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Original Article

Comparison of Demographic and Clinical Characteristics among X-Linked and Autosomal Recessive Agammaglobulinemia

Parham Mardi[1], Mahnaz Jamee[2,3], Mohammad Hossein Eslamian[4]*

[1] *Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran*
[2] *Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[3] *Pediatric Infections Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4] *Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran*

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Abstract

Background: Congenital agammaglobulinemia is an inborn error of immunity, resulting in the impairment of effective antibody production. Agammaglobulinemia may be due to X-linked or autosomal genetic abnormalities. The primary defect in X-Linked agammaglobulinemia (XLA) and autosomal recessive agammaglobulinemia (ARAG) is the B cell precursors' failure to mature B-lymphocytes and, ultimately, plasma cells. This study aims to evaluate the differences in clinical and paraclinical characteristics of XLA and ARAG patients.

Method: A total of 58 patients were enrolled in this retrospective study. The data were extracted from the Iranian primary immunodeficiency registry (IPIDR). Forty-eight of the patients were diagnosed with XLA, while the other ten were diagnosed with ARAG. Measures including demographic data, clinical manifestations, and laboratory data of the patients were compared between the groups.

Results: Patients with ARAG, presented manifestations at an earlier age and had a lower diagnosis delay compared to XLA patients. However, the mortality rate was not significantly affected. The pattern of organ involvement also differed between the two groups, as patients with ARAG showed manifestations that are more chronic in nature (e.g., autoimmunity, lymphoproliferation, and allergy). In contrast, XLA patients were more prone to infections and other associated complications (e.g., meningitis, sinusitis, diarrhea, and bronchiectasis). Meningitis was exclusively observed in the XLA group. The number of CD19+ B cells was significantly higher in the ARAG group (*P=0.002*), While the level of IgM was significantly higher in the XLA group (*P=0.045*).

Conclusion: Identifying the clinical presentations of XLA and ARAG, may assist clinicians in early diagnosis in the setting of limited available genetic studies.

Keywords: X-Linked Agammaglobulinemia; Autosomal Agammaglobulinemia; Bruton; Inborn Errors of Immunity

***Corresponding Author:** Mohammad Hossein Eslamian, MD
Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran
E-mail: mheslamian9@gmail.com

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Introduction

Agammaglobulinemia is one of the most common types of inborn errors of immunity in the pediatric population (1). It is characterized by low mature B cells, which leads to antibody deficiency and a higher risk of infections (2, 3). For instance, children with more than eight episodes of ear infections per year, two episodes of documented sinus infections per year, two episodes of pneumonia per year, one episode of pneumonia per year, two episodes of infectious bronchitis per year, or two deep-seated tissue infections should be suspected for an immune system disorder (4). A maturation defect in B lymphocyte development is noted in both X-Linked agammaglobulinemia (XLA) and autosomal recessive agammaglobulinemia (ARAG) (5). Mutations in the gene encoding bruton tyrosine kinase *(BTK),* are the primary etiology of XLA, while there are various mutations attributed to ARAG, including μ heavy chain deficiency (6, 7). As a result of these mutations, a lack of antibodies occurs, and these patients are subsequently at a higher risk of infection (8, 9).

Due to the maternal transferred IgG during the gestational period, affected newborns have normal levels of serum IgG at birth. Following the decline of antibody levels, patients develop respiratory tract complications including pneumonia, otitis media, sinusitis, bronchiectasis, and clubbing as the most prominent clinical features in these patients (10). These complications are among the main reasons of morbidity and mortality among patients. Moreover, an unusual susceptibility to infections with enteroviruses is prevalent in these patients, which may result in vaccine-related paralytic poliomyelitis or a dermatomyositis-meningoencephalitis syndrome. In patients diagnosed with agammaglobulinemia, gastrointestinal tract problems, enterovirus infections, autoimmunity, and malignancies are also common (11, 12).

Absent or small tonsils and cervical lymph nodes, in addition to higher susceptibility to infections, should arouse concern (7). Paraclinical findings include a decline in circulating immunoglobulin (Ig) levels (IgG, IgA, IgM, IgE) and disability to make specific antibody responses. As a result of the difference in clinical manifestations, diagnosis, and outcome of XLA and ARAG, genetic evaluation is also indicated in these patients (13, 14). In the present study, we aim to compare the clinical manifestations of patients with XLA and ARAG.

Methods

This retrospective study was performed on patients whose data were recorded in the Iranian Primary Immunodeficiency Registry (IPIDR) established by the National Primary Immunodeficiency Network in the Research Center for Immunodeficiency(15).

A total of 58 patients with agammaglobulinemia were registered in the database, 48 patients diagnosed with XLA, and ten patients diagnosed with ARAG. The inclusion criteria for agammaglobulinemia, were based on the criteria of the European Society for Immunodeficiency, which consists of declined serum immunoglobulins, decreased numbers of circulating B-cells (less than 1%), and normal T-cell counts and functions as assessed by flow cytometry and antigen-induced (Candida and Purified Protein Derivative (PPD), tetanus toxoid) T-cell function assays.

All patients underwent the gene analysis of Bruton Tyrosine Kinase (*BTK*) and μ heavy chain, which confirmed the diagnosis of XLA and ARAG, respectively. All samples underwent whole-exome sequencing and were confirmed by Sanger sequencing

Patient characteristics, including the median age at the onset of symptoms, the median age at diagnosis, delay in diagnosis, parental consanguinity, clinical manifestations, and outcomes, were gathered using a questionnaire. The number of cells was counted using flow cytometry. The level of patients' immunoglobulin was measured using the standard kits. Statistical analyses were performed by the SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). , The variables were compared within groups by Mann-Whitney, Chi-square, or Fisher exact tests. A p-value of <0.05 was considered to be statistically significant.

Results

Demographics

Overall, 54 male and 4 female patients were enrolled in the study. The median (IQR) age of participants at the onset of symptoms was 12.0

(5.3-28.5) months, and the age of diagnosis was 58 (22.5-96.0) months, both of which were significantly lower in the ARAG group than in the XLA group (*P*=0.044 and *P*=0.001, respectively). Delay in diagnosis was relatively longer in the XLA group (38.5 (19.2-77.2)) in comparison to the ARAG group (7.5 (1.0-21.75)) (*P*=0.016). The demographic data of the participants are summarized in **Table 1**. The two groups were not significantly different in terms of positive family history, but consanguinity was more frequently seen in the ARAG group (*P*=0.004).

Clinical and molecular characteristics

There was no significant difference in the frequency of clinical manifestations except for meningitis, which was exclusively observed in the XLA group (*P*=0.048). Otitis media (54.1% vs. 33.3%), sinusitis (62.5% vs. 33.3%), bronchiectasis (31.2% vs. 11.0%), clubbing (19.0% vs. 12.5%), chronic diarrhea (29.1% vs. 20.0%), and conjunctivitis (27.0% vs. 20.0%), were more common in XLA compared with ARAG group. On the other hand, the frequency of pneumonia (80.0% vs. 68.7%), autoimmunity (30.0% vs. 10.4%), splenomegaly (20.0% vs. 8.3%), and hepatomegaly (30.0% vs. 10.4%), were higher in ARAG patients. In terms of patient outcomes, there was no significant difference in the rate of death (*P*=0.315).

In the patients with XLA, the most frequent mutations were missense mutations (47.9%). Furthermore, almost half of the mutations (45.8%) were found in the tyrosine kinase domain, while in the autosomal type, stop-gain or significant deletion mutations in the CH1 domain were the most frequent type.

Immunologic profile of patients

Table 2 provides information on the number of white blood cells, lymphocytes, neutrophils CD3+ T cells, CD4+ T cells, CD8+ T cells, and CD19+ T cells. Apart from the number of CD19+ T cells, which was significantly higher in the ARAG group (*P*-value<0.05), there was no significant difference in the number of cells in ARAG and XLA patients. On the other hand, the level of IgM was significantly higher in the XLA group, while there was no significant difference in the amount of IgG, IgA, or IgE in the two groups.

Table 1. Demographic characteristics, risk factors and clinical manifestations of XLA and ARAG patients

Parameters	XLA (n = 48)	ARAG (n = 10)	*P*-value
Gender number of males (%)	48 (100)	6 (60)	0.001**
Median age at the onset of symptoms (month) (IQR)	12.0 (6.0-36.0)	7.0 (3.0-12.0)	0.044*
Median age at diagnosis (month) (IQR)	60.0 (36.0-105.0)	13.0 (4.75-28.5)	0.001**
Delay in diagnosis (month) (IQR)	38.5 (19.2-77.2)	7.5 (1.0-21.75)	0.016*
Consanguinity, n (%)	18 (37.5)	9 (90.0)	0.004**
Positive family history, n (%)	26 (56.5)	4 (57.1)	1.0
Otitis media, n (%)	26 (54.1)	3 (33.3)	0.288
Sinusitis, n (%)	30 (62.5)	3(33.3)	0.139
Pneumonia, n (%)	33 (68.7)	8 (80.0)	0.713
Bronchiectasis, n (%)	15 (31.2)	1 (11)	0.421
Clubbing, n (%)	9 (19)	1 (12.5)	1.0
Autoimmunity, n (%)	5 (10.4)	2 (30)	0.131
Splenomegaly, n (%)	4 (8.3)	2 (20.0)	0.274
Hepatomegaly, n (%)	5 (10.4)	3 (30.0)	0.131
Lymphoproliferation, n (%)	8 (16.6)	2 (20.0)	1.0
Allergy, n (%)	3 (6.2)	2 (20.0)	0.202
Chronic diarrhea, n (%)	14 (29.1)	2 (20.0)	0.710
Conjunctivitis, n (%)	13 (27.0)	2 (20.0)	1.0
Meningitis, n (%)	16 (33.3)	0.0 (0.0)	0.048*
Paralysis following vaccination, n (%)	1 (2.0)	1 (10.0)	0.318

*P-value < 0.05

**P-value <0.01

Table 2. Immunologic profile of patients with XLA and ARAG

Parameters	Total	XLA (n=48)	ARAG (n=10)	*P*-value
WBC × 103 (cell/uL), median (IQR) (n=48)	9750 (7132-14622)	9630 (7177-14072)	14615 (4920-27362)	0.455
Absolute lymphocytes count × 103 (cells /µL), median (IQR) (n=47)	3560 (2465-5145)	3543 (2539-4936)	5024 (2365-10217)	0.354
Absolute neutrophils count × 103 (cells /µL), median (IQR) (n=47)	4672 (2349-6960)	5169 (2470-7380)	2487 (1677-4672)	0.209
CD3+ T cells, %, median (IQR) (n=49)	91 (84-93)	91 (85-94)	87 (65-93)	0.276
CD4+ T cells, %, median (IQR) (n=47)	44 (32-52)	43 (32-53)	44 (22-47)	0.611
CD8+ T cells, %, median (IQR) (n=47)	40 (30-45)	38 (28-46)	42 (38-44)	0.269
CD19+ B cells, %, median (IQR) (n=43)	**0 (0-1)**	**0 (0-0.2)**	**1 (1-5)**	**0.002***
IgG, mg/dL, median (IQR) (n=53)	112 (42.5-298.5)	122 (46-299)	90 (24-446)	0.687
IgA (mg/dL), median (IQR) (n=51)	5 (0-10)	5 (0-16.5)	2 (0-9)	0.303
IgM (mg/dL), median (IQR) (n=53)	**17 (2.5-29.5)**	**19 (5-36)**	**4.5 (0-19)**	**0.045***
IgE (IU/ml), median (IQR) (n=16)	1 (0-4.8)	1 (0-4.7)	1 (0.3-81.2)	0.453

Ig, Immunoglobulin; WBC, White blood cell; IQR, Interquartile range.
The median is shown [with 25th and 75th percentiles].
* *P*-value is statistically significant <0.05

It should be noted that all ARAG patients had µ heavy chain defects.

Discussion

Herein, we presented the demographic and clinical characteristics of Iranian patients diagnosed with agammaglobulinemia. This study also illustrates a considerable difference between XLA and ARAG regarding the risk factors, clinical manifestations, and diagnostic limitations.

In this study, patients with µ heavy chain deficiency were diagnosed at an earlier age and had more chronic complications than the *BTK* -deficient patients, as in the previous reports about patients with early defects in B-cell development (16). The onset of symptoms and the median age of diagnosis were about 1 and 5 years old, respectively. Iranian XLA patients are diagnosed at an age notably older than their peers reported in the literature (17, 18). For instance, Winklestein et al. study demonstrate that American XLA patients are 2.59 years old at the time of diagnosis (19). This difference can be justified by the differences in the ability of the healthcare systems to diagnose immunodeficiencies (20). Another explanation is, the differences in the severity of mutations in each population. Lee et al. study revealed that patients with severe mutations are diagnosed at a younger age than less severe mutations (21). Splice-site defects at base pairs that allow protein production, were considered less severe mutations, whereas frameshift and nonsense mutations were considered severe mutations (22-24).

In the current study, the age at the time of diagnosis is younger in ARAG patients than in XLA patients. ARAG patients' age at diagnosis is similar to previous studies (25).

Family history is a crucial risk factor in agammaglobulinemia patients. On the other hand, a positive family history accelerates the diagnosis, and subsequently improves the diagnosis. In this study, the frequency of the family history was similar in both groups.

Consanguinity is also a significant risk factor prevalent to the Middle East and North Africa (26). Consanguinity was more frequent in the ARAG group than in the XLA group, as expected by the autosomal recessive mode of inheritance.

Splenomegaly, hepatomegaly, autoimmunity, allergy, and lymphoproliferation are the most common non-infectious findings in patients with agammaglobulinemia. Nevertheless, no significant difference was seen between the two groups regarding the frequency of these signs and symptoms.

Respiratory infection is the most common cause of death in the agammaglobulinemia patients (27). Like the previous studies (28), respiratory complications, including pneumonia, were the most common complications among XLA and

ARAG patients. However, these complications are more prevalent in ARAG patients in comparison to XLA patients. Bryan et al. demonstrated that the respiratory complications in agammaglobulinemia patients are associated with lower quality of life and higher morbidity and mortality (29).

One patient in each XLA and ARAG group developed paralytic polio infection due to Oral Polio Vaccine (OPV) intake. In previous reports, a much lower rate of OPV-caused paralysis is reported in *BTK* and μ heavy chain deficient patients (30). As immunity against enteroviruses is predominantly antibody-mediated, patients suspected of significant B-cell dysfunction are recommended to receive Inactivated Polio Vaccine (IPV) instead of OPV.

Apart from respiratory manifestations, gastrointestinal complications are also more common in the ARAG group. The frequency of gastrointestinal manifestations, ranges from 10 percent in Quartier et al. (31) study, to 73 percent in Van der Hilst et al. (32) study. Other clinical manifestations' frequency is similar to previous studies.

The level of CD19+ T cells was decreased in both groups compared to the normal population. Moreover, the level of CD19+ T cells was higher in the ARAG group than in the XLA group. As one of the etiologies of ARAG is a defect in pre-B cell receptors, which consists of a pseudo-light chain and the μ heavy chain of the IgM, the lower level of IgM in ARAG patients compared to XLA patients can be justified.

This study had some limitations, including its retrospective design and relatively small sample size, making it difficult to determine if the differences between the two groups are actual findings. Further studies on the greater study population are required to precisely identify clinical, immunological, and molecular characteristics among different etiologies of agammaglobulinemia. Identifying the clinical presentations of XLA and ARAG, assists clinicians in early diagnosis, especially in developing countries, where access to genetic testing is limited (33).

Conclusion

The current study revealed that patients with ARAG present manifestations at an earlier age and have a lower diagnosis delay than the XLA patients.

The pattern of organ involvement also differs between the two groups, as patients with ARAG show manifestations that are more chronic in nature (e.g., autoimmunity, lymphoproliferation, and allergy). In contrast, XLA patients are more prone to infections and associated complications (e.g., meningitis, sinusitis, diarrhea, and bronchiectasis).

Identifying the clinical presentations of XLA and ARAG, assists clinicians in early diagnosis, especially in developing countries, where access to genetic testing is limited.

Conflict of interest

The authors have no conflicts of interest to disclose.

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