A single center 14 years study of infectious complications leading to hospitalization of patients with primary antibody deficiencies

ABSTRACT

Primary antibody deficiencies (PADs) are a heterogeneous group of disorders, characterized by hypogammaglobulinemia and increased susceptibility to bacterial infections, leading to hospitalizations. This study was performed to determine the main infectious causes of hospital admissions in selective Iranian patients with PADs. Forty patients with PADs, who were admitted to the Infectious Ward of Children's Medical Center Hospital during a 14-year period, were reviewed in this study. There were 115 documented episodes of hospital admission during a 14-year period. The average length of hospital stay was 33.30 ± 25.72 days. Pneumonia was the most prominent infection leading to hospitalization among these patients (n = 48), followed by gastroenteritis (n = 23). Other less frequent causes of hospitalization were fever and neutropenia, septic arthritis, encephalitis, orbital cellulitis, sepsis, urinary tract infection, meningitis, oral ulcer, and lung abscess. The most common causative organisms of diarrhea were: *Giardia lamblia*, followed by *Candida albicans*, and *Salmonella* sp. Many patients with PADs suffer from repeated infections leading to hospitalization, in spite of immunoglobulin replacement therapy. Respiratory tract infections were the prominent cause of hospitalization among studied patients, followed by gastrointestinal infections.

Keywords: infection, hospitalization, primary antibody deficiencies.

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INTRODUCTION

Primary antibody deficiencies (PADs) are a heterogeneous group of disorders that range from a severe reduction of all serum immunoglobulin isotypes with absent B cells to selective antibody deficiency with normal serum immunoglobulins. PADs consist of more than half of all primary immunodeficiency diseases.[1-3] The predominant symptomatic forms of PADs are common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), and Hyper IgM syndromes (HIGM).[1-4]

Hypogammaglobulinemia, the major defect in these diseases, leads to increased susceptibility to bacterial infections, especially in the respiratory and gastrointestinal tracts.[5-9]

Recurrent infections and related complications could require hospitalizations. Immunoglobulin replacement therapy is the treatment of choice, as it reduces episodes and severity of infection and improves quality of life; however, hospitalization due to infectious complications may occur either before or after treatment.[10-14]

There are few studies dealing with the clinical manifestations and complications of patients with PADs. This retrospective study was performed to determine the main infectious causes of hospital admissions, to obviate complications, and to help implementation of faster and fuller treatment.

PATIENTS AND METHODS

Study design

Medical records of 40 selective patients with PADs, who were admitted to the Infectious Ward of the Children's Medical Center Hospital during a 14-year period (1994-2008), were reviewed in this study. All patients were under regular intravenous immunoglobulin therapy (400-500 mg/kg) every 3-4 weeks.

The Children's Medical Center Hospital is the main referral center for primary immuno-

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deficiency diseases in Iran. This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine in Tehran University of Medical Sciences.

Inclusion and exclusion criteria

Patients were diagnosed on the grounds of standard criteria, introduced by the European Society for Immunodeficiencies (ESID) and the Pan-American Group for Immunodeficiency (PAGID).[15] XLA is an agammaglobulinemia disease in male patients with reduced number of B cells (< 1%), which is caused by mutations in bruton tyrosin kinase (*BTK*) gene.[8] CVID is a heterogeneous group of disorders, characterized by hypogammaglobulinemia, variable number of B cells (> 2%), and exclusion of other well-known single gene defects.1 HIGM is characterized by reduced serum levels of IgG and IgA and normal or elevated IgM level, resulting from mutations in different genes including CD40 ligand, CD40, activation induced cytidine deaminase (*AID*), and Uracil g (*UNG*).[16,17]

Statistical analysis

SPSS statistical software package (version 14.0) was used for data analysis. p-value of less than 0.05 was considered significant.

RESULTS

Characteristics of patients

In this study, medical records of 40 PADs patients (27 male and 13 female) aged between 9 months and 16 years (median: 6, mean: 6.98 ± 4.0 years) were reviewed. These included 26 patients with CVID, seven patients with XLA, and seven patients with HIGM (Table 1). During hospitalization, nine patients died due to infection.

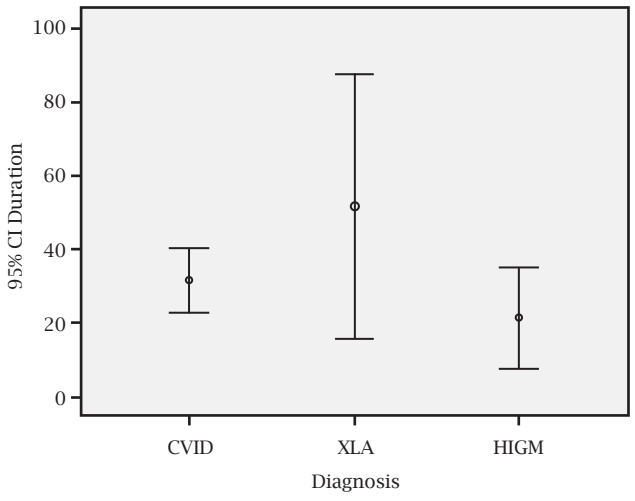
Hospitalization episodes and length of stay

There were 115 documented episodes of hospital admission during the 14-year period. Seventy-two of them occurred in CVID patients, while 26 and 17 in XLA and HIGM patients, respectively. On average, a patient was hospitalized for 33.30 ± 25.72 days (median: 29, range: 2-109 days); XLA patients had a longer mean length of stay (51.57 ± 38.90 days) compared to HIGM patients (21.43 ± 14.89 days) and CVID patients (31.58 ± 21.90 days). However, these differencee were not statistically significant (p-value = 0.073) (Figure 1).

Table 1. Characteristics of studied patients

	Total	CVID	XLA	HIGM
Characteristic				
Number of cases	40	26	7	7
Sex (male/female)	27/13	15/11	7/-	5/2
Age at the time of last admission (mean ± SD) years	6.99 ± 4.01	6.87 ± 4.15	6.86 ± 4.95	7.57 ± 2.76
Serum Ig level (mg/dL)				
IgG [median (range)]	235 (0 - 740)	292 (0 - 740)	100 (18 - 530)	230 (5 - 460)
IgA [median (range)]	15 (0 - 220)	15 (0 - 220)	20 (0 - 20)	10 (5 - 45)
IgM [median (range)]	28.5 (0 - 1400)	25 (0 - 230)	12.5 (1.6 - 27)	480 (75 - 1400)
Surface CD marker (absolute count)				
CD19+ B-cell [median (range)]	156.2 (0 - 1784.3)	176.4 (12.3 - 1784.3)	11.5 (0 - 47.8)	358.3 (136.3 - 1258.9)
CD3+ T-cell [median (range)]	1999.2 (162.0 - 6210.8)	1767.8 (196.9 - 5037.7)	3259.2 (162.0 - 5426.2)	2151.8 (1066.1 - 6210.8)
CD4+ T-cell [median (range)]	845.5 (43.2 - 3776.8)	575.8 (79.3 - 2898.4)	1563.1 (43.2 - 3014.2)	986.5 (495.9 - 3776.8)
CD8+ T-cell [median (range)]	971.7 (140.4 - 4765.8)	885.0 (241.2 - 4765.8)	1307.9 (140.4 - 2966.7)	1289.3 (307.6 - 2014.3)

Figure 1: Mean duration of hospitalization among immunodeficient patients (p-value = 0.073).



Causes of hospitalization

Pneumonia was the most prevailing infection leading to hospitalization among these patients (n = 48), followed by gastroenteritis (n = 23). Figure 2 shows seasonal distribution of these two predominant infections.

Sixteen out of 26 CVID patients were admitted at least once (61.5%) due to pneumonia, but one CVID patient was admitted four times. Four out of seven XLA patients were hospitalized at least once (57%) due to pneumonia, with one such patient being admitted eight times. Four out of seven HIGM patients were hospitalized (57%) with pneumonia, but one patient had three admissions.

Other less frequent causes of hospitalization were fever and neutropenia, septic arthritis, encephalitis, orbital cellulitis, sepsis, urinary tract infection, meningitis, oral ulcer, and lung abscess (Table 2).

Figure 2: Seasonal distributions of pneumonia and gastroenteritis leading to hospitalization.

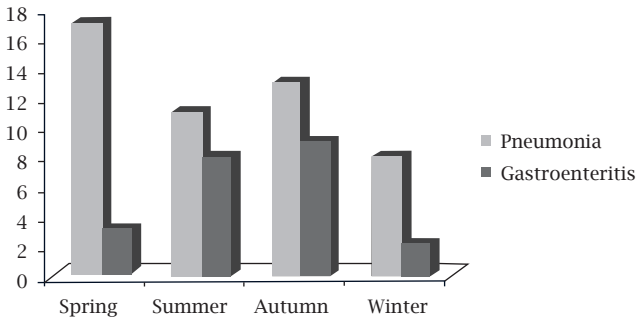


Table 2. Complications leading to hospitalization

	Total	CVID	XLA	HIGM
Pneumonia	49	31	11	7
Gastroenteritis	22	20	1	1
Fever and neutropenia	6	3	2	1
Septic arthritis	4	2	2	-
Aseptic arthritis	3	1	-	2
Urinary tract infection	2	2	-	-
Meningitis	2	-	2	-
Fever	5	4	1	-
Cellulitis	3	-	1	2
Lung abscess	2	-	2	-
Sepsis	4	3	-	1
Hepatitis	1	1	-	-
Encephalitis	3	-	-	3
Skin infection	1	-	1	-
Pneumonia + gastroentritis	2	2	-	-
Oral ulcer	2	-	2	-
Parotid abcess	1	1	-	-
Purulent adenitis	1	1	-	-
Peritonitis	1	1	-	-
Hepatic failure	1	1	-	-
Total admissions	115	73	25	17

Associated features

Prevalence of consanguineous marriages was of 47.5% among patients' parents. Also a history of death due to infection in siblings of the affected patient was found in 11 families. Four patients had a positive family history of immunodeficiency. Thirty patients (75%) had a history of recurrent otitis media (20 CVID, 4 XLA, 3 HIGM), 25 patients (62.5%) had sinusitis. Seven patients developed bronchiectasis. Lymphocytic interstitial pneumonia was found in one patient. Recurrent diarrhea occurred in 17 patients (42.5 %), while one patient had inflammatory bowel disease (ulcerative colitis). One subject had Hirschsprung disease. Eleven patients underwent upper endoscopy, and the most common findings were: duodenitis (seven cases), esophagitis (four cases), gastritis (four cases), and villous atrophy (six patients). One CVID patient developed Hodgkin's disease, while autoimmune diseases were detected in three CVID cases; one had idiopathic thrombocytopenic purpura and two had hemolytic anemia.

Microorganisms

Microbiological cultures were performed in some patients before empiric therapy. The most common causative organ-

isms of diarrhea were: *Giardia lamblia* (n = 9), followed by *Candida albicans* (n = 4), and *Salmonella* sp. (n = 3). *Shigella flexneri* was the causative organism in one patient, and *Cryptosporidium parvum* in another case. In four patients, the etiologic pathogen of the diarrhea was not isolated. Urine culture of patients hospitalized due to urinary tract infection was positive for *E. coli.* Blood cultures were taken in 66 episodes of infections, but turned out positive in only 9% (n = 6). *Pseudomonas* sp. was detected in four cases, and *Pneumococcus* and *Acinetobacter* in two cases. Bone marrow culture performed in four episodes grew acid fast bacilli in one case.

DISCUSSION

Primary antibody deficiencies are a heterogeneous group of rare disorders, characterized by decreased serum levels of immunoglobulin isotypes and increased susceptibility to bacterial infections, especially in the respiratory and gastrointestinal tracts.[2,3,18] Despite immunoglobulin replacement therapy, many patients still suffer from repeated infections leading to recurrent hospitalization.

This study demonstrated the frequency and the main causes of hospital admission among Iranian PADs. Respiratory tract infec tions were the prominent cause of hospitalization among studied patients, followed by gastrointestinal infections. Approximately 60% of CVID, XLA, and HIGM patients were admitted at least once due to pneumonia. Previous reports on PADs patients revealed that lower respiratory tract infections were the most common manifestation in this group of patients. In a previous study on 248 patients with CVID, the majority of patients had at least one episode of pneumonia (78%) prior to their diagnosis.[6] A study reviewing records from 201 XLA patients in the United States, reported pneumonia in 62% of subjects.[7] Another study on 79 patients with HIGM syndrome reported 81% with at least one episode of pneumonia.[19]

The second most frequently affected organ system in our study was the gastrointestinal tract comprising almost 20% of all hospital admissions. In other studies, gastrointestinal disorders were reported from 20-47% of patients with PADs.[6,20,21] Recurrent diarrhea occurred in 42.5% of the patients. Other studies reported that chronic diarrhea of unspecified cause occured commonly in PADs, with frequencies ranging from 40% to 60%.[22-24] The diarrhea is often infectious. *Giardia lamblia* was the most common organism among patients with diarrhea. Other common causative organisms for diarrhea were *Candida* and *Salmonella* spp.; other studies showed that the most frequently identified organisms causing infectious diarrhea were *Giardia lamblia*, *Campylobacter* sp., and *Salmonella* sp.[6,7,25] Although *Crypotosporidium parvum* is a common pathogen among HIGM patients,[19] it was found in only one patient in our study, which could be due to the small number of these patients in the current series.

PADs are the conditions that make patients prone to a variety of complications, some made worse by delayed diagnosis and insufficient treatment. Despite immunoglobulin replacement therapy and current management plans, patients remain at risk of outbreaks of bacterial infections. The delay in diagnosis and treatment of patients often entails complications that are more pronounced, which may be widespread and cause negative effects on both morbidity and mortality.

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