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Original Article

Clinical, Molecular, Immunological Properties and Our Clinical Experiences in Patients Diagnosed with X-linked Agamaglobulinemia

X'e Bağlı Agamaglobulinemi Tanısı Alan Hastalarda Klinik, Moleküler, İmmünolojik Özellikler ve Klinik Deneyimlerimiz

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ABSTRACT

Objective: As a primary immunodeficiency X-linked agammaglobulinemia (XLA) that develops due to Bruton tyrosine kinase signal transduction protein deficiency which progresses with antibody deficiency was firstly described by an American pediatrician Ogden Bruton. In our study, we have aimed to evaluate the demographic, clinical, immunological, genetic characteristics and follow-up findings of patients diagnosed with XLA in our tertiary care Pediatric Immunology Clinic.

Method: Twelve patients diagnosed with XLA between 2003-2022 in our pediatric immunology clinic we're included in our study. The patient's age, sex, age at symptom onset and diagnosis, family history, laboratory findings at the time of diagnosis, complications observed during clinical follow-up and treatment modalities used were evaluated retrospectively.

Results: The median age of the patients at diagnosis was 36 [interquartile range (IQR) 10.2-69.0] months. While the median age of the patients without a family history at the time of diagnosis was 66 (IQR 41.2-66.0) months which was found to be significantly higher compared to the patients with a family history [11.5 (IQR 2.5-30.0) months] (p=0.004). Recurrent respiratory tract infections were the most common indications for admission. Agammaglobulinemia was detected in all patients except two cases. A significant decrease in B cells was detected by flow cytometry in all patients. The diagnoses were confirmed by genetic analysis for nine patients. Bronchiectasis was observed in four, arthritis in three, and inflammatory bowel disease in one case. In one patient, metaplasia was detected in the cytologic examination of the biopsy specimen obtained during endoscopy performed for the diagnosis of inflammatory bowel disease.

Conclusion: Early diagnosis, treatment and regular follow-up convey critical importance in terms of preventing complications in patients with XLA.

Keywords: X-linked agammaglobulinemia, Bruton tyrosine kinase, primary immunodeficiencies

ÖZ

Amaç: Bruton tirozin kinaz sinyal transdüksiyon proteini eksikliğine bağlı gelişen, antikor eksikliği ile seyreden X'e bağlı agammaglobulinemi (XLA), ilk kez Amerikalı çocuk doktoru Ogden Bruton tarafından tanımlanan primer bir immün yetmezliktir. Çalışmamızda merkezimizde XLA tanısı alan hastaların demografik, klinik, immünolojik, genetik özellikleri ve takip bulgularının değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmamıza 2003-2022 yılları arasında üçüncü basamak çocuk immünoloji kliniği olan merkezimizde XLA tanısıyla takip edilen 12 hasta dahil edildi. Hastaların yaşı, cinsiyeti, semptom başlangıç yaşı, tanı yaşı, aile öyküsü, tanı anındaki laboratuvar bulguları, klinik takipteki komplikasyonları ve tedavileri retrospektif olarak değerlendirildi.

Bulgular: Ortanca tanı yaşı 36 [interquartile range (IQR) 10.2-69.0] [minimum (min) 1.27- maksimum (max) 84] aydı. Aile öyküsü olmayan hastaların tanı anında ortanca yaşı 66 (IQR 41,2-66,0) ay olup, aile öyküsü olan hastalara göre anlamlı derecede yüksek bulunmuştur [11,5 (IQR 2,5-30,0) ay] (p=0,004). Hastalarımızda en sık başvuru nedeni tekrarlayan solunum yolu enfeksiyonları idi. İki olgu dışında hastaların tamamında agamaglobulinemi saptandı.

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Tüm hastalarda akım sitometride B hücrelerde anlamlı düşüklük izlendi. Dokuz hastada tanılar genetik analiz ile doğrulandı. Dört olguda bronşektazi, üç olguda artrit, bir olguda enflamatuvar bağırsak hastalığı gelişti. Bir olguda inflamatuvar bağırsak hastalığı nedeniyle yapılan endoskopi materyalinde metaplazi saptandı.

Sonuç: XLA'lı hastalarda erken tanı, tedavi ve düzenli takip komplikasyonları önleyerek hastaların yaşam kalitelerini artırması yönünden önemlidir.

Anahtar kelimeler: X'e bağlı agammaglobulinemi, Bruton tirozin kinaz, primer immün yetmezlikler

INTRODUCTION

As one of the firstly discovered genetically monogenic immunological disorders, X-linked agammaglobulinemia (XLA) is a primary immunodeficiency associated with antibody deficiency due to lack of Bruton tyrosine kinase (BTK) protein[1-3]. The disease was termed after pediatrician Ogden Carr Bruton who first described it in 1952 in an 8-year-old male patient with recurrent pneumococcal sepsis and agammaglobulinemia[4]. However, the genetic defect underlying XLA was only described simultaneously in 1994 by both Sideras et al.[5] and Ohta et al.[6]. It was found that the BTK gene, a member of the Tec kinase family, was located in the Xq21.3-Xq22 region and mostly mutated in male patients presenting with agammaglobulinemia[5,6]. Currently, 2152 different *BTK* gene mutations have been reported in the international mutation database[7]. BTK is a signal transduction protein expressed in the entire hematopoietic system excepting T and NK cells[2]. This disease develops due to a mutation in this gene, which is mapped on the long arm of the X chromosome[2], and is characterized by a significant decrease (less than 2% of total lymphocytes) or absence of mature B lymphocytes as a result of early arrest in the differentiation and maturation of B cells at the Pro B cell stage due to the deficiency of BTK protein (Figure 1)[8,9].

Since XLA is inherited as an X-linked recessive disease, males are primarily affected, and women are usually passive carriers[11]. Symptoms usually manifest after six months of life at the time when maternal IgG is lost[7]. However, rare cases diagnosed in adulthood have been reported[12-14]. Hypoplasia or absence of lymphoid tissue, normal-sized spleen and liver, significant decrease in serum immunoglobulin (Ig) levels, absence of antibody response to antigenic stimuli, and very few (<2%) or lack of B lymphocytes in the peripheral blood aid in making the clinical diagnosis. However; the importance of various factors in the clinical phenotype of the disease, such as age at diagnosis, serum B cell percentage, Ig concentrations, and polymorphic changes in Tec gene should be considered[15-17]. Recurrent bacterial infections associated with capsular, extracellular pyogenic pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are common in affected individuals[18]. Susceptibility to severe and recurrent bacterial infections such as lower and upper respiratory system infections, skin infections, otitis media, conjunctivitis and meningoencephalitis due to existing hypogammaglobulinemia has increased to a great extent[19,20]. Other clinical presentations include diarrhea caused by common pathogens such as *Campylobacter jejuni* and *Giardia lamblia*[24]; skin involvement such as pyoderma gangrenosum, drug-induced Stevens-Johnson syndrome and eczematous dermatitis[21,22]. Although rare, purulent/non-purulent arthritis, osteomyelitis, sepsis, hepatitis, vaccine-associated polio, neutropenia and autoimmune diseases may develop[20,23]. While the cellular immune response to viral infections is normal in patients, sensitivity to the

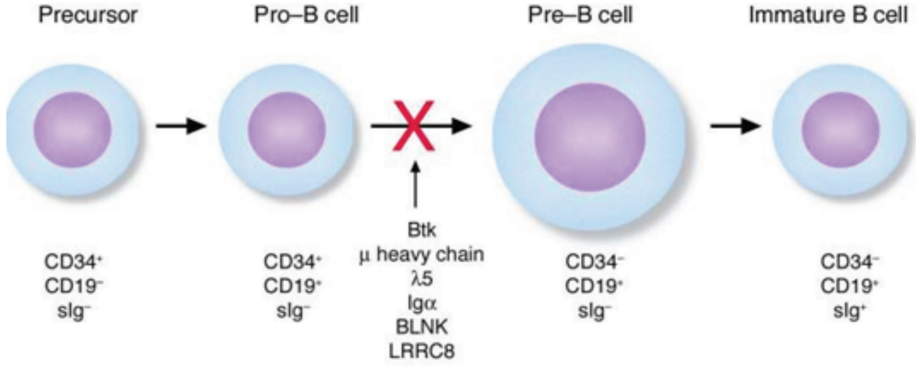

Figure 1. Early stages of B-cell differentiation can be identified by the status of the immunoglobulin genes using cell markers CD34, CD19 and surface immunoglobulin (10)

enterovirus family, in which secretory IgA is an important innate defense mechanism, increases. Therefore, disseminated infections can be observed secondary to the administration of a live virus vaccine such as oral poliovirus vaccine. Persistent enteroviral infections may rarely cause fatal encephalitis and dermatomyositis-meningoencephalitis syndromes. Bronchiectasis due to recurrent sinopulmonary infections is one of the most important complications of the disease[24]. Lifelong Ig replacement therapy is required to reduce the frequency of infections and he risk of mortality in patients with XLA[7].

The aim of this study which was performed in our pediatric immunology clinic, was to evaluate the clinical, molecular, immunological features of the disease and accompanying complications in 12 cases diagnosed with XLA, also known as Bruton's disease.

MATERIALS and METHODS

This study was carried out with 12 patients diagnosed with XLA between 2003-2022 in our tertiary care pediatric immunology clinic. The patient's age, sex, age at symptom onset and diagnosis, follow-up period, parental consanguinity and family history, laboratory findings at the time of diagnosis, complications developed during clinical follow-up and treatments they received were evaluated retrospectively. Peripheral B and T lymphocytes were identified by flow cytometry. In nine patients with suspected XLA, the diagnosis was confirmed by *BTK* gene mutation analysis. The study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision number: 2022/22-02, date: 22.12.2022) and was conducted according to the Declaration of Helsinki.

Statistical Analysis

Descriptive Analysis of the data was carried out by using IBM SPPS Statistics 22.0 program (version 22; SPSS, Chicago, IL, USA). We compared categorical variables using Fisher's exact and Pearson's chi-square tests. The Mann-Whitney U test or the t-test was used to compare numerical variables with and without normal distribution, respectively, and p-values less than 0.05 were considered statistically significant.

RESULTS

Twelve male patients followed up with XLA were included in the study. The mean age of the patients was 14.9±7.88 [minimum (min): 1.75-maximum (max): 24.75] years, and the median age at diagnosis was 36 (IQR 10.2-69.0) (min: 1.27-max: 84) months. The median age at diagnosis of patients without a family history was significantly higher when compared to patients with a family history [66 (IQR 41.2-66.0; min: 21-max: 84) months vs. 11.5 (IQR 2.5-30.0; min: 1.27-max: 48) months] (p=0.004). Respiratory tract infections were the most common indication for admission. One patient had a history of meningitis and the other patient had a history of poliomyelitis before the diagnosis of XLA was made. One of our patients presented with parechovirus encephalitis when he was one year old and diagnosis of XLA was revealed during the follow-up period. In the follow-up, bronchiectasis was diagnosed in four and arthritis in three cases. Inflammatory bowel disease was observed in a patient, and intestinal metaplasia was detected in the endoscopy material. *Helicobacter pylori* was identified as the causative pathogen in the patient who developed gastrointestinal symptoms during follow-up. Deep tissue infection leading to joint contracture developed in one patient. Physical examination disclosed absence of tonsillar tissue in eight and tonsillar hypoplasia in four patients (Table 1).

Agammaglobulinemia was detected in all but two patients aged 38 days, and 3 months who were screened in the early asymptomatic period because of the family history of XLA, in their siblings and cousins. Thanks to the presence of maternal IgG antibodies in newborns, agammaglobulinemia may not be detected in infancy especially during the first six months of life. A significant decrease in B cells was detected in the evaluation of lymphocyte subgroups by flow cytometry in all patients. The diagnoses were confirmed by genetic analysis in nine patients. However, genetic analysis was not required for three patients with confirmed family history of XLA (Table 2). Intravenous immunoglobulin (IVIG) replacement was performed for all cases. Excluding patients who received IVIG at an another center before admission, the median IgG levels of the patients were 147.5 (IQR 137.5-346.0) mg/dL before treatment and 795.50±197.99 mg/dL after six months of regular IVIG replacement. Besides the regular IVIG replacement, antibiotic prophylaxis was performed during the follow-up for nine patients.

DISCUSSION

Twelve patients with XLA were evaluated cumulatively throughout their routine treatment and follow-up periods since 2003. Although the mean age at diagnosis was similar between sporadic and

familial cases in a study coordinated by Italian Primary Immunodeficiency Network Centers so as to better define the natural history of XLA[12], in our study, the median age at diagnosis was significantly higher [66 (IQR 41.2-66.0) years] in cases without a family history, when compared with those with a family history of XLA (p=0.004). We believe that genetic and laboratory analyses performed in our clinic in some patients with a positive family history of XLA led to the diagnosis of this disease at an early stage in other words at a younger age. A similar delay in diagnosis for familial cases was observed in another cohort study in which only one-third of the patients with a positive family history were diagnosed before the disease became symptomatic[20].

Table 1. Conditions and complications that developed in our patients with XLA

	Patient no											
	P_1	P_2	P_3	P_4	P_5	P_6	P_7	P_8	P_9	P_{10}	P_{11}	P_{12}
Age at onset (m)	18	7	12	-*	12	6	8	-*	60	4	8	4
Age at diagnosis (m)	48	24	72	3	72	21	84	1.2	60	48	14	9
Present age (y)	17.9	23.5	18.5	8.91	14.3	24.7	12	5.33	21.3	23.5	1.75	6.91
Family history	+	+	-	+	-	-	-	+	-	-	+	+
Tonsils	a	a	a	a	a	a	a	h	h	h	a	h
Respiratory tract infection	+	+	+	+	+	+	+	+	+	+	+	+
Sinusitis	+	+	+	-	+	+	-	+	+	-	-	-
Otitis media	-	-	+	-	+	+	+	+	+	-	-	-
Pneumonia	-	+	+	+	+	+	+	+	+	+	-	+
Bronchiectasis	+	+	+	-	-	+	-	-	-	-	-	-
Arthritis	+	+	-	-	-	+	-	-	-	-	-	-
Menengitis/encephalitis	-	+	-	-	-	-	-	-	-	-	+	-
Poliomyelitis	+	-	-	-	-	-	-	-	-	-	-	-
Recurrent diarrhea	-	+	-	-	+	-	-	+	-	-	-	-
Malignancy	-	+	-	-	-	-	-	-	-	-	-	-
Deep tissue infection	+	-	-	-	-	-	-	-	-	-	-	-

*Asymptomatic, a: Absent, h: Hypoplastic

Table 2. Immunological evaluation of the patients on admission

	Age at diagnosis (months)	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	B cell (%-#)	Family history	BTK mutation
P_1	48	33	12.6	6	0.5	+	c.1581_1584delTTTG mutation
P_2*	24	664	0.0	24.5	0.0	+	p.His454 Arg homozygous missense mutation
P_3*	72	680	17.3	25	0.3	-	p.Trp124Ser homozygous missense mutation
P_4	3	388	4	12	0.5	+	homozygous p.Arg255x nonsense mutation
P_5	72	134	16.9	26.4	0.9	-	homozygous p.Arg255x nonsense mutation
P_6	21	<142	3.99	5.9	0.0	-	p.Gln459X homozygous mutation
P_7	84	139	8.91	6.66	0.0	-	homozygous c.1775 C>T (p.ser592Phe) hemizygous mutation
P_8	1.2	596	16.8	26.6	1.5	+	-
P_9	60	317	14.2	0.0	0.7	+	-
P_{10}	48	<140	17	24.9	0.1	-	c.1581_1584delTTTG homozygous mutation
P_{11}	14	153	4.79	6.69	0.0	+	hemizygous c.1888A>G (p.Met630Val)
P_{12}	9	332	12.3	26	0.5	+	-

*Patients who received IVIG at another center before admission

These findings underline the fact that physicians should pay attention to positive family history to ensure early diagnosis of XLA.

In our follow-up, immunological parameters of most patients met the diagnostic criteria of the European Society of Immunodeficiencies[25]. The diagnosis was made in two patients by integrating data obtained from analyzes of all five primary classes of Igs, peripheral B cell percentages, genetic analyzes and family history. It was predicted that with the use of these three parameters in combination, XLA can be diagnosed and treated earlier, thus preventing the symptomatic onset of systemic findings of the disease.

In a large-scale study of 168 patients followed for XLA, the most common clinical manifestations recorded during follow-up were respiratory tract infections[12]. In the same study, the respective percentages of patients had developed bronchiectasis (51.8%), gastrointestinal involvement (52.4%), skin infections (30.5%), arthritis (10.4%), sepsis (2.4%), and meningitis (0.6%) during follow-up[12]. In our patients, the most common indication for hospital admission was similarly recurrent respiratory tract infections. One-third of the patients developed bronchiectasis and 25% arthritis during our follow-up. Before the diagnosis, a patient had a history of meningitis and another patient had poliomiyelitis. A patient had parechovirus encephalitis and XLA was diagnosed during follow-up period. In the cranial magnetic resonance imaging of the patient, a hyperintense nodular lesion and increased signal intensity in the thalamus, and numerous millimeter-sized calcifications at the interthalamic level were observed. Parechovirus encephalitis is a rare condition in healthy pediatric populations[26]. Asis stated in the literature parechovirus encephalitis should be considered in the differential diagnosis in patients with deep and periventricular white matter damage, increased signal intensity, bilateral thalamus damage, especially in patients with comorbid disorders or immunosuppression[27].

Lougaris et al.[12] diagnosed malignancies in their 6 (3.7%) patients with XLA including 4 cases with gastrointestinal tract malignancies. Inflammatory bowel disease was observed in one of our patients, and intestinal metaplasia was detected in the endoscopy material of the same patient. Joint contracture developed in another patient following deep tissue infection. Although our incidence rates were significantly lower than those reported in their large-scale study due to our small patient population, symptoms of our patients with Bruton's disease at admission and the complications observed in the follow-up were comparable.

There are known cases of poliovirus paralysis due to administration of attenuated oral Sabin vaccine in patients with XLA[12], and polio sequelae developed in one of our patient. During follow-up of our patients, respiratory tract infections such as pneumonia, otitis media and sinusitis persisted despite routine Ig replacement. This finding reinforces the fact that polyspecific IgG replacement therapy can not adequately compensate for the mucosal IgA deficiency in patients with XLA. As a result of mucosal IgA deficiency, we observed development of bronchiectasis in four patients. Considering the impact of chronic lung disease on the patient's daily life and especially on long-term outcomes, clinicians should pay more attention to the progressive course of lung morbidity in XLA[28], and individual Ig replacement, respiratory physiotherapy program, and antibiotic prophylaxis should be initiated in the early stage of the disease in affected cases[29].

Agammaglobulinemia was detected in all cases, except for two cases aged 38 days and 3 months, who were screened in the early asymptomatic period due to the family history of XLA in their siblings and cousins. Because of the maintenance of maternal IgG levels in newborns, agammaglobulinemia may not be detected in infancy especially during the first six months of life. A significant decrease in B cells was detected in the evaluation of lymphocyte subgroups by flow cytometry in all patients.

The diagnosis was confirmed by genetic analysis in nine patients. In similar studies, the most common mutation types were missense mutations (49%), followed by indels, nonsense mutations and deletions[12]. In our study, missense mutations were found in three, nonsense mutations in two, deletions in two, and indels in two patients. Genetic analysis was not performed in three patients because they met the clinical and laboratory diagnostic criteria of XLA, and a *BTK* gene mutation was detected in a family member (Table 2).

In affected individuals XLA is usually accompanied by severe hypogammaglobulinemia[19]. However, up to 10% of XLA cases have atypical presentations and exhibit normal or almost normal serum Ig levels that usually leads to diagnosis at an older age in these patients with milder phenotypes[12,30]. The ratio of CD19+ B cell remains less than 1% similar to classical XLA, but certain "leaky"

B cells mature with higher Ig levels in these unusual cases[31]. Mutations that cause atypical XLA are similar to those that induce classical XLA, but it is thought that other genetic and environmental factors might cause the diversity of phenotypes[30].

Lifelong Ig replacement therapy is required to reduce the frequency of infection and the risk of mortality in patients with XLA[7]. IVIG replacement was performed for all cases. Excluding patients who received IVIG at another center before admission, the median IgG levels of the patients were 147.5 (IQR 137.5-346.0) mg/dL before treatment and 795.50±197.99 mg/dL after six months of regular IVIG replacement. Achieving normal serum IgG concentrations with early diagnosis, antibiotic prophylaxis and appropriately administered Ig replacement therapy in individuals diagnosed with XLA has significantly improved the prognosis and quality of life of patients in the last 25 years[7,21].

Study Limitation

This study has several limitations due to the retrospective collection of data. Additionally, our sample size is small preventing generalization of our findings; however, given the limited number of studies focusing on Bruton's disease, our study provides additional useful data to assist clinicians in early identification of the patients who need further investigation and treatment.

CONCLUSION

As a conclusion, treatment of XLA includes regular Ig replacement as well as appropriate antibiotic prophylaxis. It is important to evaluate the relevant family history during the diagnostic process and not to overlook tonsillar hypoplasia in the physical examination. To improve survival and increase quality of life in affected patients, the focus should be on the prevention and prompt treatment of associated complications, particularly chronic lung disease. By raising awareness, early diagnosis, treatment and regular follow-up will improve the quality of life of the patients with XLA by preventing development of complications.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision number: 2022/22-02, date: 22.12.2022) and was conducted according to the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer reviewed.

Author Contributions

Surgical and Medical Practices: E.B., İ.T., İ.A.H., N.G., F.G., Concept: E.B., Ö.A., N.G., F.G., Design: E.B., S.Ö.B., Ö.A., N.G., F.G., Data Collection or Processing: E.B., N.G., F.G., Analysis or Interpretation: E.B., S.Ö.B., Ö.A., N.G., F.G., Literature Search: E.B., N.G., F.G., Writing: E.B., S.Ö.B., Ö.A., N.G., F.G.

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