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Original Article

X-linked agammaglobulinemia: ınvestigation of clinical and laboratory findings, novel gene mutations and prevention of ınfective complications in long-term follow-up

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Abstract: Introduction-Objective: X-linked agammaglobulinemia (XLA) is a primary immunodeficiency disease predominantly with antibody deficiency and characterized by recurrent pyogenic infections, absence of B cells and agammaglobulinemia. In this study, it is aimed to review the demographic data of our XLA patients and examine the frequency of severe bacterial and mild infections and benefits of immunoglobulin replacement therapies to reduce the rate of infections. In addition, correlations between genotypic results and clinical and laboratory findings were searched. Patients and Methods: In this study, 20 patients who were followed-up between 1995-2019 and diagnosed with XLA by flow cytometric and genetic tests were included. Demographic data, symptoms at admission and follow-up, laboratory data and radiologic imaging findings, previous infections, immunoglobulin replacement treatments, and genetic analysis results of the patients were recorded. Results: All patients in the study were male and the mean age of onset of symptoms was 60 months. The mean age at diagnosis was 72 months. A total of 19 different mutations were identified in the Bruton-tyrosine kinase gene, six of them were novel. Our eldest patient was 34 years old and the longest follow-up period was 24 years. Respiratory tract infections were the most common in the patients, only 35% of the causative agents were found in sputum cultures and H. influenzae type b (57.8%) was isolated most frequently. Both intravenous and subcutaneous immunoglobulin replacement therapies significantly reduced the number of severe bacterial infections and other mild infections. Conclusion: XLA is a rare pediatric primary immunodeficiency disease and affected individuals require lifelong immunoglobulin replacement therapy. Immunoglobulin replacement prevents life-threatening infections and dramatically increases survival rates. The patients with regular treatment and follow-up, reach adulthood and has a high quality of life.

Keywords: Bruton, primary immun deficiency, infection

Introduction

X-linked agammaglobulinemia (XLA/Bruton) is a disease first identified by C. Ogden Bruton in 1952 and characterized by recurrent pyogenic infections, lack of B cells and agammaglobulinemia. It occurs due to mutations in the signal transmission molecule in the Bruton's Tyrosine Kinase (BTK) gene in the long arm of the X chromosome (Xq21.33-q22). Playing a role in the differentiation and maturation of B lymphocytes, the BTK gene has been associated with more than 1,000 mutations. It occurs only in males due to x-related recessive inheritance [1].

Clinical symptoms begin after the sixth month when the maternal immunoglobulin levels decrease, and the baby is unable to produce its own immunoglobulin. They have recurrent or persistent bacterial infections caused by encapsulated bacteria (*S. Pneumoniae, H. Influenzae*, etc.), otitis media, conjunctivitis, sinusitis, pneumonia, gastroenteritis, and skin infections such as impetigo, cellulite, abscess, and furuncles. Lymph nodes, tonsils, and other lymphoid tissues are unusually small or do not exist [2, 3].

As there is no curative treatment, prevention of the infections is the fundamental goal.

Furthermore, immunization with inactivated vaccines and administering symptomatic treatments during disease management is important. Live vaccines should not be applied as there will be no possibility to produce adequate antibodies. Control of the disease can be achieved through regular immunoglobulin replacement therapy. Immunoglobulin replacement is the main step of treatment. It can be applied in two ways: intravenous (400-600 mg/kg every 3-4 weeks) (IVIg) and subcutaneous (100 mg/kg each week) [4]. Studies have shown that immunoglobulin replacement in patients reduces mortality and morbidity, reduced the incidence of bacterial infection [5].

Patients with XLA need aggressive antibiotic treatment for infections either documented or suspected. If necessary, antibiotic prophylaxis may be used for recurrent infections. It is known that recurrent and subclinical infections in these patients can lead to chronic lung problems, so regular radiological monitoring is important.

In this retrospective study of patients diagnosed with XLA, complications and infections observed in XLA, the effect of immunoglobulin replacement treatment on the frequency of severe and mild infections, and the mortality rate were tried to be determined. Besides; the transition phase of these patients to adult life was examined with close follow-up and under long-term immunoglobulin replacement therapy. As the molecular analysis of all patients was carried out, we presented some novel mutations for the genetic databases.

Patients and methods

Inclusion and exclusion criteria of the study group

Twenty patients diagnosed with XLA during the 1995-2019 period were included. The inclusion criteria were as follows; a) Mild and severe infections at least six times in a year, b) beginning of infections after six months of age, c) less than 2% of B cells (CD19+) by flow cytometric examination, d) agammaglobulinemia/hypogammaglobulinemia, e) disease causing mutation detected in BTK gene analysis.

The exclusion criteria are; a) monogenetic and polygenetic diseases and chromosomal anomalies causing hypogammaglobulinemia, b) using some drugs for epilepsy or any other disease that can cause hypogammaglobulinemia, c) chronic protein losing diseases such as protein losing enteropathies and some nephropathies, d) patients who have infections that suppress immunoglobulin production, e) patients with combined immunodeficiency and common variable immunodeficiency. The present study was carried out under the principles of the Helsinki Declaration and the approval of the ethics committee was obtained on 22.01.2020-E23836). Each patient and the patient's parents were informed and their signed patient consent forms were received.

Methods

All patients were evaluated through detailed anamnesis, complete physical examination and laboratory studies such as hemogram (leukocytes, neutrophils, lymphocytes, hemoglobin and platelet counts), serum immunoglobulin G-A-M by nephelometry and lymphocyte subsets by flow cytometry (T, B, NK cell ratios and absolute values). Demographic characteristics and the frequency of immunoglobulin replacement were questioned. Specific antibodies against routine vaccines were detected by ELISA technique before the first immunoglobulin replacement. BTK gene mutations were analyzed via the Ion AmpliSeq™ Primary Immunodeficiency Panel designed on the Ion Torrent S5 platform. Posterior-anterior lung x-graphs, high-resolution computed tomography (HRCT) results, infections suffered by patients and, if any, pathogens grown in cultures during these infections were recorded. The effect of immunoglobulin replacement therapy on the frequency of infections was examined. Infections such as pneumonia, meningitis, and sepsis observed before and after replacement therapy were identified as serious infections.

Statistical analysis

Numerical data was recorded in the form of 'average' and 'percentage'. Statistical comparison of the data was carried out using Chi-squared test and independent sample T-tests in the SPSS 15 program. *P* values smaller than 0.05 were considered statistically significant.

Results

Demographic findings

Demographic information of 20 XLA patients followed-up in our institution between 1995

Table 1. Patients' demografic characteristics and laboratory values at diagnosis

Variables	Patients (N=20)
Gender, female/male	20/0
Consanguineous marriage of parents	%20 (n=4)
Mean age at onset of signs (months)	60,2 (± 67,8)
Mean age at diagnosis (months)	72,8 (± 62,7)
Mean duration of follow-up (year)	8,5 (± 3,4)
IVIg interval of application	Once monthly
White blood cell/mm^3 mean (± SD)	14.217 (± 7.452)
ANC/mm^3 mean (± SD)	8.603 (± 8049)
ALC/mm^3 mean (± SD)	4.317 (± 1929)
Hemoglobin (g/dl) mean (± SD)	11,6 (± 1,51)
Platelet count/mm^3 mean (± SD)	404.809 (± 141.919)
IgG (mg/dl) mean (± SD)	422 (± 374)
IgM (mg/dl) mean (± SD)	34,9 (± 54,5)
IgA (mg/dl) mean (± SD)	34,2 (± 69,3)
CD3 (%) mean (± SD)	84 (± 14,7)
CD19 (%) mean (± SD)	1,6 (± 4,8)
CD4 (%) mean (± SD)	45,1 (± 18,7)
CD8 (%) mean (± SD)	31,8 (± 13,9)
CD3-CD16/56 (%) mean (± SD)	7,3 (± 8.0)

ANC: absolute neutrophile count; ALS: Absolute lymphocyte count.

and 2019 is given in **Table 1**. Five of our patients are 18 years old and over and our oldest patient is 34 years old. The mean follow-up period is 8.5 years and our longest follow-up period is 24 years. One of the study patients was lost due to septic shock. The mortality rate was 5%.

Hematological and immunological results

The hemogram, lymphocyte subset values at admission of patients, and pre-treatment immunoglobulin levels were shown in **Table 1**. Specific antibody responses against vaccine antigens (anti-Hib, anti-tetanus, anti-HBs, anti-HAV, anti-rubella, anti-rubeola, anti-mumps, and anti-VZV) were all found negative/inadequate in 17 patients before IVIg treatment. Anti-HBs, anti-rubeola, and anti-mumps responses were positive in one patient, and very weak anti-HBs positive responses were determined in two patients. Neutropenia was not observed in any of our patients, both at the time of diagnosis and during the follow-up period.

Genetic studies

Molecular analysis was carried out on all patients in the study, and pathogenic mutation was detected in the *BTK* gene. Nineteen different mutations were detected in the study, six of which were first identified (novel) and shown in detail in **Table 2**. Missense mutation was observed in 15 patients, four patients had a stop-codon mutation and one patient had a frameshift (deletion) mutation.

Microbiological findings

In seven of the patients, *Haemophilus influenzae Type b*, *Streptococcus pneumoniae, Pseudomonas aeruginosa*, *and Haemophilus influenzae non-type B* microorganisms were grown in their sputum cultures. The most common agent is *H. influenzae type b* (57.8%), whereas other agents are *S. pneumoniae* (15.7%), *H. influenzae non-type b* (15.5%), and *P. aeruginosa* (11.2%). One XLA patient had paresis after an enteroviral infection. In the parasitic examinations of patients; no parasites were detected in 18 patients while one p*atient had Blastocystis spp.* cysts; and *Toxocara* was detected in another. The ratio of parasites observed in the XLA patients participating in the study was 10%.

Treatments and their effects on infections

While, Initially, intravenous immunoglobulin (IVIg) replacement therapy was administered to all patients, subcutaneous immunoglobulin (SCIg) replacement therapy was initiated for 35% of the patients in 2015 (n=7). There was a statistically significant decrease in mild infections on IVIg and SCIg treatments compared to pre-replacement therapy (**Table 3**). In addition, on SCIg therapy, which provided a more stable and high IgG concentration, infection rate was found to be significantly lower than IVIG therapy (**Table 3**). On the other hand, while both treatment models reduce the frequency of severe bacterial infections compared to pre-treatment period, there is no significant difference in their efficacy on serious infections between these two treatment modalities (p: 0.125) (Chi-squared test) (**Table 3**).

Complications

In the long term, recurrent infections often lead to chronic lung disease, with bronchiectasis

Table 2. Novel and known gene mutations in BTK gene of our XLA patients

Patient No	Mutation	Type of Mutation
1	BTK gene hemizygous C663C amino acid mutation	Missense mutation (known)
2	BTK gene c.226 G>T (p.Glu76Ter) hemizygous mutation	Stop codon mutation (known)
3	BTK gene Arg5256/g hemizygous mutation	Missense mutation (known)
4	BTK gene c.1289 A>G (p.Lys430Arg) hemizygous mutation	Missense mutation (known)
5	BTK gene complete deletion of exon 5	Frameshift (deletion) mutation (known)
6	BTK gene c.36 G>C (p.Lys12Asn) hemizygous mutation	Missense mutation (novel)
7	BTK gene c.1563 C>A (p.Asp521Glu) hemizygous mutation	Missense mutation (novel)
8	BTK gene c.1835 A>C (p.Gln612Pro) hemizygous mutation	Missense mutation (known)
9	BTK gene c.1684 C>T (p.Arg562Trp) hemizygous mutation	Missense mutation (known)
10	BTK gene c.493 T>G (p.Cys165Gly) hemizygous mutation	Missense mutation (novel)
11	BTK gene c.83 G>A (p.Arg28His) hemizygous mutation	Missense mutation (known)
12	BTK gene c.83 G>A (p.Arg28His) hemizygous mutation	Missense mutation (known)
13	BTK gene c.1573 C>G (p.Arg525Gly) hemizygous mutation	Missense mutation (known)
14	BTK gene c.337 G>A (p.Val113Ile)	Missense mutation (known)
15	BTK gene c.763 C>T (p.Arg255Ter) hemizygous mutation	Stop codon mutation (known)
16	BTK gene c.656 aa hemizygous mutation	Missense mutation (novel)
17	BTK gene 3UTR+119 nucleotide A>C homozygous substitution mutation	Missense mutation (known)
18	BTK gene c.36 G>C (p.Lys12Asn) hemizygous mutation	Missense mutation (novel)
19	BTK gene c.1383 T>G (p.Try461Ter) hemizygous mutation	Stop codon mutation (novel)
20	BTK gene c.226 G>T (p.Glu76Ter) hemizygous mutation	Stop codon mutation (known)

Table 3. The effect of intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIg) replacement therapies on infection frequency

	Pre-replacement therapy	During IVIG Treatment	During SCIG Treatment	*p* values
Annual frequency of infections (times) median (min-max)	10 (4-16)	4 (1-12)	1 (0-8)	0.000
Annual severe bacterial infections (times) median (min-max)	6 (4-10)	1 (0-6)*	0 (0-4)*	0.000 0.125*

*means that there is no significant difference in efficacy on serious infections between IVIG and SCIG treatment.

being the most common complication. In addition to posterior-anterior lung x-rays, HRCT was also demanded for progression in the follow-up of patients with a chronic lung infection. In four of the 20 patients, bilateral bronchiectasis (20%) was observed while atelectatic areas were detected in two patients (10%). Left lower lobectomy was carried out for one patient due to recurrent lung infections. Four of six patients with pulmonary complications had frameshift and stop-codon mutations. In other words, 67% of patients who developed serious lung complications had stop-codon and frameshift mutations. On the other hand, no correlation could be found between the type of mutation detected and the type of microorganisms that lead to observed infections.

Discussion

The molecular basis of XLA is the deterioration in B cell development due to the mutation in the BTK gene resulting defective transition from the pre-B cell stage to the mature B cell stage [6]. In the study of Winkelstein et al., the age at the beginning of symptoms was 6 in 95% of patients, and the mean age of diagnosis was 2.59 for those with positive family history and 5.37 for those with negative family history [2]. In our study, the mean age for being symptomatic is five and the mean age of diagnosis is smaller in patients with a positive family history (the average age of diagnosis is 1.9 in two patients with a positive history of relatives, whereas 6.05 in patients without a history of relatives) as in Winkelstein's study.

Neutropenia has not been observed in any of our patients both at the time of diagnosis and during follow-up. Conley et al. reported severe neutropenia in approximately 25% of patients during diagnosis, and neutropenia was thought to be associated with Staphylococcus and Pseudomonas sepsis [7]. There are also studies reporting that neutropenia develops 10% of XLA patients during follow-up [2, 8].

Mild and moderate low immunoglobulin levels and B cells may be observed in some atypical XLA patients. Besides these laboratory findings, if XLA is clinically and seriously considered, BTK gene analysis is exactly required for the diagnosis. One of our patients (patient no: 14) had highly near-normal immunoglobulin and B lymphocyte count. TNGS (targeted next-generation sequencing) genetic examination was performed, because of recurrent lung infections and the patient was diagnosed with a previously defined mutation c.337 G>A (p. Val113Ile) in the BTK gene. Routine IVIG replacement therapy was initiated after diagnosing XLA for the patient. The clinical findings of this patient have improved and his morbidity has decreased significantly. Similar to our patient Preece and Lear presented a 22-month-old boy with XLA masked by normal immunoglobulin levels and vaccine seroconversion. Diagnosis was made after strong clinical suspicion of immune deficiency and BTK gene analysis [14].

In Broides et al.'s study, mutations caused by 'stop codons' and 'frameshift' in the BTK gene have been clinically identified as mutations leading to more serious complications [15]. Our 15 patients had missense mutations, 4 patients had stop codon mutations and 1 patient had frameshift (deletion) mutation. In our study, the number of patients with bronchiectasis and/or atelectasis was six. Four of these patients have a frameshift and stop codon mutations that means 67% of patients who develop severe lung complications have these two mutations. This result may be a preliminary data for the genotype-phenotype relation. In addition, six novel mutations we have detected will be added to the XLA genotype databases.

CD19 ratio is below 2% in all of our patients and the number of B cells is 0% in only three patients (15%). It is known that antibody response to vaccination is disturbed in XLA patients. The ratio of our patients who produced specific antibody responses is 15% as in the study of Plebani et al. [9].

Affected individuals must receive lifelong immunoglobulin replacement therapy for their survival. The stable high immunoglobulin levels decreased acute life-threatening infections, and survival rates increased dramatically in the last 20 years [10]. Our patient, who had the maximum follow-up period, is now 34 years old, married and he is a Ph.D. student. Once every three weeks, his follow-up is carried out with the IVIg replacement. Recently, SCIg has gained popularity as routine replacement therapy in primary immunodeficiency, because it is faster and has less systemic side effects compared to intravenous application [11]. It can be given at home, and do not lead to absence from school [12, 13]. Concerning our patients; both IVIg and SCIg therapy have significantly reduced the frequency of serious infections and other mild infections in XLA patients. Although we have seven patients in SCIg using patients group, SCIg seems to be more successful in preventing mild infections, but there is no difference between them in terms of preventing serious infections such as pneumonia (**Table 3**).

Early diagnosis and early replacement therapy together have been shown to reduce the frequency of pulmonary infection. In the study of Reisi et al.; the rate of pneumonia observed at least once in XLA patients was found to be 60%, and pneumonia episodes were more common in patients diagnosed after the age of 6 [16]. It was found that 67% of the patients in our study had more than one episode of pneumonia. In patients who suffered from pneumonia, 57% of them were diagnosed after the age of six. In retrospective studies with primary immunodeficiency patients, it was reported that complications such as bronchiectasis, peribronchial thickening, air confinement, reduction of lung volume and atelectasis develop during long-term follow-up [17]. In these cases need for pneumonectomy or lung transplantation is due to bronchiectasis and other chronic lung diseases [10]. In this study, left lower lobectomy was performed due to bronchiectasis and recurrent lung infections to one of our patients. Prevention of irreversible and pro-

gressive chronic lung diseases such as bronchiectasis should be the main goal to focus on XLA patients.

The most common infections in XLA patients are respiratory infections. In infectious episodes, the agent was not often isolated; and 35% of the patients had grown some agents in cultures of sputum, the most common being *H. influenzae type b* (57.8%), and secondly, *S. pneumoniae* (15.7%). In the long-term follow-up of 66 XLA patients reported by Pac et al., *S. pneumoniae* and *H. influenzae* were also most often isolated, similar to our throat culture results [18]. However, in the study of Winkelstein et al., 86% of agents were not detected during pneumonia attacks while *S. pneumoniae* and *H. influenzae* were 10% and 4%, respectively [2].

Cases of chronic meningoencephalitis secondary to enterovirus infection have been recorded in some XLA studies [19]. In a multi-centered study of 738 XLA patients by Zeinab et al., a 4.6% frequency of enteroviral infection was reported, while vaccine-related paralytic poliomyelitis was only seen in the countries routinely vaccinated with live polio virus [20]. With the eradication of wild-type polio viruses from most of the countries in the world, paralysis is thought to be primarily caused by non-polio-enterovirus [21]. In our study, paresis was observed as secondary to enterovirus infections in a patient and there was no post-vaccination paralytic poliomyelitis. The reason for the severe enteroviral infections is related with TLR (Toll-like receptor) signaling. TLR7, which plays an important role in the immune response to enteroviral infection is defected in the dendritic cells of these patients. TLR7 is the ligand of these viruses, and therefore the frequency of enteroviral infection, especially controlled by TLR7 signaling, and morbidity due to poliovirus has increased in XLA patients.

The mortality rate was 8.5% in a study which comprises 201 XLA patients and enteroviral infections, pulmonary infections, and hepatitis are the most common causes of death [2]. In our study, the mortality rate was 5%, and this patient was lost due to septic shock caused by a lung infection. The *BTK* mutation of this patient is a previously defined one (c.226G>T, p.Glu76Ter). The low mortality rate in our study is probably due to the regular immunoglobulin replacement treatments of all patients.

In conclusion, XLA is one of the common causes of pediatric primary immunodeficiency, and patients must receive lifelong immunoglobulin replacement therapy for their survival. Immunoglobulin replacement decreases life-threatening infections. XLA patients reach adulthood with regular treatment and follow-up, and almost all of them can pursue normal lives.

Disclosure of conflict of interest

None.

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