Immunology and Genetics Journal

Original Article

Received: 19 July 2019
Accepted: 24 August 2019
Published online: 22 September 2019
Doi: 10.22034/igj.2019.200932.1025

Gastrointestinal Manifestations in Patients with Agammaglobulinemia

Kawthar Jasim Mohammad Rida Al-Hussieni[1], Erfan Rasouli1, Gholamreza Azizi[2], Mehdi Mosavian[3], Rahman Matani[3], Marzieh Tavakol[2, 4*]

[1] Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran

[2] Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

[3] Department of Gastroenterology and Hepatology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

[4] Department of Allergy and Clinical Immunology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

Abstract

Background/objectives: The most frequent symptoms of agammaglobulinemia are recurrent respiratory and gastrointestinal problems. The purpose of this study was to define the prevalence and type of gastrointestinal (GI) manifestations in those patients with agammaglobulinemia.

Methods: totally, 147 patients with agammaglobulinemia were included in this study. For each patient, clinical, immunological and laboratory data were documented.

Results: The GI manifestations as the first presentation of the immunodeficiency diseases were reported in 14.5% of patients, mostly because of chronic and recurrent diarrhea. History of GI manifestations was evident in 67 patients (45.6%).

Recurrent, chronic or bloody diarrhea (36.1%), vomiting (10.2%) and gastroenteritis (6.1%) were the most common manifestations of GI in patients with agammaglobulinemia, respectively.

Conclusions: The bowel is exposed to multiple antigens including gut microbiota and pathogens from the environment. Mucosal antibodies play a major role in protection and homeostasis; therefore, decreasing level of IgA can provide the opportunity for infectious diarrhea and more pathogen to attack.

Keywords: Gastrointestinal, Agammaglobulinemia, Diarrhea, Vomiting, Gastroenteritis.

* Corresponding author: Marzieh Tavakol
E-mail: m.tavakol@abzums.ac.ir

1. Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

2. Department of Allergy and Clinical Immunology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

Introduction

X-linked agammaglobulinemia (XLA) was first recognized in 1952 as hereditary agammaglobulinemia, it is a primary immunodeficiency disease (PID) that affects approximately three to six cases per one million people1)). X-linked agammaglobulinemia is recognized as one of the first inherent mistakes of the immunity system that indicates a PID with considerable data on results and clinical outcomes. Bruton tyrosine kinase(*BTK*), which was detected by two independent groups, is the gene affected in XLA and is located on X-chromosome (2, 3). BTK plays an important role in B cell development and XLA patients with pathogenic mutations manifested by the universal B cell deficiency mostly less than 2%. Patients with agammaglobulinemia, have some problems with antibody generation in their blood and tissues. In these patients, lymphocytes fail to generate plasma cells, so they have reduction in producing all classes of immunoglobulin with defective antibody function (4).

The most common symptoms of XLA are recurrent respiratory tract infections (RTI), and particularly bronchitis and pneumonia. Recently, autoimmune and inflammatory manifestations have been introduced as a feature of XLA (5). In the USIDNet XLA patient cohort, the prevalence of inflammatory bowel diseases (IBD)/enteritis was higher than what was reported earlier about the prevalence (0.4%) in the general population (5). In a cohort study by Pac et al. 26 of 28 XLA patients with GI disease complained of diarrhea, which was resolved generally after introducing IVIG therapy. Single but prolonged episodes of Campylobacter jejuni diarrhea were reported in 2 patients. IBD with mild to moderate activity was diagnosed in a patient, and along with that local enteritis with mild activity was found in another patient (6).

The purpose of this study was to define the prevalence and type of gastrointestinal manifestations in those patients with agammaglobulinemia.

Materials and methods

Population study

The Immunodeficiency Clinic at the Children's Medical Center affiliated to Tehran University of Medical Sciences is a referral center for PID. Totally, 147 patients, who were diagnosed and treated at this center from 1998 to 2018, were enrolled in this study. Agammaglobulinemia was diagnosed with respect to the basis of low serum level of all immunoglobulin isotypes associated with very low number of circulating B cells (< 2%), in addition to normal number of T cells in a symptomatic patient who their disease were commenced before the age of 5 years old. Genetic defects associated with combined immunodeficiency (CID) were also excluded in patients with agammaglobulinemia. All patients received Ig replacement therapy following diagnosis along with prophylactic antibiotic therapy. Individuals who had ended up Ig replacement or lacking adequate compliance to regular treatment, were excluded from this study. Clinical information were achieved from medical and chart records at Children's Medical Center.

Data collection

Since past 20 years, a comprehensive questionnaire was designed and the following data were collected, and also documented for each case: age at the initial clinical presentation, consanguinity, the first presentation, age at the time of diagnosis and age at last follow up, diagnostic delay, history of chronic and recurrent infections, bronchiectasis, autoimmunity, associated allergy, enteropathy, failure to thrive (FTT), tonsils atrophy, lymphoproliferation and malignancies. For each patient, laboratory data including complete blood count, white blood cell (WBC) differential and lymphocyte subsets percentage (CD3, CD4, CD8 and CD19) and serum levels of IgM, IgG, IgE and IgA were documented. The questionnaire was thoroughly completed for all patients at the time of diagnosis. Moreover, all patients received regular immunoglobulin replacement therapy. Follow-up visits were documented every month

at the time of hospital Ig administration either by the patients interviewing or by reviewing patients' hospital records for occasional admissions. Diagnostic delay was defined as the time between the onset of symptoms and time of diagnosis. The course of disease was measured as the time between diagnosis and the time of either the death or the last visit.

Statistical analysis

Values were presented as appropriate as frequency (number and percentage), mean ± standard deviation and median (IQR). Fisher's exact test and chi-square tests were applied for 2 × 2 comparisons of categorical variables, while t-tests and nonparametric equivalent were applied in order to compare numerical variables. Pearson's and Spearman correlation coefficient were calculated for assessing the correlation between parametric and non-parametric variables, respectively. Shapiro-Wilks test was used for checking the normality assumption for the variable; consequently with respect to the established assumptions, parametric or nonparametric test was accomplished. In addition, Statistical analyses were performed using SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA)

Results

Baseline demographic data

In this retrospective study, after exclusion of transient forms of agammaglobulinemia and also excluding those patients without complete clinical information, finally 147 patients [126 (85.7%) males and 21 (14.3) females] were enrolled in this study. Demographic and corresponding immunologic data for the agammaglobulinemia are presented in **Table1**. The most prevalent first presentation was upper respiratory tract (URT) infection (**Figure 1**). The gastrointestinal manifestations, as the first presentation of the immunodeficiency disease, were reported in 19 patients (14.5%), mostly because of

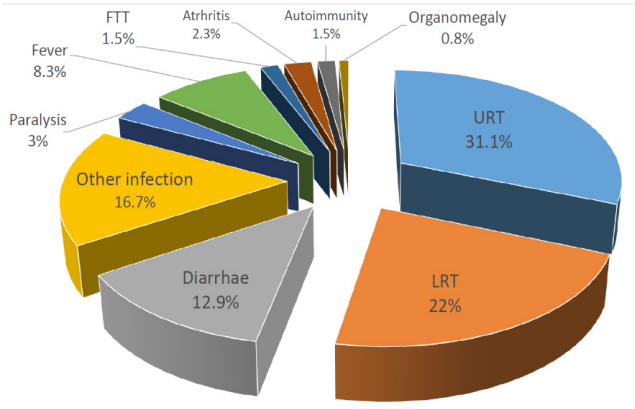

Figure 1. The first presentation of patients with agammaglobulinemia chronic and recurrent diarrhea. Abbreviations: URT and LRT were the most frequent first presentation. Diarrhea as the most frequent gastrointestinal manifestations was report as the first presentation in 12.9% of patients. URT; upper respiratory tract, LRT; lower respiratory tract, FTT; failure to thrive

Table 1. Demographic data of agammaglobulinemic patients with and without gastrointestinal complications

Parameters	Total (n=147)	With GI complications (n=65)	Without GI complications (n=82)	p-value
Sex ratio, M/F	126/21	59/8	67/13	0.457
Family history	56 (38.1%)	22 (32.8%)	34 (42.5%)	0.229
Consanguinity	59 (40.1%)	22 (32.8%)	37 (46.3%)	0.098
Dead, %	21 (14.3%)	16 (23.9%)	5 (6.3%)	0.003*
Current age, y, median (IQR)	15.0 (6.0-24.0)	15.0 (6.0-24.0)	14.0 (4.0-24.0)	0.726
Age at onset, y, median (IQR)	11.0 (4.0-24.0)	8.5 (3.0-18.5)	12.0 (6.0-24.0)	0.060
Age at diagnosis, y, median (IQR)	48.0 (16.0-84.0)	36.0 (17.0-78.0)	48.0 (14.0-96.0)	0.371
Delay in diagnosis, y, median (IQR)	24.0 (6.0-54.0)	25.0 (12.0-53.0)	24.0 (5.0-55.0)	0.868

Abbreviations: M; Male, F; Female, Y; Year
The median is shown [with 25th and 75th percentiles].
* p-value is statistically significant <0.05

Clinical evaluation

The most prevalent clinical manifestation in those patients with agammaglobulinemia was recurrent infection (68%), pneumonia (55.1%) and otitis media (44.9%). History of gastrointestinal manifestations was evident in 67 patients (45.6%). The most frequent gastrointestinal manifestations in patients with agammaglobulinemia were recurrent, chronic, or bloody diarrhea (36.1%), vomiting (10.2%), and gastroenteritis (6.1%), respectively (**Figure 2**). The most prevalent pathogen that was detected, was Giardia lamblia (4.8%). The median age of onset of patients with GI manifestations was lower than patients without this manifestation [8.5 (3.0-18.5) vs. 12.0(6.0-24.0), p=0.06]; however, the differences were not significant. The prevalence rate of GI disease was 8 out of 21 (38.1%) in female patients, and 59 out of 126 (46.8%) in male patients, however the differences were not significant (p=0.457). Among patients with consanguineous parents, 22 patients (32.8%) had a manifestation of GI complications, while the frequency of GI manifestations was 45 (51.1%) in those patients with non-consanguineous parents. The frequency of recurrent infection (79.1% vs. 58.8%, p=0.008), sinusitis (43.3% vs. 23.3%, p=0.030), bronchiectasis (26.9% vs. 11.3%, p=0.015), otitis (53.7% vs. 37.5%, p=0.049), lymphoprolifrative (23.9% vs. 7.5%, p=0.006), FTT (22.4% vs. 6.3%, p=0.004), conjunctivitis (22.4% vs. 7.5%, p=0.10) and URTI (67.2% vs. 43.1%, p=0.002) were higher in patients with GI manifestation in comparison with those without GI manifestation. Biopsy proven chronic entropathy was also reported in 2 agammaglobulinemic patients.

Table 2. Clinical manifestations of agammaglobulinemic patients with and without gastrointestinal complications

Parameters	Total (n=147)	With GI complications (n=65)	Without GI complications (n=82)	p-value
Recurrent infection (%)	100 (68.0)	53 (79.1)	47 (58.8)	0.008*
Pneumonia (%)	81 (55.1)	41 (61.2)	40 (50.0)	0.174
Sinusitis (%)	50 (34)	29 (43.3)	21 (26.3)	0.030*
Bronchiectasis (%)	27 (18.4)	18 (26.9)	9 (11.3)	0.015*
Otitis (%)	66 (44.9)	36 (53.7)	30 (37.5)	0.049*
Clubing (%)	14 (9.5)	5 (7.5)	9 (11.3)	0.436
Splenomegaly (%)	3 (2.0)	3 (4.5)	0 (0.0)	0.092
Lymphoprolifrative (%)	22 (15.0)	16 (23.9)	6 (7.5)	0.006*
Allergy (%)	9 (6.1)	3 (4.5)	6 (7.5)	0.510
Oral ulcer (%)	16 (10.9)	10 (14.9)	6 (7.5)	0.150
Failure to thrive (%)	20 (13.6)	15 (22.4)	5 (6.3)	0.004*
Conjunctivities (%)	21 (14.3)	15 (22.4)	6 (7.5)	0.010*
Meningitis (%)	21 (14.3)	9 (13.4)	12 (15.0)	0.787
Paralysis (%)	11 (7.5)	3 (4.5)	8 (10.0)	0.205
Autoimmunity (%)	21 (14.3)	10 (14.9)	11 (13.8)	0.839
Upper Respiratory tract (%)	78 (53.1)	45 (67.2)	33 (43.1)	0.002*
Lower Respiratory tract (%)	88 (59.9)	43 (64.2)	45 (56.3)	0.329
Urinary tract (%)	9 (6.1)	6 (9.0)	3 (3.8)	0.190
Malignancy (%)	3 (2.0)	1 (1.5)	2 (2.5)	1.000

* p-value is statistically significant <0.05

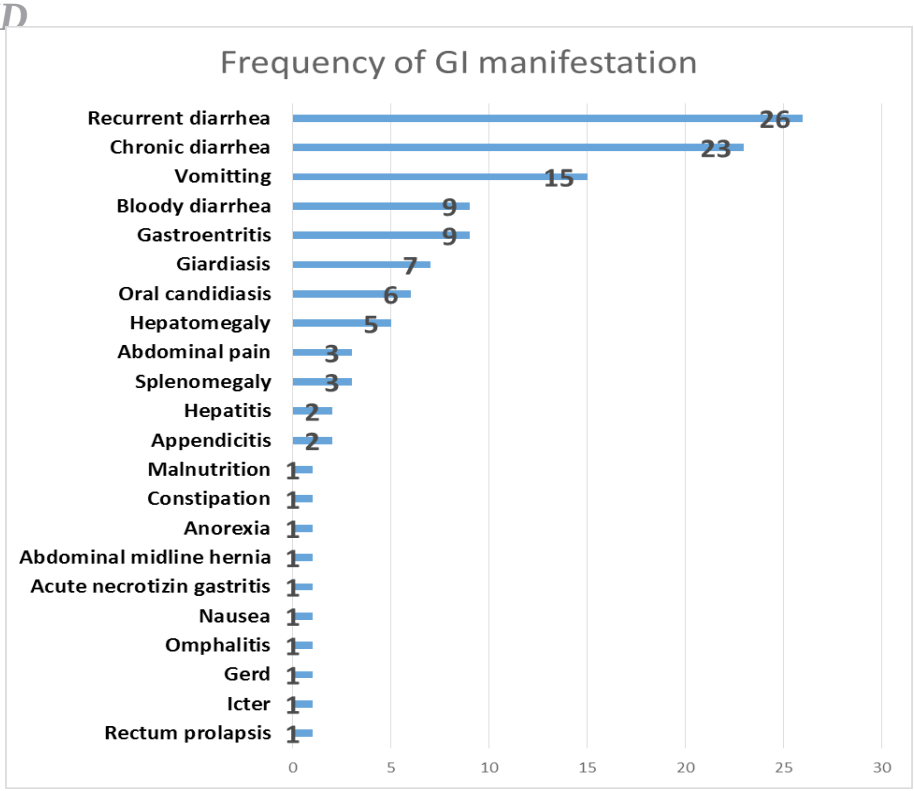

Figure 2. The frequency of GI manifestation in patients with agammaglobulinemia. GERD; Gastroesophageal reflux disease

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

Parameters	Total	With GI complications (n=65)	Without GI complications (n=82)	p-value
WBC	9700 (7030-13420)	8400 (5500-11500)	10300 (7455-14630)	0.012*
Neutrophils percentage	50 (28-62.5)	50 (23.75-60.7)	49 (28-64)	0.190
Lymphocte percentage	39 (29-57.5)	41 (31.95-60.5)	39 (23-56.7)	0.210
CD3+ T cells × 103 (cell/µL), median (IQR) (n=35)	87 (79-92)	86.5 (75-92)	87 (81.7-91.6)	0.852
CD4+ T cells × 103 (cell/µL), median (IQR) (n=44)	44 (35-54)	42.5 (26.7-51)	44 (35-54)	0.048*
CD8+ T cells × 103 (cell/µL), median (IQR) (n=41)	37 (27.7-47)	40 (27.5-49)	35 (27-45)	0.248
CD19 (cell/µL), median (IQR) (n=35)	0 (0.0-0.0)	0 (0.0-0.5)	0.05 (0.0-1.0)	0.012*
CD20	0 (0.0-0.0)	0 (0.0-0.1)	0.0 (0.0-0.0)	0.494
CD1656	5 (3-10)	5.5 (2.5-12)	4 (3.5-8)	0.635
IgM, mg/dL, median (IQR) (n=63)	16 (1-30)	13 (0.3-28)	17.5 (4-34)	0.575
IgA (mg/dL), median (IQR) (n=53)	5.5 (0.0-18.7)	4 (0.0-19)	7 (0.0-18.2)	0.363
IgG (mg/dL), median (IQR) (n=50)	101.5 (19-295.5)	120 (20.5-296)	100 (16.5-273.5)	0.102

Abbreviations: Ig; Immunoglobulin, WBC; White blood cell
* p-value is statistically significant <0.05

Immunological evaluation

Agammaglobulinemic patients with GI manifestations had lower number of WBC, $CD4^+$ T cells, $CD8^+$ T cells, compared to those patients without GI manifestations [(8400 vs. 10300, p=0.012), (42.5 vs. 44, p=.048), (0 vs. 0.05, p=0.012)]. Agammaglobulinemia patients with GI Manifestations had a lower level of IgA [4 (0.0-19.0) vs. 7(0.0-182), p=0.363] compared to patients without GI Manifestations. Patients with history of diarrhea had lower WBC [8000 (5300-11300) vs. 10100 (7410-14597), p=0.005] and B cell count [0.00 (0.0-0.5) vs. 0.00 (0.00-1.0), p=0.060] in comparison with those patients without history of diarrhea. Patients with history of vomiting had higher level of lymphocyte [53.5 (31.4-74.5) vs. 39 (26-55), p=.0.095] and lower count of neutrophil [27 (15.7-63.5) vs. 50 (32-62), P=0.063] and CD3 [83.5 (73.5-87) vs. 87.5 (79.7-92), p=0.07] compared to patients without history of vomiting, however these differences were not statistically significant.

Discussion

Primary immunodeficiencies (PIDs) are a heterogeneous group of diseases affecting distinct components of the immune system7)). The characteristic clinical presentation of XLA is agammaglobulinemia in a patient with recurrent bacterial infections. Immunologically, the notable feature is the lack or reduction in total B cell count in the blood (1). We identified 147 patients with PID at the Immunodeficiency Clinic at the Children's Medical Center. The majority of them experienced GI symptoms during the study period; and among them the most common GI symptom was diarrhea. Agarwal et al. reported GI disorders present in 5% to 50% of patients with PID (8). Barmettler et al. reported in other study that GI manifestations present in more than 35% of XLA patients (1). Rezaei *et al.* reported 127 of 930 patients (13.7%) with PID, who their most common presentation was diarrhea (9). In other study accomplished by Mahdaviani et al. on 19 patients with LRBA (a rare genetic PID), the most common presentations of immunodeficiency at the onset of disease were diarrhea (21.1%), and also FTT (5.3%), respectively. Chronic diarrhea was found in 16 patients (84.2%), 11 of whom (57.8%) manifested three or more episodes of diarrhea during follow-up. Chronic bloody diarrhea was also observed in one patient (6.3%) (10), which was in agreement with our results. Our data indicated that chronic and recurrent diarrhea was the first presentation of the immunodeficiency disease among 12.9% of patients. Furthermore, rate of FTT was higher in patients with GI manifestation compared to those without GI manifestation.

In a recent study by Gupta et al. conducted on 120 patients with PID, GI symptoms such as persistent diarrhea and FTT were amongst the most common warning signs in PID patients (11). In the current study, URT was higher in patients with GI manifestation than those without GI manifestation. It was earlier reported that multiple infections, severe diarrhea, and FTT-related problems had resulted in high mortality rate in patients with agamaglubolinemia. Our results demonstrated that, the frequency of mortality was higher in those with GI manifestation than those without GI manifestation. Moreover, in the study by Rezaei et al. conducted on 930 patients with PID, 160 patients died (17.2%) as a result of recurrent and severe infections9)).Among the pathogens causing diarrhea in immunodeficient patients, Giardia lamblia was identified as the leading case. Eren et al. described GI infections related to Giardia lamblia with an increased frequency in PID patients (12). In the current study, we found 7 patients with the Giardiasis, which were consistent with a previous European study assessing infections in 252 CVID patients (13). In a study by Parvaneh et al. among 32 patients with PID, 41 infectious agents including 16 parasitic (39.0%, the most common Giardia lamblia),

8 viral (19.5%, the most frequent group A rotavirus), 11 bacterial (26.8%, the most common salmonella spp) and 6 fungal organisms (14.7%, the most common Candida albicans) were identified. These results proposed that in agammaglobulinemic patients, parasites (Giardia lamblia and cryptosporidium) were the leading causes of chronic diarrhea. These studies suggest considering both usual and unusual pathogens in laboratory investigation and also in the diarrhea treatment in patients with agammaglobulinemia. Opportunistic pathogens should be taken into account in agammaglobulinemic patients when no other pathogen is identified, especially in those on long-term treatment or prophylaxis with antifungal/antibiotics14)).

Conclusion

The bowel is exposed to multiple antigens including gut microbiota and environmental pathogens. Locally secreted IgA plays a significant role in containing these microbes (15); therefore, decreasing level of IgA can provide the conditions for infectious diarrhea and more pathogen to attack.

Conflicts of interest: The authors declare that they have no conflicts of interest.

References

1. Barmettler S, Otani IM, Minhas J, Abraham RS, Chang Y, Dorsey MJ, et al. Gastrointestinal manifestations in X-linked agammaglobulinemia. J Clin Immunol. 2017;37(3):287-94.
2. Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, Klisak I, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell. 1993;72(2):279-90.
3. Vetrie D, Vořechovský I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature. 1993;361(6409):226-33.
4. El-Sayed ZA, Abramova I, Aldave JC, Al-Herz W, Bezrodnik L, Boukari R, et al. X-linked agammaglobulinemia (XLA): Phenotype, diagnosis, and therapeutic challenges around the world. World Allergy Organ J. 2019;12(3):100018.
5. 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):627-32.
6. Pac M, Bernatowska EA, Kierkuś J, Ryżko JP, Cielecka-Kuszyk J, Jackowska T, et al. Gastrointestinal disorders next to respiratory infections as leading symptoms of X-linked agammaglobulinemia in children–34-year experience of a single center. Arch Med Sci. 2017;13(2):412-7.
7. Bal SK, Haskologlu S, Serwas NK, Islamoglu C, Aytekin C, Kendirli T, et al. Multiple presentations of LRBA deficiency: a single-center experience. J Clin Immunol. 2017;37(8):790-800.
8. Agarwal S, Mayer L. Diagnosis and treatment of gastrointestinal disorders in patients with primary immunodeficiency. Clin Gastroenterol Hepatol. 2013;11(9):1050-63.
9. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, et al. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol. 2006;26(6):519-32.
10. Mahdaviani SA, Shirkani A, Chavoshzadeh Z. Gastrointestinal manifestations of Iranian patients with LRBA deficiency. Immunol Genet J. 2018;1(2):93-102.
11. Gupta D, Thakral D, Kumar P, Kabra SK, Lodha R, Kumari R, et al. Primary Immunodeficiency Disorders Among North Indian Children. Indian J of Pediatr. 2019:1-7.
12. Eren M, SALTIK-TEMIZEL IN, YÜCE A, ÇAĞLAR M, Kocak N. Duodenal appear-

ance of giardiasis in a child with selective immunoglobulin A deficiency. Pediatr Int. 2007;49(3):409-11.
13. Oksenhendler E, Gérard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46(10):1547-54.
14. Parvaneh L, Sharifi N, Azizi G, Abolhassani H, Sharifi L, Mohebbi A, et al. Infectious etiology of chronic diarrhea in patients with primary immunodeficiency diseases. Eur Ann Allergy Clin Immunol. 2019;51(1):32-7.
15. Ghoshal UC, Goel A, Ghoshal U, Jain M, Misra A, Choudhuri G. Chronic diarrhea and malabsorption due to hypogammaglobulinemia: a report on twelve patients. Indian J Gastroenterol. 2011;30(4):170-4.