Original paper

Retrospective evaluation of adults with primary immunodeficiency disease

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Abstract

Introduction: Primary immunodeficiency diseases (PIDs) are a group of heterogeneous disorders that result from one or more immune system abnormalities and have a wide range of clinical manifestations.
Aim: To evaluate the demographic, clinical, and radiological features of adult patients with PID.
Material and methods: We retrospectively reviewed the data of adult patients with PID who had been receiving immunoglobulin therapy at the adult allergy and immunology outpatient clinic between November 2017 and April 2022.
Results: Of the 23 patients included, 4 (17.4%) were females and 19 (82.6%) were males. The mean age was 38.7 ±16.2 (range: 18–75) years. Time of delay in the diagnosis of immunodeficiency was 14.9 ±15.7 (range: 0.5–49) years. The most common complaint on admission was sinopulmonary infection, and 65% of the patients had bronchiectasis. A total of 6 patients had a history of lymphoma, and 3 of them were diagnosed during the study period. Recurrence of lymphoma was observed in 1 patient.
Conclusions: Patients with PID frequently have findings related to more than one organ system, and the diagnosis is often delayed in adults. Recognition and increased awareness of these manifestations is essential for early diagnosis and reducing morbidity and mortality.

Key words: primary immunodeficiency, adult, diagnostic delay.

Introduction

Primary immunodeficiency diseases (PIDs) include more than 400 inheritable and heterogeneous disorders [1, 2]. The prevalence of PID is estimated to be 1 in 1000–2000 live births and has high morbidity and mortality [3, 4]. Early diagnosis and effective, timely treatment may prevent morbidity and mortality. The presentation of PID is highly variable because different components of the immune system may be affected. Increased severity or frequency of infection; infection with opportunistic microorganisms; multiorgan or early-onset autoimmune diseases; and the presence of clinical findings of immunodeficiency in patients with syndromic features or malignancy should suggest the diagnosis of PID [5]. In addition, the presence of a positive family history, failure to thrive, lymphopenia, hypogammaglobulinemia, or the need for prolonged intravenous antibiotics should alert the physician to the diagnosis of immunodeficiency. Among all PIDs, predominant antibody deficiencies are the most common type (e.g., agammaglobulinemia, common variable immunodeficiency disease (CVID)) [5].

Aim

The aim of this study was to evaluate the demographic, clinical, and radiological features of adult patients with PID.

Material and methods

This was a retrospective data review conducted at the adult allergy and immunology outpatient clinic. The study included adult patients with predominant antibody deficiencies or combined immunodeficiency who had been receiving immunoglobulin therapy between November 2017 and April 2022. Clinical diagnosis was made in accordance with the European Society of Immunodeficiencies (ESID) guidelines [5]. Data regarding demographic features including age, sex, autoimmunity,

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enteropathy, malignancy, comorbidities, age of diagnosis, diagnostic time delay, complete blood count, radiological findings, and treatments used, including immunoglobulin therapy and antimicrobial prophylaxis, were collected from the medical files of patients and electronic recording systems.

Informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the ethics committee (approval number 9/104-26.5.2022).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, N.Y., USA). Results were shown as mean±standard deviation for continues variables. Categorical variables were presented as frequencies and percentages.

Results

Of the 23 patients included, 4 (17.4%) were females and 19 (82.6%) were males. The mean age at the time of the study was 38.7 ±16.2 (range: 18–75) years. Time of delay in the diagnosis of immunodeficiency was 14.9 ±15.7 (range: 0.5–49) years. Fourteen (60.9%) patients were diagnosed after the age of 18. Seven (30.4%) patients were newly diagnosed. Five (21.7%) patients had genetic diagnosis. The rate of consanguineous marriage was 36.4%, and the rate of positive family history was 18.2%. Six relatives (two cousins, one nephew, one sister, one brother, and one son) of the patients had PID. General characteristics of the patients are shown in Table 1.

When the patients' main complaints were evaluated on admission before the diagnosis, sinopulmonary infection was present in 16 (69.6%) patients, pneumonia in 6 (26.1%) patients, diarrhoea in 3 (13%) patients, and lymphadenopathy in 3 (13%) patients. Two patients who were followed up for immune thrombocytopenic purpura (ITP) were diagnosed with CVID. Six (26.1%) patients had hearing loss associated with recurrent otitis media. Prior to immunoglobulin treatment, 19 patients were hospitalized at least once with a diagnosis of lower respiratory tract disease. During the follow-up period, benign pleural effusion and acute pericarditis developed in 1 patient. A deep vein thrombus developed in another patient with Sjogren's syndrome and primary biliary cirrhosis, and an inferior vena cava filter was inserted.

Seven (30.4%) patients had gastrointestinal problems. Upper gastrointestinal tract endoscopy was performed in 10 patients, while lower gastrointestinal tract endoscopy was performed in 9 patients. Inflammatory bowel disease was observed in 3 patients. One patient had colon adenocarcinoma.

When the complete blood counts of the patients were evaluated, thrombocytopenia was found in 7 (30.4%) patients, and neutropenia in 2 (8.7%) patients. Bronchiectasis was present in 13 (65%) patients. Sixteen (72.7%) patients had splenomegaly and/or hepatomegaly. Lymphadenopathy was found in 13 (59.1%) patients. A total of 6 patients had a history of lymphoma, and three of them were diagnosed during the study period. Recurrence of lymphoma was observed in 1 patient who also had Kaposi sarcoma (Table 2).

Ten (43.5%) patients had coronavirus 2019 disease (COVID-19), and only 1 patient was hospitalized due to COVID-19 pneumonia. No deaths were observed as a result of COVID-19.

All patients were given immunoglobulin therapy. Twenty-one (91.3%) patients were treated with intravenous immunoglobulin (IVIG), and 2 (8.7%) patients were treated subcutaneously. Eight (34.8%) patients were using antibiotic prophylaxis. The immunoglobulin dose was modified based on the patient's clinical condition and immunoglobulin level. Immunoglobulin levels, complete blood counts, liver and renal function tests, and urinalysis were checked on a regular basis. No complications were observed in any of the patients due to immunoglobulin therapy. Two patients with lymphoma diagnoses died during the follow-up period.

Table 1. General characteristics of the patients with primary immunodeficiency

Characteristics		Value
Sex (male/female)		19 (82.6%)/4 (17.4%)
Current age [years] mean ± SD (min.–max.)		38.7 ±16.2 (18–75)
Age at diagnosis [years] mean ± SD (min.–max.)		29.8 ±20.6 (0.5–67)
Delay in diagnosis [years] mean ± SD (min.–max.)		14.9 ±15.7 (0.5–49)
Consanguinity, *n* (%)		8/22 (36.4)
Family history of PID, *n* (%):		4/22 (18.2)
Comorbidity *n* (%)	Obstructive lung disease	3 (13)
	Heart disease	3 (13)
	Sjögren's syndrome and primary biliary cirrhosis	1 (4.3)
	Transverse myelitis	1 (4.3)
	Osteoporosis	1 (4.3)
	Osteomalacia	1 (4.3)
	Hypothyroidism	1 (4.3)
	Drug allergy	2 (8.7)
	Psoriasis	1 (4.3)
Antibiotic prophylaxis, *n* (%)		8/23 (34.8)
Coronavirus 2019 disease history, *n* (%)		10/23 (43.5)
Deaths, *n* (%)		2/23 (8.7)

SD – standard deviation, PID – primary immunodeficiency.

Table 2. Clinical and radiological characteristics of the patients with primary immunodeficiency

Parameter	*n* (%)
Hepatosplenomegaly	7/22 (31.8)
Splenomegaly	7/22 (31.8)
Hepatomegaly	2/22 (9.1)
Lymphadenopathy	13/22 (59.1)
Lymphoma	6/23 (26.1)
Bronchiectasis	13/20 (65)
Anaemia	9/23 (39.1)
Thrombocytopenia	7/23 (30.4)
Lymphopenia	6/23 (26.1)
Neutropenia	2/23 (8.7)
Enteropathy	7/23 (30.4)
Warts or skin abscesses	2/23 (8.7)

Discussion

Primary immunodeficiency diseases encompass a group of heterogeneous disorders that predispose individuals to recurrent infections, autoimmunity, and malignancies [1, 6]. In the present study, we reviewed the demographical, clinical, and radiological features of adult patients with PID.

Early diagnosis and effective treatment can limit morbidity and mortality, and improve the prognosis of PIDs. However, it is estimated that adults account for 25–40% of all PID diagnoses [7]. The median diagnostic time delay was reported as 10 months in Iran, 29.9 months in Egypt and 5 years in Poland [8–10]. In a study conducted in Turkey, the median diagnostic time delay was found to be 14 years in adult patients with CVID [11]. In our study, 14 of our patients were diagnosed after the age of 18, and the median diagnostic time delay was found to be 10 years.

The rate of consanguinity observed in our study was 36.4%. This rate was reported as 2.9% in the United Kingdom, 8% in Germany, 60.1% in Iran and 62.5% in Egypt [8, 9, 12, 13]. In other studies from Turkey, the consanguinity rates were found to be 12.9% and 40.9% [11, 14].

In patients with PID, pulmonary complications are prevalent and contribute considerably to morbidity and mortality. Recurrent respiratory infections are frequently the first warning signs and are major causes of death [15]. Approximately 70% of our patients' first manifestations were recurrent sinopulmonary infections, and 19 patients had a history of hospitalization due to lower respiratory tract disease. One of the most frequent infections among PID patients is recurrent otitis media, and the rates were reported as 71.6% and 29.2% in studies [16, 17]. In our study, 26.1% of patients had hearing loss associated with recurrent otitis media. The risk of developing bronchiectasis is much higher in patients with primary antibody deficiency [18]. In a study from the European Chest CT Group, bronchiectasis was reported to be the most common radiological abnormality (61%) in the respiratory system in patients with primary antibody deficiency [19]. In this study, 20 patients were evaluated with chest computed tomography and bronchiectasis was found to be 65%.

Another site beyond the respiratory system for complications is the gastrointestinal system, which is the second most common. Nearly one-third of PID patients have gastrointestinal system manifestations [20, 21]. Symptoms such as diarrhoea, weight loss, and abdominal pain may be seen as a consequence of infection, inflammation, autoimmunity, or malignancy of the gastrointestinal system. In our study, inflammatory bowel disease was observed in 3 patients, and 4 patients complained of diarrhoea with weight loss. Sixteen patients had splenomegaly and/or hepatomegaly.

According to the literature, PID patients have a 10-fold greater risk of lymphoma when compared to age- and sex-matched individuals [22]. In adults, lymphoma is reported in 8% of patients with CVID [23]. Epstein-Barr Virus (EBV) is reported in 30% to 60% of lymphoma patients associated with PIDs [24]. In this study, the rate of lymphoma was found to be 26.1%. In one of these patients, who also had a recurrence of lymphoma, EBV-associated lymphoproliferation was detected by biopsy.

Most PID patients have major defects in at least one component of adaptive immunity. A tendency for viral and bacterial infections is likely [8]. However, there are few studies reporting COVID-19 cases with underlying PID. In a study conducted in the UK, the hospitalization and mortality rates were found to be 53.3% and 20%, respectively, among PID patients [25]. In another study from Iran, the mortality rate was reported as 42.1%, which is ten times greater than Iran's general population [26]. In a study from Turkey, the hospitalization rate was found to be 38.4%, and the mortality rate was 7.69%, which is eight times higher than in Turkey's general population [27]. Among our 23 patients, 10 patients had COVID-19 disease, and only 1 patient with CVID needed hospitalization. None of our patients died due to COVID-19 disease.

In patients with PID, treatment should be initiated promptly as soon as the diagnosis is made. Immunoglobulin therapy is very important in the prevention of complications related to infections. Primary antibody deficiency disorders require intravenous or subcutaneous immunoglobulin therapy and may require antibiotic prophylaxis [28]. Among our patients, 34.8% were using antibiotic prophylaxis. During the study period, no complications were observed in any of the patients due to immunoglobulin therapy.

Conclusions

Primary immunodeficiency diseases have a wide range of clinical manifestations, including severe or un-

usual infections, autoimmune diseases, and malignancies. Early diagnosis and prompt treatment can improve patient's prognosis. As reported in previous studies and our own study, patients frequently have findings related to more than one organ system, and the diagnosis is often delayed in adults. Recognition and increased awareness of these manifestations is essential for early diagnosis and reducing morbidity and mortality.

Conflict of interest

The author declares conflict of interest.

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