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Original Article

The Evaluation of Neutropenia in X-Linked Agammaglobulinemia Patients

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Abstract

Objectives: X-Linked Agammaglobulinemia (XLA) is a primary immunodeficiency disease, characterized by severe hypogammaglobulinemia and the low numbers of peripheral B cells. Neutropenia is a rare complication among the XLA patients, which may lead to a higher rate of infections and morbidity. The aim of the authors is to assess the correctness of this issue.

Methods: In this study, we compared demographic, clinical and laboratorial data between two groups of XLA patients, with and without neutropenia.

Results: Frequency of neutropenia was 15% in our population. Infectious complications were the most prevalent clinical manifestations, regardless of the presence of neutropenia. However, Lymphoproliferative complication was significantly higher in the neutropenic patients ($p = 0.001$). No significant difference in mortality rate was observed between the groups.

Conclusion: Neutropenia is a rare complication among the XLA patients, and significantly decreases the mean age of XLA diagnosis in the patients. But it is not related to the higher frequency of infectious diseases in the neutropenic patients compared to non-neutropenic ones.

Keywords: X-Linked Agammaglobulinemia; Neutropenia; Bruton's Tyrosine Kinase; Immunodeficiency

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Introduction

The X-linked Agammaglobulinemia (XLA), is an inherited immunodeficiency and one of the commonest primary immune deficiencies in pediatrics. It is characterized by the very low numbers of peripheral B cells and lack of all the immunoglobulin isotypes, and is mainly caused by the mutation of Bruton's Tyrosine Kinase (BTK) gene. The BTK gene is located on the long arm of the X-chromosome (Xq21.3---Xq22) and is composed of 5 distinct structural domains, namely, the Pleckstrin Homology (PH), Tec Homology (TH), Src Homology (SH3), SH2, and the catalytic kinase (SH1) domains. The protein which is encoded by the BTK gene, is essential for the physiological development and proliferation of the B cells. Recent reports suggested the genotype-phenotype correlation in XLA, which is in contrast with the earlier studies [1-4]. The XLA patients, usually become symptomatic between the ages of 6 to 12 month, when the passively transferred maternal IgG is decreased. More than half of the patients had at least one serious infection, before the 3rd year of their life. The clinical manifestations encountered in these patients have a wide variety, including the recurrent infections, autoimmune disease, malignancies, and so on. The immunoglobulin replacement, is the main method of treatment. Aggressive antibiotic therapy or prophylactic antibiotics may be required in some cases [5, 6].

Neutropenia may be seen in some of the XLA patients. In these patients, recurrent infections are not only associated with hypogammaglobulinemia, but also sometimes it might be associated with neutropenia too [7, 8].

In this survey, we compared the demographic, clinical and laboratory findings between the XLA patients with and without neutropenia, in a population of Iranian XLA patients.

Materials and methods

Study population

This is a retrospective cohort study with a total number of 153 patients, which were diagnosed with XLA and were followed up at the Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran). Diagnosis of the XLA, was based on the newest criteria defined by the European Society of Immune Deficiencies, which is illustrated below:

People with at least one of the following symptoms:

- Onset of recurrent bacterial infections, in the first 5 years of life
- Autoimmune manifestations
- Maternal cousins, uncles or nephews with less than 2% CD19+ B cells
- Mutation in Btk
- Absent Btk mRNA on northern blot analysis of neutrophils or monocytes
- Absent Btk protein in monocytes or platelets
- Marked decrease of the IgG, IgA, and IgM

And at least one of the following:

- Poor antibody response to vaccines (and/or absent isohaemagglutinins)
- Low switched memory B cells (<70 % of age-related normal value)

Other causes of hypogammaglobulinemia have been excluded.

The patients who were reluctant to participate in the study and those with incomplete data were excluded.

Overall, 120 patients with a diagnosis of XLA, were included in the present retrospective cohort study. The ethics committee of Tehran University of Medical Science, approved all of the processes of this study, and a written informed consents were obtained from all of the participants or their parents or the legal guardians, prior to the study enrollment.

Data collection

A two-page questionnaire was designed to retrospectively collect all the required information from the patients' medical records. These data consisted of demographic data, the age of onset, age of the diagnosis, delay in the diagnosis, the course of the disease, consanguinity, familial history, episodes of neutropenia, clinical manifestations, laboratory data and the mortality information. The other causes of hypogammaglobulinemia were ruled out, with a confirmed persistent low level of the serum immunoglobulins in addition to, the persistent presence of other XLA diagnostic criteria in the regular follow-up of these patients. Diagnostic delay and the course of the disease, were respectively considered as the time between

the onset of symptoms and the time of diagnosis, and as the time period between onset of clinical manifestations and the patient's current age, or the age of demise.

Classification of the patients

The patients were divided into neutropenic and non neutropenic groups, based on the presence of persistent neutropenia. Neutropenia was defined as an Absolute Neutrophil Count (ANC) below 1500/mm3. Neutropenia was considered mild, moderate, and severe when the ANC was between 1000-1500, 500-1000 and below 500/mm3, respectively [9]. The persistence of neutropenia was defined as, presence of neutropenia for more than 3 months and the exclusion of conditions leading to a transient neutropenia, including infections and specific medications, as well as some inflammatory and autoimmune diseases.

Statistical analysis

Statistical analysis was conducted with SPSS (version 24) software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to test for the normality of the data. The central and descriptive statistics were reported for the quantitative data. For variables with skewed distribution, the median and Interquartile Range (IQR) were reported as the index of the data dispersion. Analytical analyses were performed using the Mann-Whitney, and Chi-square or Fisher's exact tests. The P value <0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 120 XLA patients with 7.57:1 male to female ratio and the median (IQR) course of disease period of 11 (2.16-20) years, were enrolled in the study. **Table 1**, demonstrates the demographic characteristics of the studied patients. Persistent (recurrent or chronic) neutropenia was found in 18 (15%) of the patients. Clinical features of the disease, occurred at a younger age in the neutropenic group compared to the non-neutropenic group. The difference was statistically significant [median (IQR): 0.42 (0.17-0.83) vs. 1 (0.5-2.17) years, P = 0.014]. The patient's age, at the time of diagnosis was significantly lower in the neutropenic XLA patients in comparison to the non-neutropenic patients [median (IQR): 2 (1-2.67) vs. 4.17 (1.92-8) years, P = 0.009], while

Table 1. Demographic characteristics of XLA patients with and without neutropenia

Parameters	Total (n=120)	With neutropenia (n=18)	Without neutropenia (n=102)	*P*-value
Vital status, number (%)				
Dead/Alive ratio	21/78	3/14	18/64	1.000
Alive, (%)	78 (65)	14 (77.8)	64 (62.7)	-
Dead, (%)	21 (17.5)	3 (16.7)	18 (17.6)	-
Unknown, (%)	21 (17.5)	1 (5.6)	20 (19.6)	-
Gender, number (%)				
Sex ratio, M/F	106/14	16/2	90/12	1.000
Male, (%)	106 (88.3)	16 (88.9)	90 (88.2)	-
Female, (%)	14 (11.7)	2 (11.1)	12 (11.8)	-
Consanguinity (%)	59 (51.3)	9 (56.3)	50 (50.5)	0.670
Age, y, median (IQR)	15 (6-24)	5.5 (2.75-22)	15.5 (7.25-24)	**0.026***
Age at onset, y, median (IQR)	0.87 (0.42-2)	0.42 (0.17-0.83)	1 (0.5-2.17)	**0.014***
Age at diagnosis, y, median (IQR)	4 (1.47-7.69)	2 (1-2.67)	4.17 (1.92-8)	**0.009***
Delay in diagnosis, y, median (IQR)	2 (0.5-4.56)	1.33 (0.17-2)	2.5 (0.5-5)	0.075
Course of disease, y, median (IQR)	11 (2.16-20)	4.46 (1-16.12)	12 (3-20.75)	0.087
Positive family history (%)	47 (42.3)	5 (29.4)	42 (44.7)	0.241

IQR, interquartile range 25–75%.
M, Male; F, Female; N, Count; Y, Year.
The median is shown [with 25th and 75th percentiles].
** P-value is statistically significant <0.05*

the difference of diagnostic delay between the two groups, was not significant [median (IQR): 1.33 (0.17-2) vs. 2.5 (0.5-5) years, P = 0.075]. About half of the patients were born to consanguineous parents (59 (51.3%)), and 47 (42.3%) of them had a positive family history of immunodeficiency. However, the last two of the aforementioned variables, were not significantly different between the patients with neutropenia and the patients without neutropenia (P > 0.05).

Clinical manifestations

The most common, first presentation of the XLA, was lower respiratory tract infections (28.4%), followed by upper respiratory tract infections (19.9%), and gastrointestinal tract complications (10.3%). Clinical manifestations during the course of the disease are provided in **Table 2**. Respiratory tract infection (88.5%), immune disorder (75.8%), and neurologic disorders (50.7) were the most frequent

Table 2. Clinical manifestations of XLA patients with and without neutropenia

Parameters	Total (n=120)	With neutropenia (n=18)	Without neutropenia (n=102)	*P*-value
Lymphoproliferative complication (%)	19 (27.1)	8 (72.7)	11 (18.6)	**0.001***
Splenomegaly (%)	9 (7.6)	3 (16.7)	6 (6.0)	0.139
Hepatomegaly (%)	14 (11.9)	5 (27.8)	9 (9.0)	**0.039***
Respiratory tract infection (%)	100 (88.5)	13 (86.7)	87 (88.8)	0.683
Upper respiratory tract involvement (%)	70 (63.1)	10 (66.7)	60 (62.5)	0.756
Sinusitis (%)	49 (43.8)	5 (33.3)	44 (45.4)	0.382
Otitis (%)	56 (50)	8 (53.3)	48 (49.5)	0.781
Lower respiratory tract involvement (%)	79 (69.3)	12 (75)	67 (68.4)	0.773
Pneumonia (%)	73 (64.6)	11 (68.8)	62 (63.9)	0.708
Bronchiectasis (%)	27 (24.3)	3 (20)	24 (25)	1.000
Allergy (%)	8 (13.1)	0 (0)	8 (14.3)	1.000
Neurologic disorder (%)	35 (50.7)	1 (20)	34 (53.1)	0.198
Meningitis (%)	19 (31.7)	0 (0)	19 (34.5)	0.168
Paralysis (%)	10 (16.1)	1 (20)	9 (15.8)	1.000
Gastrointestinal manifestation (%)	46 (38.3)	10 (55.6)	36 (35.3)	0.103
Chronic diarrhea (%)	31 (25.8)	7 (38.9)	24 (23.5)	0.241
Recurrent diarrhea	16 (28.6)	3 (50)	13 (26)	0.338
Oral ulcer (%)	13 (10.8)	2 (11.1)	11 (10.8)	1.000
Liver involvement (%)	16 (24.6)	6 (66.7)	10 (17.9)	**0.005***
Hematologic disease (%)	36 (48)	18 (100)	18 (31.6)	**<0.001***
Anemia (%)	10 (8.3)	1 (5.6)	9 (8.8)	1.000
Eye involvement (%)	25 (20.8)	4 (22.2)	21 (20.6)	1.000
Conjunctivitis (%)	21 (32.8)	4 (66.7)	17 (29.3)	0.084
Immunological disorders (%)	91 (75.8)	12 (66.7)	79 (77.5)	0.373
Autoimmunity (%)	18 (15.0)	1 (5.6)	17 (16.7)	0.304
Rheumatologic manifestation (%)	35 (29.2)	4 (22.2)	31 (30.4)	0.482
Failure to thrive (%)	17 (14.2)	5 (27.8)	12 (11.8)	0.133
Clubbing (%)	14 (12.8)	1 (6.7)	13 (13.8)	0.687
Urinary tract infection (%)	8 (13.6)	1 (16.7)	7 (13.2)	1.000
Dermatologic disease (%)	37 (48.1)	3 (37.5)	34 (49.3)	0.713
Musculoskeletal disorder (%)	16 (27.6)	2 (40)	14 (26.4)	0.609
Cardiovascular disease (%)	5 (8.5)	0 (0)	5 (9.3)	1.000
Malignancy (%)	3 (2.5)	1 (5.6)	2 (2)	0.389

** P-value is statistically significant <0.05*

manifestations during the course of the disease. Among the two classified groups, respiratory tract infection (86.7) followed by lymphoproliferative complications (72.7%), immune disorder (66.7%), and conjunctivitis (66.7) in neutropenic group and the respiratory tract involvement (88.8) followed by immune disorder (77.5), neurologic disorder (53.1), and the dermatologic disease (49.3) in the non-neutropenic group were the most commonly observed features. The lymphoproliferative complication and liver involvement, were significantly higher in the neutropenic patients. No other analytical significant differences were observed between the two groups.

Laboratory findings

Table 3 demonstrates the laboratory findings of the studied patients. According to the findings, neutrophil absolute count median was 895.8 in the neutropenic group and 5438 in non-neutropenic group. The leukocyte count was significantly lower (P = 0.001), and the lymphocyte absolute count was significantly higher (P = 0.001) in the patients with neutropenia compared to the patients without neutropenia. Serum levels of the IgA, IgG and IgM antibodies, were lower among neutropenic patients in comparison to the non-neutropenic patients, even though the difference between two groups was not significant.

Outcome and mortality

During the course of our study, 21 (17.5%) patients died, while 78 patients stayed alive and the vital status of 21 patients was unknown. In the neutropenic group, 3 (16.7%) patients died, 14 (77.8) patients stayed alive and the vital status of one of the cases was unknown at the end of the study. There was no significant differences in the frequency of death, between the neutropenic and non-neutropenic patients. The commonest complication among the deceased neutropenic patients was, pneumonia. We did not find any significant differences in the clinical manifestations, between the deceased neutropenic patients and the living. Also no significant differences in the clinical manifestations, between the neutropenic and non-neutropenic groups was found. Furthermore, we found no significant correlations, between the mortality rate and median of ANC in the neutropenic patients. At last, statistically, no significant differences in the survival rate was observed between the neutropenic and non-neutropenic patients.

Discussion

In this study, we compared the demographic, clinical and immunologic characteristics of XLA, between the neutropenic and non-neutropenic patients. To the best of our knowledge, this article is the largest cohort study in the literature,

Table 3. Immunologic profile of XLA patients with and without neutropenia

Parameters	Total (n=120)	With neutropenia (n=18)	Without neutropenia (n=102)	*P*-value
WBC Median (IQR), cells/µl	9800 (7025-14050)	5010 (3450-7350)	10500 (7700-14590)	**<0.001***
Lymphocyte absolute count Median (IQR), cells/µl	39 (27-54.75)	64.5 (53.25-80.5)	35.5 (22-49)	**<0.001***
Neutrophil absolute count Median (IQR), cells/µl	4313 (1960.27-7601)	895.8 (455.3-1370)	5438 (2676.5-8223)	**<0.001***
Hb, Median (IQR), g/dl	11.45 (10-13)	11 (10-12.3)	12 (10-13)	0.608
$CD3^+$ T cells percentage, median (IQR)	87 (76.25-92)	84 (69-92.5)	87 (78-92)	0.544
$CD4^+$ T cells percentage, median (IQR)	43 (34-51)	35 (20-54)	44 (35-51)	0.074
$CD8^+$ T cells percentage, median (IQR)	38 (26-47.5)	41.5 (13-58.25)	37 (26-46)	0.495
CD1656 (cell/µL), median (IQR)	5.5 (3.25-11.25)	6.5 (1-25.5)	5.5 (4-8.25)	0.902
IgG, mg/dL, median (IQR)	111 (20-297)	30 (2.5-356)	120 (23-297)	0.503
IgA (mg/dL), median (IQR)	4.5 (0-19)	2 (0-18)	5 (0-19)	0.841
IgM (mg/dL), median (IQR)	16 (1-31)	7 (1-22.5)	18 (1-33.25)	0.471
IgE (mg/dL), median (IQR)	4 (1-5.7)	3 (0.75-452.25)	4 (1-5.7)	0.664

WBC, white blood cell; Hb, hemoglobin; CD, cluster of differentiation; Ig, immunoglobulin; IQR, interquartile range 25–75%; µl, microliter; dl, deciliter; g, gram; mg, milligram.
** P-value is statistically significant <0.05*

exclusively evaluating neutropenia in XLA.

The XLA manifestations are variable, and one of these various manifestations is neutropenia, which is not common. In our study, 15% of the XLA patients suffer from persistent (recurrent or chronic) neutropenia. In two studies which was done by Winkelstein et al., and Lederman et al., the rate of neutropenia in the studied populations were 10% and 11%, respectively [10, 11]. A study by Rodriguez et al. showed consistent results to the previous two studies [12]. However, studies by Kanegane et al., Farrar et al., and Aghamohammadi et al. reported a much higher prevalence of neutropenia, 18%, 26%, and 26.7%, respectively [6, 7, 13]. The differences between the reports, are probably due to the different definition of neutropenia that was applied in each study. Also, underlying genetic predispositions could play a major role in the occurrence of neutropenia in different populations.

Recurrent infections, especially respiratory tract infections, were the commonest manifestations in the both groups and there was not any significant differences in this field between the two groups. The rate of the conjunctivitis and candidiasis is approximately twice in the neutropenic group compared to the non- neutropenic group, though the differences were not significant. In theory, the XLA patients with neutropenia are at more risk of infections, especially opportunistic ones; but we did not observe any significant differences in the frequency of infectious complications among the groups. On the other hand, the median age of onset and diagnosis was significantly lower in the neutropenic group compared to the other one. It may be due to the fact that, clinical complications of the neutropenic patients were more severe.

The lymphoproliferative disorders, were significantly higher in the neutropenic group in comparison to the non-neutropenic group. Both hepatomegaly and splenomegaly, have a higher incidence rate in the neutropenic patients, but only the former, is statistically significant. In a previous survey, the hepatomegaly and splenomegaly were observed in 18.2% and 15.2% of the cases, respectively [14]. It is higher than our results in this study, in which the hepatomegaly and splenomegaly were seen in 11.9% and 7.6% of the cases, respectively. The difference may be due to the differences in the method of measurement.

15% of all the cases, suffer from autoimmune problems. In the non-neutropenic patients, the incidence of autoimmune disease is much higher than those with neutropenia, 16.7 % and 5.6%, respectively; but this difference, is not statistically significant. The commonest autoimmune disease, was the Juvenile Rheumatoid Arthritis (JRA). In a research by Vivian P, et al, it has been shown that the incidence of autoimmune diseases in the XLA patients, is higher than the previous expectations. The assumed mechanisms of the autoimmune disease includes, the production of autoantibodies by B cells, impaired clearance of apoptotic cells and residues, and diminished tolerance of the cytotoxic T cell [15]. Due to the diminished B cells and their disability to produce immunoglobulins in the XLA patients, the first theory is rejected. In the XLA patients, macrophages and T cells are functionally normal, so the other two theories are not probable. It is likely, that there is no significant relation between the XLA and autoimmune disorders.

An insignificant higher ratio of Failure To Thrive (FTT), is observed among the patients with neutropenia (27.8%) compared to the patients without neutropenia (11.8%). There are various reports of XLA patients who developed FTT [16, 17]. The main cause of FTT in these patients may be due to recurrent infections, gastrointestinal tract complications and malabsorption.

The causes of neutropenia in XLA, are not fully understood yet; but some findings showed that the BTK gene is an important regulator of neutrophils cell cycle and maturation, and its defects may affect both the lymphocyte B cells and neutrophils [18]. In a study, Jefferies et al. revealed that the BTK protein interacts with Toll-like Receptor (TLR) 4, 6, 8, and 9 [19]. Anita Mangla et al. reported that, the absence of BTK, leads to the reduction of the granulocyte-monocyte progenitor cell population [20].

In our study, median delay of the diagnosis, was 2 years. In the studies by Alizadeh et al., and Suri et al. the diagnostic delay was 4.8 and 3.25 years, respectively [6, 21]. The cause of the differences, is probably the difference in the method of statistical analysis of data.

In a study by Mohammad Ghorbani et al., neutropenia and its complications were assessed in the Common Variable Immune Deficiency

(CVID) patients. The frequency of neutropenia in their study was 8.1%. They reported a significantly higher rate of the candida infection, autoimmunity, septicemia, and mortality rate in the neutropenic group compared to the non-neutropenic group [22]. In another study evaluating the neutropenia in the CVID patients, it is concluded that neutropenia is related to the more severe clinical outcomes and higher mortality rate [23]. But we did not find a significant difference in infections and mortality rate between the neutropenic and non-neutropenic XLA patients.

Conclusion

Neutropenia is an uncommon manifestation of XLA. Although the age of onset and diagnosis, is significantly lower in the XLA patients with neutropenia in comparison to the non-neutropenic patients, the rate of infection is not higher in the neutropenic patients compared to non-neutropenic ones. The exact mechanism of neutropenia, is not clear in the XLA patients, so further studies are needed in this regard. Early diagnosis of the disease and the initiation of appropriate treatment will increase the quality of life and reduce its complications; therefore, physician's awareness in this field should be increased.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Chen XF, Wang WF, Zhang YD, Zhao W, Wu J, Chen TX. Clinical characteristics and genetic profiles of 174 patients with X-linked agammaglobulinemia. Medicine. 2016;95(32):e4544.
2. Lee PPW, Chen TX, Jiang LP, Chan KW, Yang W, Lee BW, et al. Clinical characteristics and genotype-phenotype correlation in 62 patients with X-linked agammaglobulinemia. J Clin Immunol. 2009;30(1):121–131.
3. El-Sayed ZA, Abramova I, Aldave JC, Al-Herz W, Bezrodnik L, Boukari, et al. X-linked agammaglobulinemia (XLA): Phenotype, diagnosis, and therapeutic challenges around the world. World Allergy Organ J. 2019;12(3):100018.
4. López-Granados E, Pérez de Diego R, Ferreira Cerdán A, Fontán Casariego G, García Rodríguez MC. A genotype-phenotype correlation study in a group of 54 patients with X-linked agammaglobulinemia. J Allergy Clin Immunol. 2005;116(3):690–697.
5. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr. 2002;141(4):566–571.
6. Suri D, Rawat A, Singh S. X-linked agammaglobulinemia. Indian J Pediatr. 2016;83(4):331–337.
7. Asghar A, Taher C, Nima R, Hirokazu K, Sina A, Mojtaba T-K, Golnaz H, et al. Neutropenia associated with X-Linked agammaglobulinemia. Iran J Allergy Asthma Immunol. 2009;8(1):43-47.
8. Kanegane H, Taneichi H, Nomura K, Futatani T, Miyawaki T. Severe Neutropenia in Japanese Patients with X-Linked agammaglobulinemia. J Clin Immunol. 2005;25(5):491–495.
9. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. Semin Hematol. 2013;50 (3):198–206.
10. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia. Medicine, 1985;64(3):145–156.
11. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, at al. X-linked agammaglobulinemia. Medicine, 2006;85(4):193–202.
12. Plo Rodriguez F, Garcia Rodriguez MC, Ferreira Cerdan A, Fontan Casariego G. Neutropenia as early manifestation of X-linked agammaglobulinemia. Report on 4 patients. An Esp Pediatr 1999; 51(3):235-40.
13. Farrar JE, Rohrer J, Conley ME. Neutropenia in X-linked agammaglobulinemia. Clin Immunol Immunopathol. 1996;81(3):271-6.
14. Moin M, Aghamohammadi A, Farhoudi A, Pourpak Z, Rezaei N, Movahedi M, et al. X-Linked Agammaglobulinemia: A survey of 33 iranian patients. Immunol Invest. 2004;33(1):81–93.
15. Hernandez-Trujillo VP, Scalchunes C, Cunningham-Rundles C, Ochs HD, Bonilla FA, Paris K, et al. Autoimmunity and inflammation in X-linked agammaglobulinemia. J Clin Immunol. 2014;34(6):627–632.
16. Bruele T, Mourad-Baars PEC, Claas ECJ, Plas RN, Kuijper E J, Bredius RGM. Campylobacter jejuni bacteremia and Helicobacter pylori in a patient with X-linked agammaglobulinemia. Eur J Clin Microbiol Infect Dis.. 2010;29(11):1315–1319.
17. Cuccherini B, Chua K, Gill V, Weir S, Wray B, Stewart D, et al. Bacteremia and Skin/Bone Infections in Two Patients with X-linked agammaglobulinemia Caused by an Unusual Organism Related to Flexispira/Helicobacter Species. Clin Immunol.

2000;97(2):121–129.
18. Fiedler K, Sindrilaru A, Terszowski G, Kokai E, Feyerabend TB, Bullinger L, et al. Neutrophil development and function critically depend on Bruton tyrosine kinase in a mouse model of X-linked agammaglobulinemia. Blood. 2010; 117(4):1329–1339.
19. Jefferies CA, Doyle S, Brunner C, Dunne A, Brint E, Wietek C, et al. Bruton's tyrosine kinase Is a Toll/Interleukin-1 Receptor domain-binding protein that participates in nuclear factor κB activation by Toll-like receptor 4. J Biol Chem. 2003;278(28):26258–26264.
20. Mangla A. Pleiotropic consequences of Bruton tyrosine kinase deficiency in myeloid lineages lead to poor inflammatory responses. Blood, 2004;104(4):1191–1197.
21. Alizadeh Z, Dashti P, Mazinani M, Nourizadeh M, Shakerian L, Tajik S, et al. Clinical and genetic study of X-linked agammaglobulinemia patients (The Benefit of Early Diagnosis). Iran J Allergy Asthma Immunol. 2020;19(3):305-309.
22. Ghorbani M, Fekrvand S, Shahkarami S, Yazdani R, Sohani M, Shaghaghi M, et al. The evaluation of neutropenia in common variable immune deficiency patients. Expert Rev Clin Immunol. 2019;15(11):1225-1233.
23. Guffroy A, Mourot-Cottet R, Gerard L, et al. Neutropenia in patients with common variable immunodeficiency: a rare event associated with severe outcome. J Clin Immunol. 2017;37(7):715–726.