. Normal values for anti-A titer is 1:16 or higher and anti-B titer is 1:8 or higher. Isohemagglutinins titer is low in XLA patients due to poor IgM synthesis.

Individuals with XLA fail to make antibodies against vaccine antigens or pathogens such as tetanus, *H. influenzae*, or *S. pneumoniae*. Since children are vaccinated with diphtheria–tetanus—acellular pertussis (DTaP), conjugated *H. influenzae* type b, and conjugated pneumococcal vaccine (PVC), the measurement of antibodies against these antigens is informative. The measurement of specific antibodies against diphtheria and tetanus before and 2 weeks after DTaP or booster DT immunization reveals a patient's ability to produce IgG antibodies against protein antigens. Pneumococcal polysaccharide vaccine or conjugated pneumococcal vaccine (PVC) is used to evaluate a patient's ability to respond to polysaccharide antigen (IIb C). The

measurement of pneumococcal antibody titers before and 4 to 8 weeks after vaccination should be done in patients more than 2 years of age (Ib A). The normal response to each pneumococcal serotype is defined as a titer equal to or greater than 1.3 mg/mL antibody (IIb C) [83]. The ability of antibody production against antigens and the response to vaccination are severely impaired in XLA patients.

Patients who have agammaglobulinema need lymphocyte phenotyping. The number of B lymphocytes in the peripheral blood can be enumerated by flow cytometry using dye-conjugated monoclonal antibodies (CD 19 and CD 20), which are specific B-cell markers. B cells constitute 4–10% of the peripheral lymphocyte. The reduced number of $CD19^+$ B cells in the peripheral blood would be indicative of defective B-cell differentiation and would suggest XLA if not combined with depleted T-cell numbers. B cell is markedly reduced below <1% in patients with XLA [76–79, 83].

Mutations in *BTK* gene can be scanned by sequence analysis, which can detect approximately 90% of mutations in *BTK*.

10. BTK protein testing

BTK mutations occur in the absence of the BTK protein in monocytes. The detection of BTK protein in monocytes by immunofluorescence or western blot [84, 85] can confirm the diagnosis of XLA.

Female carriers may be determined by mutation analysis or Btk protein expression on blood cells by flow cytometry. They have normal immune functions, but they have a 50% chance of transmitting the disease to each of her sons.

The following diagnostic criteria for X-linked agammaglobulinemia were published by Conley et al. in 1999 [86]:

Definitive diagnosis—males with less than 2% $CD19^+$ B cells and at least one of the following:

- Mutation in *BTK*
- Absent Btk mRNA on northern blot analysis of neutrophils or monocytes
- Absent Btk protein in monocytes or platelets
- Maternal cousins, uncles, or nephews with less than 2% $CD19^+$ B cells

Probable diagnosis—males with less than 2% $CD19^+$ B cells and the following:

- Onset of recurrent bacterial infections in the first 5 years of life
- Serum IgG, IgM, and IgA more than 2 SD below normal for age
- Absent isohemagglutinins and/or poor response to vaccines
- Exclusion of other causes of hypogammaglobulinemia

Possible diagnosis—males with less than 2% $CD19^+$ B cells in whom other causes of hypogammaglobulinemia have been excluded and who has at least one of the following:

- Onset of recurrent bacterial infections in the first 5 years of life
- Serum IgG, IgM, and IgA more than 2 SD below normal for age
- Absent isohemagglutinins

Chest X-ray or CT scan of patients with XLA reveals bronchiectasis most commonly distributed in the middle or lower lobes, atelectasis, and bronchial wall thickening. CT scan of sinuses may suggest the presence of chronic sinusitis.

Prenatal diagnosis—this may be achieved by using mutation analysis in amniotic fluid cells and Btk protein expression on cord blood cells by flow cytometry.

11. Newborn screening

Kappa-deleting recombination excision circles (KRECs) are chosen as markers for B lymphopenia at birth, indicative of X-linked agammaglobulinemia. The measurement of KRECs in newborn would help the early diagnosis of XLA patients [87].

12. Differential diagnosis

Differential diagnosis should be done by other disorder with hypogammaglobulinemia such as CVID, X-linked hyper IgM syndrome, and X-linked lymphoproliferative disease.

It had been known for several years that there were girls who had an immunodeficiency that looked just like XLA, and immunologists had suggested that there were forms of agammaglobulinemia with autosomal recessive inheritance (ARA). Since 1996, several genes (μ heavy chain deficiency, λ5 deficiency, Igα deficiency, Igβ deficiency, BLNK deficiency, PI3 kinase deficiency, and E47 transcription deficiency) that can cause ARA have been identified. All of these genes code for proteins that work with BTK to support the maturation of pro-B cells into pre-B cells. Patients with mutations in any of these genes have clinical and laboratory findings that are very similar to those seen in patients with mutations in Btk (Table 3) [35–39].

Disease	Genetic defect	Inheritance	Serum Ig	Associated features
Btk deficiency	Mutation in Btk, a cytoplasmic tyrosine kinase activated by cross-linking the BCR	XL	All isotypes decreased	Severe bacterial infections: normal numbers of pro-B cells

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Disease	Genetic defect	Inheritance	Serum Ig	Associated features
μ heavy chain deficiency	Mutation in μ heavy chain: essential component of the pre-BCR	AR	All isotypes decreased	Severe bacterial infections: normal numbers of pro-B cells
λ5 deficiency	Mutation in 15: part of the surrogate light chain in the pre-BCR	AR	All isotypes decreased	Severe bacterial infections: normal numbers of pro-B cells
Igα deficiency	Mutation in Igα (CD79α) : part of pre-BCR and BCR	AR	All isotypes decreased	Severe bacterial infections: normal numbers of pro-B cells
Igβ deficiency	Mutation in Igβ (CD79β) : part of pre-BCR and BCR	AR	All isotypes decreased	Severe bacterial infections: normal numbers of pro-B cells
BLNK deficiency	Mutation in BLNK: a scaffold protein that binds to Btk	AR	All isotypes decreased	Severe bacterial infections: normal numbers of pro-B cells
PI3 kinase deficiency	Mutation in PIK3R1; a kinase involved in signal transduction in multiple cell types	AR	All isotypes decreased	Severe bacterial infections: decreased or absent pro-B cells
E47 transcription deficiency	Mutation in TCF3:a transcription factor required for control of B-cell development	AD	All isotypes decreased	Recurrent bacterial infections
Myelodysplasia with hypogammaglobulinemia	May have monosomy 7, trisomy 8,or dyskeratosis congenita	Variable	One or more isotypes may be decreased	Infections: decreased numbers of pro-B cells
Thymoma with immune deficiency	Unknown	None	One or more isotypes may be decreased	Bacterial and opportunistic infections: autoimmunity: decreased numbers of pro-B cells

Table 3. Diseases with absent or decreased B cells and markedly reduced in serum immunoglobulin isotypes (Al-Herz et al., *Front Immunol*, 2014)

13. Treatment

There is no curative treatment for XLA. Therapeutic measures consist of intravenous immunoglobulins (400–600 mg/kg monthly in order to maintain the IgG levels at 500–800 mg/dL), specific treatment of bacterial infections with antibiotics, and bronchodilators. The mainstay of treatment consists of immunoglobulin replacement therapy and prolonged antibiotic treatment of suspected bacterial infections. Immunoglobulin replacement therapy is essential

for the XLA patients who are unable to produce sufficient antibodies against antigens. IgG is purified from thousand of human plasma and contains a wide range of antibodies against so many infections. Thus, it is life saving for XLA patients, and they have to continue to receive to survive. The aim of immunoglobulin treatment given by intravenous (IVIG) or subcutaneous (SCIG) infusions is to avoid acute infections, to decrease the number of bacterial infections, to improve quality of life, and to increase life expectancy of patients [8, 9, 47, 88–92].

IVIG infusions have to be done at hospital or home by professionally educated staff if possible. The common recommended dose of IVIG treatment for antibody replacement is between 0.3 and 0.6 g/kg, administered every 2 to 4 weeks via the intravenous route. The first IVIG infusion must be given slowly starting with a rate of 0.5 to 1.0 mg/kg per minute. Patient should be monitored closely for any adverse reactions during infusion. If the patient tolerates well, the infusion rate may be increased to 1.5 to 2.5 mg/kg per minute after 15 to 30 minutes. The maximal infusion rate is 4 mg/kg per minute, and infusion of an IVIG product should last 2 to 4 hours. The aim of IVIG therapy in patients with PID is to maintain serum IgG levels between 350 and 500 mg/ dL. Since there is a large variation in individual IgG elimination rates, the periodic measurement of serum IgG concentration is critical to monitor the adequacy of replacement during therapy. Retrospective studies in patients with XLA revealed that the severity and the number of infections especially pulmonary diseases are decreased depending on IVIG dose [88]. Serious bacterial illnesses and enteroviral meningoencephalitis were prevented when maintained IgG levels were above 800 mg/dL [89–95].

A 5-year multicenter prospective study on 201 patients with CVID and 101 patients with XLA was conducted to identify the effects of long-term immunoglobulin treatment and the IgG trough level to be maintained over time required to minimize infection risk. Overall, 24% of patients with XLA remained infection free during the study. In addition, in XLA, the comorbidity risk factor identified for pneumonia was the presence of bronchiectasis [96].

Infusion-related adverse effects and transmission of blood-borne viruses are adverse effects of immunoglobulin replacement therapy [97]. Reduced adverse reactions are reported with improved and new IVIG products. The subcutaneous IG (SCIG) therapy was reported to be effective, safe, and well tolerated in children and adults. High treatment satisfaction (TS) scores and health-related quality of life (HRQOL) were advantages of SCIG. Subcutaneous infusions are recommended to patients who are small children, reactive to IVIG, or have problem with vascular access. SCIG is given as a parent-managed or a self-managed treatment. Norway, Sweden, United Kingdom, and Belgium are the countries in which SCIG is often applied to children [98, 89]. Clinical records of 1151 XLA patients identified from ESID were included in ESID registry. According to ESID registry, 305 XLA patients were treated with IVIG (73%) and 114 patients were treated with SCIG (27%) [98, 99].

Bacterial infections treated with a high dose of selected antibiotics or antibiotics sensitive to yielded pathogens for prolonged periods.

Six young patients with XLA treated with cord blood or bone marrow transplants were reported. No one benefited from transplantation, and expected increase in serum IgM or blood B-cell number was not observed [100].

14. Vaccination

Live viral vaccines, such as oral polio, rotavirus, yellow fever, live attenuated influenza, and live bacterial (e.g., typhoid [*Salmonella typhi*, Ty21a]) vaccines should not be applied to patients with X-linked agammaglobulinemia. Therefore, inactivated polio vaccine (Salk) should be given to patients with XLA and their family contacts. These patients may develop vaccine-acquired diseases such as central nervous system infection due to oral poliovirus vaccine.

The effectiveness of the measles and varicella vaccines are uncertain because most patients receive IVIG and do not have capacity to produce antibody responses [101, 102].

However, bacille Calmette–Guérin (BCG) vaccine applied to 50 patients with X-linked agammaglobulinemia did not reveal any systemic infection [102].

15. Complications

The most common secondary complications of XLA are chronic sinusitis, chronic lung disease, malabsorption, and enteroviral infection. The delay in diagnosis of XLA remains a significant problem, as a consequence of recurrent pneumonias, bronchiectasis, pulmonary hypertension, and finally cor pulmonale may develop. Many patients have been diagnosed after chronic sequel had already been existed. The aggressive use of antibiotics can decrease the incidence of chronic sinusitis and lung disease. Hearing loss is a consequence of chronic otitis media. Early diagnosis and treatment of bowel infections may decrease the risk of inflammatory bowel disease. Renal AA amyloidosis had been reported in 38-year-old patient with Bruton's disease [103].

16. Mortality

Chronic lung diseases and infections, especially disseminated viral infections, and meningoencephalitis due to enterovirus are major causes of mortality. Treatment with newly developed and improved immunoglobulin products and antibiotics and improvement of care of immunodeficient patients would reduce the mortality rates and increase the survival of XLA patients. Registered 41 XLA patients were followed up 20 years until 2010. Among 41 patients, 26.8% died during the follow-up period. All of the complications existed before the initiation of treatment was reduced after immunoglobulin replacement therapy, except sinusitis and conjunctivitis. The associations between some immunological and clinical characteristics such as lymphocyte subsets, consanguinity marriage, and mortality were documented [104].

17. Prognosis

In the case of the early diagnosis of XLA and an appropriate therapy before the appearance of sequel, prognosis is well. They are encouraged a full active lifestyle and children can attend

to all regular school. Attention should be paid to pulmonary infections and complications in the long-term follow-up of patients. XLA is a chronic disease; patients need immunoglobulin replacement therapy to avoid infections and care of a multidisciplinary team of specialists for the rest of their lives [98, 99].

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