

# Evaluating Autoimmunity in Patients with Agammaglobulinemia

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## Abstract

**Background/objectives:** Agammaglobulinemia is considered as a primary immunodeficiency disorder (PID) which is identified with increasing susceptibility to the bacterial infections, significant low antibodies and isohemagglutinins and decreasing peripheral B cells counts. It could be observed different clinical manifestations in these patients. Some of the patients with agammaglobulinemia manifest autoimmune disorders, while association of autoimmunity and agammaglobulinemia has not been clarified yet. In this study, we evaluated the frequency of autoimmunity in agammaglobulinemia patients and compared their demographic, clinical and laboratory data in two groups of the patients with and without autoimmunity.

**Methods:** The present study included 147 patients with agammaglobulinemia who were diagnosed at Research Centre for Immunodeficiencies at the children's medical Centre.

A comprehensive history, demographic information, clinical manifestations, laboratory data were obtained from all patients to evaluate the autoimmune complications.

**Results:** Among 147 agammaglobulinemia patients, we identified 21 patients (14.2%) who had autoimmune disorders (18 males and 3 females). Respiratory infections were the most prominent clinical symptom among all the patients (72.4%). Among autoimmune disorders, Juvenile Rheumatoid Arthritis (JRA) was the most important autoimmunity (38%) then, Immune Thrombocytopenia (ITP) with the frequency of 14%.

**Conclusion:** Autoimmune diseases are not very common among agammaglobulinemia patients; however, these disorders should be considered as an important factor for management in the patients. Early diagnosis and suitable management of autoimmunity leads to enhancement of patient's life quality in agammaglobulinemia cases.

**Keywords** Agammaglobulinemia, Autoimmunity, Primary immunodeficiency disorders (PIDs), B-cell.

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## Introduction

Agammaglobulinemia is considered as a primary immunodeficiency disorder (PID) which is characterized by increasing susceptibility to the bacterial infections, significant low antibodies and isohemagglutinins and decreasing the number of peripheral B cells (1). The majority of agammaglobulinemia patients have mutations in Bruton tyrosine kinase (BTK) gene, while a small group with autosomal recessive inheritance have mutations in m heavy chain, Iga (CD79A), Igb (CD79B), 15IGGL1), B-cell linker protein, the subunits of phosphoinositide3-kinase (phosphatidylinositol 3-kinase regulatory, phosphatidylinositol-3-kinase-Delta, and phosphatase and tensin homolog), and the transcription factor E47 (transcription factor 3) (2). Agammaglobulinemia patients with mutation in BTK are entitled as X-linked agammaglobulinemia (XLA) or Bruton, and this disorder is observed in males (3). However, autosomal recessive agammaglobulinemia (ARA), which is another inheritance pattern form for agammaglobulinemia patients, is observed in both males and females (4).

The risk of autoimmunity is almost inevitable due to the defects in antibody response and the low serum immunoglobulin levels, and the studies have showed that this rate may be up to 15% (5). In this regard, various types of autoimmune and inflammatory diseases, including dermatomyositis, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), alopecia, scleroderma, autoimmune hemolytic anemia and also membranoproliferative glomerulonephritis (MPGN)

have been reported in agammaglobulinemia patients (6-8). Furthermore, several studies have reported Kawasaki, Uveitis, Vitiligo, Guillain-Barré syndrome (GBS) and Immune thrombocytopenia (ITP) are considered as autoimmune and inflammatory disorders in agammaglobulinemia patients (9, 10). The pathophysiology mechanisms that are underlying the autoimmunity in agammaglobulinemia patients are poorly understood. BTK- dependent mechanisms play a major role in the pathophysiology of autoimmunity in XLA disease (11). These mechanisms are uncommon TLR9 signaling pathways, during reactivation of NF- $\kappa$ B, RelA and also a shortage in the dendritic cell (12, 13). It has been showed that selective defects of dendritic cell subsets may also play an important role in this pathway (10). Our limited knowledge about unknown factors and autoimmunity pathways in the agammaglobulinemia patients supports the notion that more studies emphasize on this subject which are required to be conducted.

Therefore, this study was finally conducted to evaluate the clinical symptoms and laboratory results of the agammaglobulinemia patients and to compare these parameters between patients with and without autoimmunity.

## Materials and methods

### Study population

A total of 147 patients who were diagnosed with agammaglobulinemia were included in this retrospective cohort study. The input criteria of the study were according to the ESID criteria to diagnose the agammaglobulinemia including very

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low circulating B cells (<2%) with a normal count of T cells, low level of serum IgG (200 mg/dl <12 months of age and 500 mg/dl >12 months of age) with documented recurrent infections before 5 years age. Written informed consent was gained from the participants and their parents when they were under the age of consent.

## Methods

Clinical manifestations in the agammaglobulinemia patients are commonly observed between the ages of 6-12 months, when the transferring maternal IgG is reduced. Recurrent infections are the most prevalent symptoms; however, other complications such as gastrointestinal problems (particularly chronic diarrhea), meningitis, lymphoproliferative disorders, autoimmunity, and neutropenia have been also observed in these patients (14).

A comprehensive questionnaire was designed for collecting data of the patients. This questionnaire had items for demographic information (such as, sex, age, consanguinity and family history of the disease), clinical manifestations (including first presentations, recurrent infections, gastrointestinal disorders, lymphoproliferative disorders, autoimmunity, types of autoimmunity and other complications) and laboratory data (such as the serum IgG, IgM, and IgA levels, completing blood counts with differential, lymphocyte subsets, specific antibody response). Specific antibody response to polysaccharide (non-conjugated pneumococcal polyvalent vaccine) and protein antigens (tetanus and diphtheria vaccine) were measured by the enzyme-linked immunosorbent assay (ELISA).

Autoimmune manifestation was recorded before or after diagnosis for each patient. The autoimmunity diagnosis was conducted by an immunologist and a subspecialist according to the clinical manifestations of the patient. Additional paraclinical observations including endoscopy,

colonoscopy, and biopsy were added to the results for further analysis. To compare clinical and laboratory data, all patients were categorized into two groups of agammaglobulinemia patients with and without autoimmunity.

## Statistical analysis

Statistical analyses were conducted using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA). Qualitative values were indicated as the number and percentage (frequencies), while quantitative results were expressed as the mean of  $\pm$  standard deviation (SD) and median (interquartile range, IQR, presented as a range with 75th–25th percentiles). Statistical test including Fisher's exact and Chi-Square test which were conducted for  $2 \times 2$  comparisons of categorical variables, Mann–Whitney U and Kruskal–Wallis H test, and the parametric equivalent of them, were also evaluated to compare the numerical variables. Shapiro–Wilks test was conducted to estimate the normality assumption for the variable.

## Results

In this retrospective study, a total of 147 patients with agammaglobulinemia with average age of 15 years (between 6-24 years) which included 126 (77.3 %) males and 21 (12.9 %) females. Age at diagnosis, and delay of diagnosis was 48 (16-84) and 24 (6-54) months, respectively. Age at onset of the patients was 11 (4-24) months. Among 147 agammaglobulinemia patients, 59 patients (36.2%) declared a consanguineous marriage and 56 patients (34.4%) had a family history of immunodeficiency diseases. 64.4% of patients were alive while 12.9% were dead. **Table 1** shows more demographic data in details.

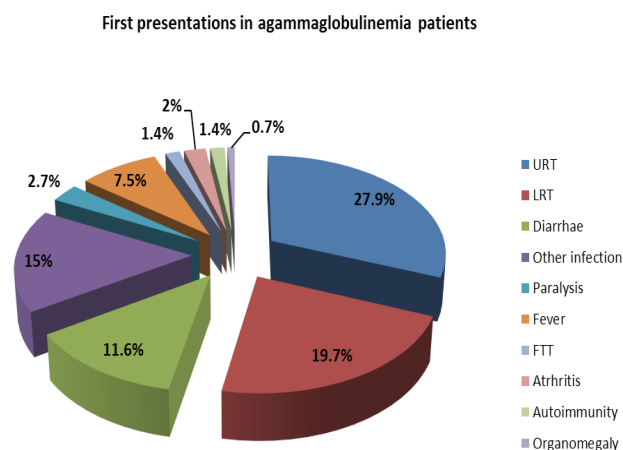
According to the **Table 2**, the most prominent clinical symptoms were respiratory infections (72.4%).

**Table 1.** The demographic data and immunological parameters of autoimmune and non-autoimmune agammaglobulinemia patients

Parameter	AID (n=21)	No AID (n=126)	p-value
Age at the study time, y (IQR)	15 (6.5–28)	15 (6–24)	0.591
Age at diagnosis, m (IQR)	60 (27–96)	45 (14–84)	0.296
Delay of diagnosis, m (IQR)	38.5 (7.5–66.25)	24 (6–53.75)	0.392
Age of onset, m (IQR)	11 (6.5–30)	11 (3–24)	0.437
Course of Disease, m (IQR)	144 (68–296)	162 (55.75–262.5)	0.653
Sex, N (%)			
Male	18 (85.7)	108 (85.7)	1.000
Female	3 (14.3)	18 (14.3)	
Consanguinity, N (%)	59 (36.2)	88 (54)	0.492
Family history, N (%)	56 (34.4)	91 (55.8)	0.627
Mortality, N (%)			
Alive	16 (76.2)	89 (70.6)	0.887
Dead	2 (9.5)	19 (15.1)	

\*p-value <0.05 have been regarded as significant. Abbreviations: AID; autoimmune disease, No AID; no autoimmune disease. Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles], N; Count

Considering different primary symptoms in the patients, upper respiratory tract infections (27.9%) and lower respiratory tract infections (19.7%) were reported to be the most significant manifestations among the patients (**Figure 1**). Furthermore, Table 3 shows laboratory findings for agammaglobulinemia patients. Among 147 agammaglobulinemia patients, we identified 21 patients (18 males and 3 females, 14.2%) who had autoimmune disorders. Several autoimmune disorders including: Guillain–Barré syndrome (GBS), immune thrombocytopenia (ITP), juvenile rheumatoid arthritis (JRA), rheumatoid arthritis (RA), alopecia, Kawasaki, and Takayasu arthritis were recognized. According to our results, JRA was the most important autoimmune disorder (38%) following ITP with the frequency of 14%. Figure 2 shows the prevalence of autoimmune diseases. Furthermore, respiratory tract infections with the prevalence of 76.2% were the most frequent clinical manifestations among autoimmune the agammaglobulinemia patients. Distribution of autoimmune disorders in males was higher than females. Alive autoimmune and non-autoimmune patients were 76.2% and 70.6%, respectively.

**Figure 1.** First presentations in agammaglobulinemia patients

Abbreviations: URT; Upper respiratory tract infection, LRT; Lower respiratory tract infection, FTT; Failure to thrive

The frequency of expired autoimmune patients and dead non-autoimmune patients was 9.5% and 15.1%, respectively. **Table 1** shows the comparison between demographic information of autoimmune and non-autoimmune patients.

The rate of thrombocytopenia in the non-autoimmune patients was significantly higher than the patients with autoimmunity (19% vs. 1.5%;  $p=0.004$ ). Moreover, rheumatoid problems in the autoimmune patients (52.4%) was significantly higher than the non-autoimmune patients (19.8%) and ( $p=0.001$ ) respectively. Although, other factors in laboratory results of the agammaglobulinemia

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patients were not significant, neutrophil count in the autoimmune and non-autoimmune patients were 7510 and 3565, respectively. Although this difference was not significant ( $p=0.071$ ).

**Table 2.** Clinical manifestations and organ involvement of agammaglobulinemia patients with and without autoimmunity

Parameter	Total patients (n=147)	AID (n=21)	No AID (n=126)	p-value
Pneumonia, N (%)	81 (49.7)	11 (52.4)	70 (55.6)	0.787
Sinusitis, N (%)	50 (30.7)	9 (42.9)	41 (32.5)	0.356
Bronchiectasis, N (%)	27 (16.6)	4 (19)	23 (18.3)	1.000
Clubbing, N (%)	14 (8.6)	2 (9.5)	12 (9.5)	1.000
Oral ulcer, N (%)	16 (9.8)	3 (14.3)	13 (10.3)	0.703
FTT, N (%)	20 (12.3)	3 (14.3)	17 (13.5)	1.000
Recurrent diarrhea, N (%)	18 (11)	1 (4.8)	17 (13.5)	0.471
Chronic diarrhea, N (%)	33 (20.2)	5 (23.8)	28 (22.2)	1.000
Recurrent infection, N (%)	100 (61.3)	14 (66.7)	86 (68.3)	0.885
Otitis, N (%)	66 (40.5)	10 (47.6)	56 (44.4)	0.787
Allergy, N (%)	9 (5.5)	2 (9.5)	7 (5.6)	0.617
Splenomegaly, N (%)	12 (7.4)	0(0.0)	12 (9.5)	0.216
Hepatomegaly, N (%)	16 (9.8)	0(0.0)	16 (12.7)	0.129
Conjunctivitis, N (%)	21 (12.9)	2 (9.5)	19 (15.1)	0.739
Eyes problem, N (%)	25 (15.3)	2 (9.5)	23 (18.3)	0.530
Malignancy, N (%)	3 (1.8)	1 (4.8)	2 (1.6)	0.372
Paralysis, N (%)	11 (6.7)	3 (14.3)	8 (6.3)	0.194
Respiratory tract infections, N (%)	118 (72.4)	16 (76.2)	102 (81)	0.566
First presentation with non-respiratory symptoms, N (%)	53 (32.5)	10 (47.6)	43 (34.1)	0.233
Urinary tract problem, N (%)	9 (5.5)	9 (7.1)	0(0.0)	0.359
Heart problem, N (%)	7 (4.3)	2 (9.5)	5 (4)	0.268
Hematologic problem, N (%)	42 (25.8)	6 (28.6)	36 (28.6)	1.000
Anemia, N (%)	13 (8)	1 (4.8)	12 (9.5)	0.693
Neutropenia, N (%)	19 (11.7)	1 (4.8)	18 (4.3)	0.311
Leukopenia, N (%)	3 (1.8)	1 (4.8)	2 (1.6)	0.372
Thrombocytopenia, N (%)	6 (3.7)	2 (1.6)	4 (19)	0.004*
Pancytopenia, N (%)	5 (3.1)	1 (4.8)	4 (3.2)	0.543
Gastrointestinal problem, N (%)	55 (33.7)	10 (47.6)	45 (35.7)	0.297
Rheumatoid problem, N (%)	36 (22.1)	11 (52.4)	25 (19.8)	0.001*
Skeletal problem, N (%)	23 (14.1)	4 (19)	19 (15.1)	0.745
Neurologic problem, N (%)	36 (22.1)	6 (28.6)	30 (23.8)	0.638
Dermatologic problem, N (%)	38 (23.3)	8 (38.1)	30 (23.8)	0.166
Multiple sites problem, N (%)	88 (54)	16 (76.2)	72 (57.1)	0.099

p-value <0.05 have been regarded as significant.

Abbreviations: AID; autoimmune disease, No AID; no autoimmune disease, y; year, FTT; failure to thrive

Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N; Count

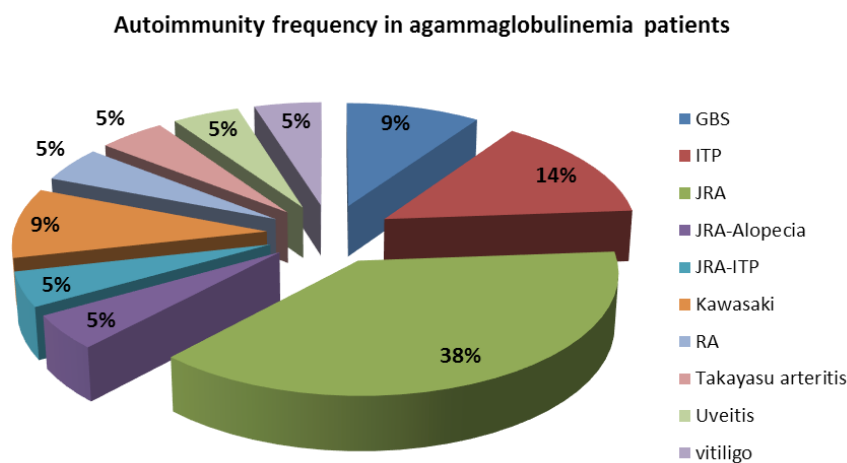
**Table 3.** Immunologic profile of agammaglobulinemic patients with and without gastrointestinal complications

Parameter	Total patients (n=147)	AID (n=21)	No AID (n=126)	p-value
WBC, 1000/ $\mu$ L (IQR)	9700 (7030-13420)	11250 (7680-14620)	9070 (7000-12700)	0.110
Neutrophil, Count, N (IQR)	4510 (2016-7520)	7510 (2572-9294)	3565 (1973-6900)	0.071
Neutrophil, % of total WBC (IQR)	50 (28-62.5)	57 (22-72)	49 (28-60)	0.282
Lymphocyte, % of total WBC (IQR)	39(29- 57)	31(18-56)	40(31.42-59.25)	0.143
Hb, g/dl (IQR)	11.8 (10-12.95)	11 (10-13)	11.85 (10-12.9)	0.569
Platelet, cell/ $\mu$ L (IQR)	393 (246.5-486.75)	399.5 (281.5-639.2)	391 (244.2-471)	0.494
IgG, mg/dl (IQR)	101.5(19-295.5)	206.5(19.75-330.25)	99(19-283.75)	0.228
IgA, mg/dl (IQR)	5.5(0-18.75)	5.5 (0-15.42)	5.5 (0-19)	0.938
IgM, mg/dl (IQR)	16(1- 30)	15 (1-30)	16 (1.25-30.75)	0.701
IgE, IU/ml (IQR)	2.5 (0.96-6.12)	1 (0.9-108)	3 (0.9-5.7)	0.948
CD3+ lymphocytes, cell/ $\mu$ L (IQR)	87(79–92)	85.5 (68.75-91.25)	87 (80.25-92)	0.220
CD4+ lymphocytes, cell/ $\mu$ L (IQR)	44(35–54)	42 (32-48.5)	45 (35-54)	0.236
CD8+ lymphocytes, cell/ $\mu$ L (IQR)	37(27.75–47)	42 (30-48.5)	37 (26.5–45.5)	0.209
CD16+ lymphocytes, cell/ $\mu$ L (IQR)	8(4.8-10.25)	8(2.4-15)	8(2.8-10)	0.944
CD56+ lymphocytes, cell/ $\mu$ L (IQR)	6.15(2.7–9.75)	42 (32-48.5)	6.4 (2.8-10)	0.503
CD19+ lymphocytes, cell/ $\mu$ L (IQR)	0(0–1)	0 (0-1)	0 (0-1)	0.624
CD20+ lymphocytes, cell/ $\mu$ L (IQR)	0(0–0)	0 (0-0.05)	0 (0-0)	0.985

\*p-value <0.05 have been regarded as significant.

Abbreviations: AID; autoimmune disease, WBC; white blood cells, Hb; Hemoglobin, Ig; Immunoglobulins, CD; Cluster of Differentiation, y; year

Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N; Count

**Figure 2.** Autoimmunity frequency in agammaglobulinemia patients

Abbreviations: GBS; Guillain–Barré syndrome, ITP; Immune thrombocytopenia, JRA; Juvenile Rheumatoid Arthritis, RA; Rheumatoid arthritis

## Discussion

This study was conducted on the extract information of 147 agammaglobulinemia patients who were diagnosed and submitted in the Research Centre for Immunodeficiencies at the Children's Medical Centre during 1999-2019.

In this study, we evaluated 147 agammaglobulinemia patients (14.2%) with different auto-

immune disorders. Our results showed that all individuals had typical clinical presentations including recurrent infections. Respiratory tract infections were the most frequent clinical manifestations in the patients (72.4%) (15) that is consistent with the previous study. Furthermore, our results are quiet consistent with the study by Plebani et al., in which they reported respiratory

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tract infections are as the most frequent clinical manifestations with the frequency of 68.5% (14).

Among primary antibody Immunodeficiencies, the frequency of autoimmunity in CVID is higher than other forms, because the frequency of autoimmunity is commonly higher in CVID and selective IgA deficiency, compared with agammaglobulinemia and hyper IgM diseases (16). However, autoimmunity could be observed in the patients with agammaglobulinemia (17). BTK is essential for human B-cell tolerance, and defect in this molecule could be associated with the manifestation of autoimmunity in these patients (18), as it has been demonstrated that BTK could be a good target for controlling auto-reactive B cells in the SLE patients.

In addition, this association has been observed in the experimental models of SLE and RA disease through activating the small-molecule inhibitors of BTK (19). Furthermore, it has been reported that, the “leaky” production of autoantibodies and defects in B-cell central tolerance is observed in agammaglobulinemia patients, although these patients do not produce autoantibodies (18).

Although the risk of autoimmunity is not high in the agammaglobulinemia patients in comparison with other PIDs, some of these patients may manifest some autoimmune disorders including RA, IBD, alopecia, enteropathy, AIHA, ITP, neutropenia, and Kawasaki disease (20). We identified 21 agammaglobulinemia patients (14.2%) who had autoimmune disorders. Autoimmune disorders in males were higher than females; this could be related to the high number of XLA patients which has been observed in males. JRA and ITP were the most frequent autoimmune disorders in the agammaglobulinemia patients with the frequencies of 38% and 14%, respectively, according to our results. Other autoimmune disorders including GBS, Kawasaki, RA, Uveitis, Vitiligo and Takayasu arthritis had the frequencies below 9%. Data from the USIDNET registry

indicated that 12% of XLA patients who reported arthralgia or joint swelling, had 16% diagnosis of arthritis (21). The most frequent autoimmune disorders in the primary immunodeficiency patients specifically agammaglobulinemia, needs to be more focused in this era. It should be noted that increasing sample size in the studies which are related to these diseases, helps to obtain more significant results.

Several studies showed that rheumatologic involvement is the most frequent autoimmune manifestation in the patients with agammaglobulinemia (22). However classical form of RA is more uncommon in these patients (22, 23). Previous studies showed that B cells and also RA are associated with autoantibodies, like rheumatoid factor which play a role in pathogenesis of RA (23). In the current study the frequency of rheumatoid problems was 52.4% in the autoimmune patients. However, Vivian et al., reported only 7 % diagnosis of arthritis from 20 % reported painful joints and 11 % joints swelling, in the X-linked agammaglobulinemia patients (17). However, in USIDNET registry 16% of patients had diagnosis of arthritis. In addition, arthralgia and joint swelling was reported 12% (1). These reports are not consistent with our results. Thus, it is important for clinicians to recognize agammaglobulinemia as a cause of arthritis in the patients and elicit relevant history and physical findings.

Regarding the laboratory data, there was not any significant difference between the agammaglobulinemia patients with and without autoimmunity. The only interesting result is related to higher number of neutrophil counts in our autoimmune patients compared with non-autoimmune patients, although that was near to be significant but was not significant. Generally, the exact role of neutrophils in autoimmune disorders is poorly understood. It has been demonstrated that neutrophils could be associated with autoimmune disorders by production of neutrophil extracellular traps (24), therefore higher number of neutrophils in agammaglobulinemia patients with autoimmu-

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nity might lead to high production of neutrophil extracellular traps and manifestation of autoimmunity. Possibly, higher number of patients in future studies could make a significant difference in this finding.

### Conclusion

Primary antibody deficiencies including agammaglobulinemia have variable autoimmune manifestations. Autoimmune diseases should be considered as an important factor for management in patients with agammaglobulinemia for primary and better diagnosis and suitable treatment of the patients. Furthermore, primary diagnosis of autoimmunity in agammaglobulinemia cases leads to reducing subsequent complications including recurrent respiratory infections and increasing patient's life quality.

**Conflicts of interest:** There is no conflict of interests.

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