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ORIGINAL PAPER

Evaluation of primary immunodeficiency awareness of physicians in Türkiye

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ABSTRACT

Introduction: Despite recent advances in diagnosing and treating primary immunodeficiency (PID), delay in diagnosis is still an important health problem.

Aim: To evaluate the awareness of physicians in Türkiye about PID.

Material and methods: Internal medicine, infectious diseases, and family physicians were included in the study. The questionnaire included questions about demographic characteristics, PID education, and knowledge. The '10 warning signs of PID' developed by the Jeffrey Modell Foundation (JMF) as warning signs of PID were also scored. The total score was calculated, and an awareness comparison was made between the three physician groups.

Results: A total of 320 physicians were included in the study. The mean age of the participants was 32 years (IQR: 25–68 years). Approximately one-third of physicians stated that they had never received any training on PID, and only 20% had followed a patient diagnosed with PID. Recurrent opportunistic infections were the most common symptom of PID (77.8%). Only 6.6% of the physicians were familiar with all the warning signs of PID, and no significant difference was found between the physician groups.

Conclusions: In this study, it was revealed that there is a significant lack of awareness about PID among physicians. Delay in PID diagnosis and treatment is one of the most important reasons for the deterioration of patients' quality of life. Increasing the awareness of this disease by increasing physicians' education about PID is an essential step toward early diagnosis and treatment.

KEY WORDS

primary immunodeficiency, evaluation, awareness, physicians in Türkiye.

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INTRODUCTION

Primary immunodeficiency (PID) is a rare, heterogeneous and broad group of diseases that includes over 400 innate immune defects that affect the development and function of the immune system [1]. PID has a prevalence reported between 1 : 16 000 and 1 : 50 000 [2]. The International Union of Immunology Societies (IUIS) updated in 2022, bringing the total number of PIDs to 485 [3]. PID is characterized by predisposition to severe recurrent infections, malignancies, atopy and autoimmune conditions [4]. The resulting complications lead to decreased quality of life and increased mortality in PID [5]. Over the last decade, studies have led to a better understanding of the pathophysiology of PID, enabling the development of more diagnostic and therapeutic strategies [6]. In many countries, lack of awareness of physicians about PIDs is one of the biggest problems that play a role in delayed diagnosis [7]. Published data on physicians' awareness of PID are limited. In a study conducted in the United States of America and Iran, PID awareness was found in 32% of physicians [8, 9].

AIM

The aim of this study was to evaluate PID awareness in internal medicine, infectious disease and family physicians who are likely to encounter PID and to contribute to early diagnosis and timely treatment of patients.

MATERIAL AND METHODS

STUDY DESIGN AND POPULATION

This cross-sectional study included internists, infectious disease physicians and family physicians working in university hospitals, private hospitals, public hospitals and family health centers in Türkiye between May 2023 and October 2023. The study was approved by the local ethics committee of the Necmettin Erbakan University Faculty of Medicine (Decision no. 2023/4417).

An electronic questionnaire was created using the Google Forms platform (Google Inc., San Francisco, USA). The survey was distributed through WhatsApp (WhatsApp Inc., Mountain View, CA, USA) and email. Physicians answered the questions using the forms sent to them, but the doctor's name was not disclosed in the forms. Electronic informed consent was obtained from each participant in accordance with the Helsinki Declaration. Survey questions presented to participants. The survey consisted of 15 questions developed by the authors and was conducted in Turkish. The English version of the questionnaire is provided in Supplementary material. Physicians were asked to complete the questionnaire only once.

The first part of the questionnaire identified the participating doctors by age, gender, academic degrees, years of work experience, specialty type and type of hospital (public hospital, university hospital, private hospital, family health center). The second part presented 8 questions about PID training and knowledge (clinical findings, auxiliary tests for diagnosis, treatment agents and follow-up etc.).

All participants evaluated the 'PID 10 warning signs' developed by the Jeffrey Modell Foundation (JMF) to assess the level of PID suspicion. Each correct answer was given 1 point, and the total was scored from 0 to 10. A comparison was made between specialties [10].

STATISTICAL ANALYSIS

Categorical and ordinal variables were presented using frequency distribution, and proportions were compared using the χ^2 test. Continuous variables were presented as median with interquartile range (IQR). The analysis of variance (ANOVA) presupposes the data normality. Due to lack of normality in the data, which was checked by the Kolmogorov-Smirnov test, the nonparametric Kruskal-Wallis test was used to compare the medians among more than two groups. All analyses were conducted using the SPSS statistical package (ver. 22.0; IBM Corp., Armonk, NY, USA). For all data analyses, differences were considered statistically significant when $p < 0.05$.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF PHYSICIANS

A total of 320 physicians were included in the study and 44.7% of them were male. The median age of participants was 32 years (IQR: 25–68 years) and the median years of practicing medicine was 7 (IQR: 1–42). Most of the participants (46.3%) worked in the university hospitals. Internal medicine was the most common specialty, and research assistant was the most common academic degree (45% and 57.2%, respectively) (Table 1).

PID TRAINING

Most participants (67.8%) had previously received training about PID, and 22% had followed a patient diagnosed with PID throughout their career.

DISTRIBUTION OF PHYSICIANS' ANSWERS TO QUESTIONS

Among the questions regarding the clinical presentation of PID, the most common response was 'recurrent oppor-

tunistic infections' (77.8%), and only 6.9% of physicians answered all of them correctly. Among the questions regarding the warning signs of PID, the most common response rate was 'two or more new otitis media within 1 year' (75%), and only 6.6% of physicians answered all of them correctly. The most common response to questions regarding the clue findings of PID was 'lymphoid hyperplasia' (81.9%), and only 4% of physicians answered all of them correctly. The most common response to questions regarding tests helpful in diagnosing PID was 'immunoglobulins' (98.1%), and 11.6% of physicians answered all of them correctly. In PID, the rate of those who answered the questions about vaccination incorrectly was 40%, and those who gave all the correct answers were 25%. The most common response to questions regarding treatment in PID was 'immunoglobulin replacement therapy' (98.8%), and 14.6% of physicians answered all of them correctly (Table 2).

PID 10 WARNING SIGNS COMPARISON BETWEEN SPECIALTIES

6.6% of participants were familiar with all PID warning signs. According to specialties, the most frequently familiar group was infectious disease and internal medicine physicians (14.6% and 6.9%, respectively). However,there was no statistically significant difference between groups ($p = 0.058$). 'One pneumonia per year for more than 2 years' was the most frequently observed warning sign by internal medicine physicians (90.2%). 'Need for intravenous antibiotics to clear infections' was the most frequently observed warning sign by infectious diseases physicians (85%). 'Two or more new otitis media within 1 year' was the most frequently observed warning sign by family medicine physicians (87.6%). However, there was no statistically significant difference ($p = 0.4$, $p = 0.28$, $p = 0.68$, respectively) (Table 3). There were no significant differences in other warning signs between the groups.

According to the JMF 10 warning signs, the total median score of internal medicine physicians was 7 points (IQR: 2–10), the total median score of infectious disease physicians was 7 points (IQR: 3–10), and the total median score of family physicians was 6 points (IQR: 2–10). However, no significant difference was observed between groups ($p = 0.45$) (Table 3).

DISCUSSION

In this study, physician awareness and physician practices regarding the diagnosis and treatment of PID were evaluated. Early diagnosis and treatment of PID offers the best opportunity to reduce mortality and morbidity. It is estimated that the presence of PID is more common than expected and 70% to 90% of PIDs go undiagnosed [1]. In this study, internal medicine, infectious disease, and family physicians who are likely to encounter PID were included. It has been observed that approximately one third of the physicians have never received any training on PID and only 20% of them have followed a patient diagnosed with PID. Physicians most frequently chose recurrent opportunistic infections as the symptom of PID, while non-infectious findings (such as autoimmunity, malignancy) were less preferred. According to another important finding, only 6.6% of physicians were familiar with all of the JMF PID warning signs, which play an important role in the early diagnosis of PID. The rate of physicians who correctly answered all questions related to the diagnosis and management of PID was very low (4–14.6%). Complications of PID are usually detected after complications have occurred. It has been reported that the average delay in the diagnosis of common variable immunodeficiency (CVID), the most common symptomatic PID, is 6–7 years [11]. In developed countries, delay in diagnosis is an important problem regardless of the socioeconomic level, and a 5–10-year delay in the diagnosis of CVID has been found [12]. Furthermore, it was found that the delay in diagnosis decreased with the im-

TABLE 1. Distribution of the physicians by demographic characteristics, academic degree, specialty, and hospital type

Variables	Value
Age, median (IQR)	32 (25–68)
Sex, *n* (%):	
Male	143 (44.7)
Female	177 (55.3)
Practicing medicine [years] median (IQR)	7 (1–42)
Degree, *n* (%):	
Research assistant	183 (57.2)
Specialist	105 (32.8)
Associate professor	24 (7.6)
Professor	8 (2.5)
Specialty, *n* (%):	
Internal medicine	144 (45)
Infectious diseases	39 (12.2)
Family physicians	137 (42.8)
Hospital type, *n* (%):	
Family health center	50 (15.6)
Governmental hospital	38 (11.9)
City hospital	80 (25)
University hospital	148 (46.3)

IQR – interquartile range.

TABLE 2. Distribution of physicians' answers to questions

Questions	Answer (Yes/No)	*N* (%)
1. Clinical features		
Have you ever received training on PID before?	Yes	217 (67.8)
Have you ever followed up a patient diagnosed with PID during your career?	Yes	71 (22)
What clinical findings can PID present with?	Yes	
Recurrent opportunistic infections	Yes	249 (77.8)
Autoimmune disease	Yes	153 (48)
Cytopenia	Yes	192 (60)
Enteropathy	Yes	160 (50)
Chronic liver disease	Yes	109 (34.1)
Autoinflammatory conditions	Yes	121 (38)
Malignancy	Yes	112 (35)
Granulomatous lesions	Yes	96 (30)
Allergy	Yes	132 (41.3)
All of the above	Yes	22 (6.9)
2. What are the warning signs of infection in terms of PID		
Two or more new otitis media within 1 year	Yes	240 (75)
Two or more new severe sinusitis within 1 year, repetitively	Yes	160 (50)
One pneumonia per year for more than 2 years	Yes	208 (65)
Recurrent, deep abscesses in skin or organs (*e.g.* liver, lungs)	Yes	144 (45)
Need for intravenous antibiotics to clear infections	Yes	192 (60)
Persistent oral candidiasis or fungal skin infection	Yes	128 (40)
Infection with non-tuberculous mycobacteria	Yes	112 (35)
Recurrent or severe viral infections (herpes, Epstein-Barr virus, cytomegalovirus infection, condyloma)	Yes	80 (25)
Chronic diarrhea with weight loss	Yes	166 (52)
Family history of primary immunodeficiency	Yes	153 (48)
All of the above	Yes	21 (6.6)
3. Which of the following could be a clue to PID		
Lymphoid hyperplasia	Yes	262 (81.9)
Splenomegaly	Yes	206 (64.4)
Hepatomegaly	Yes	134 (41.9)
Bronchiectasis	Yes	191 (59.7)
Skin findings (eczema, alopecia, vitiligo etc.)	Yes	211 (65.9)
All of the above	Yes	13 (4)
4. Which of the following helps us in diagnosis a PID patients		
Complete blood count	Yes	294 (92)
Blood urea nitrogen, creatinine	Yes	129 (40.3)
Hepatic function panel	Yes	135 (42.2)
Immunoglobulins	Yes	314 (98.1)
Lymphocyte subtype determination	Yes	256 (80)
Serum isohemagglutinins	Yes	168 (52.5)
Antibacterial antibody response to previous vaccines	Yes	252 (78.8)

TABLE 2. Cont.

Questions	Answer (Yes/No)	*N* (%)
Viral serology	Yes	179 (55.9)
Culture	Yes	112 (35)
Radiological imaging	Yes	201 (64.7)
Genetic testing	Yes	120 (37.5)
All of the above	Yes	37 (11.6)
5. Managing PID patients		
5.1 Which of the following vaccines should not be given to a patient with PID		
Inactive influenza	Yes	192 (60)
Hepatitis B	Yes	176 (55)
Live vaccines	Yes	128 (40)
All of the above		80 (25)
5.2 What are the agents used in the treatment of PID		
Immunoglobulin replacement therapy	Yes	316 (98.8)
Antibiotic prophylaxis	Yes	258 (80.6)
IFN-γ therapy	Yes	178 (55.6)
Stem cell transplant	Yes	230 (71.9)
Genetic therapy	Yes	194 (60.6)
Immunosuppressive therapy	Yes	62 (19.4)
Monoclonal treatment	Yes	84 (26.3)
All of the above	Yes	47 (14.6)

PID – primary immunodeficiency, IFN-γ – interferon γ.

TABLE 3. Distribution of the answers given by physicians to the questions related to the Jeffry model according to their specialty

Variables	Internal medicine Yes, *n* (%)	Specialty Infectious diseases Yes, *n* (%)	Family medicine Yes, *n* (%)	*P*-value*
Two or more new otitis media within 1 year	108 (75)	30 (77)	120 (87.6)	0.68
Two or more new severe sinusitis within 1 year, repetitively	67 (46.5)	19 (48.7)	60 (43.7)	0.44
One pneumonia per year for more than 2 years	130 (90.2)	30 (77)	102 (75)	0.40
Recurrent, deep abscesses in skin or organs (*e.g.* liver, lungs)	80 (55.6)	17 (45)	50 (36.4)	0.33
Need for intravenous antibiotics to clear infections	113 (78.5)	33 (85)	111 (69.2)	0.28
Persistent oral candidiasis or fungal skin infection	72 (50)	17 (43.5)	60 (43)	0.87
Infection with non-tuberculous mycobacteria	92 (63.9)	26 (66.7)	70 (51)	0.94
Recurrent or severe viral infections (HSV, EBV, CMV, condyloma)	116 (80.6)	32 (81)	102 (75)	0.30
Chronic diarrhea with weight loss	82 (56.9)	18 (46.2)	58 (42)	0.44
Family history of primary immunodeficiency	91 (63.2)	20 (51.3)	61 (45)	0.34
All of the above	10 (6.9)	6 (14.6)	5 (3.7)	0.058
**Total score, median (IQR)	7 (2–10)	7 (3–10)	6 (2–10)	0.45

*χ^2 test (data were shown as numbers and percentages). **Kruskal-Wallis test was used to compare the medians. HSV – herpes simplex virus, EBV – Epstein-Barr virus, CMV – cytomegalovirus.

plementation of an educational program for early diagnosis of PID [13]. According to the JMF, physician education plays an important role in the early diagnosis of PIDs [14]. About 70% of physicians had received PID training in specialty training or medical school, but 45% were not familiar with PID warning signs [15]. Similarly, in this study, approximately one third of the physicians had never received any PID training before. Insufficient education of physicians about PID and difficulties in accessing training programs are among the main problems associated with delay in diagnosis or misdiagnosis [16]. The correct response rate of physicians to the questions in previous survey studies on PID awareness was very low (11.4% and 26%) and it was emphasized that there was a deficiency in PID knowledge [17, 18]. In this study, similarly, the correct response rate of physicians to questions related to the diagnosis and management of PID was very low (4–14.6%). The range of immune defects and clinical presentations may have reduced the awareness of PID. Nevertheless, the omission of PID-related presentations such as autoimmunity, autoinflammation and malignancy is a concern in the 10 warning signs proposed by the JMF [19]. It is therefore recommended that autoimmunity be included in the list of 10 warning signs of PID [20]. Majority of physicians associate infectious conditions due to opportunistic or unusual organisms with immunodeficiencies. More typical infectious findings enable physicians to better recognize PID [21]. Similarly, in this study, it was found that the highest level of awareness among the clinical presentations of PID was in the direction of recurrent infections, while awareness of non-infectious symptoms such as autoimmunity and malignancy was lower. In many studies, the 10 warning signs scale determined by the JMF has been reported to be useful in screening and early diagnosis of PID [14, 22]. In a similar previous study, the three most common clinical conditions recognized among the 10 warning signs of PID were pneumonia once a year for more than 2 years, two or more new otitis media within 1 year, and the need for recurrent intravenous antibiotics, respectively [23]. In a previous study, the most common warning signs of PID reported by physicians were recurrent otitis media and two or more pneumonias within one year [24]. In similar previous studies, it was observed that more than half of the physicians were not familiar with the JMF warning signs [23, 24]. In this study, similarly, familiarity with JMF warning signs was not found in the majority of physicians. PID 10 warning sign is frequently used in the comparison of PID awareness among physicians [23, 24]. In a comparison of PID awareness in hematology, general internal medicine physicians and pediatricians, familiarity with the PID 10 warning signs was higher in pediatricians than in other specialties. These differences were due to the experience of the doctors. Nevertheless, familiarity was similar between hematology and general internal medicine physicians, which are specialties related to adult patients [23]. Likewise, no significant difference was found between specialties in terms of familiarity with the '10 warning signs of PID' in this study. For early and accurate diagnosis of PID, consideration of medical history and immunological evaluation is essential. The JMF's '4 Stages of PID Test' is useful for immunological evaluation in the diagnosis of PID. In accordance with the '4 Stages of PID Test', 1st stage is general medical examination, differential complete blood count, serum immunoglobulin G (IgG), IgA, IgM, IgM, IgE and C-reactive protein (CRP) analysis, 2nd stage is serum IgG2 analysis, 3rd stage is lymphocyte subtype analysis, 4th stage is genetic tests [23]. Nevertheless, difficulty in access to laboratory tests and physicians and high test costs constitute an obstacle in the diagnosis of PID [17]. In a former study, most physicians responded in favor of evaluation of serum immunoglobulin levels after CRP and differential complete blood count tests [23]. Another study indicated that differential complete blood count and serum immunoglobulin levels were the most frequently requested tests, followed by IgG subgroup determination and chest X-ray [25]. In this study, the most frequently ordered test was serum immunoglobulins, followed by complete blood count. It is thought that genetic tests are necessary for the differential and definitive diagnosis of PID [26]. In recent 10 years, the discovery of monogenic causes of PID has been accelerating with next-generation sequencing (NGS) and has become the first-line diagnostic tool for most patients with suspected PID [27]. Genetic diagnosis, however, remains limited due to difficult access to NGS tests, high cost, and lack of information on the use of whole exome sequencing (WES) and targeted panels [28]. Similar to this study, in a previous study, genetic tests were among the least requested tests by physicians at the first stage in suspected PID [23]. New advances in the pathogenesis of PIDs have led to targeted therapies, hematopoietic stem cell transplantation (HSCT) and gene therapy in addition to symptomatic and maintenance therapy (immunoglobulin replacement therapy, antimicrobial, anti-inflammatory and immunosuppressive therapies) [28]. As to the awareness of PID treatment, the majority of physicians prefer immunoglobulin replacement therapy [9]. In the present study, immunoglobulin replacement therapy was the most preferred PID treatment option. However, as in a previous study, the majority of physicians in this study were not familiar with all treatment options [23]. Inactivated vaccines can be administered in the routine vaccination program in patients with PID. Live-attenuated vaccines (e.g., Bacillus Calmette-Guerin (BCG), oral polio virus, varicella) are generally contrain-

dicated in PID due to the risk of side effects [29]. In case a child has a family history of immunodeficiency, clinicians should postpone BCG vaccination until immunodeficiency is excluded [30]. The majority of physicians in a previous study marked BCG vaccination as no in suspected PID. In this study, the majority of physicians predicted that live vaccines were contraindicated in PID. There are several limitations of this study. The first one is that this study was limited to physicians working in the departments of general internal medicine, infectious diseases, and family physicians, so the distribution of physicians may not be homogeneous. Secondly, as participation in the study was not compulsory, not all physicians to whom the questionnaire was sent could be included in the study, which may have reduced the participation rate. Despite the limitations, this study is one of the important studies that draws attention to PID awareness among physicians who are likely to encounter PID.

CONCLUSIONS

We demonstrate the lack of awareness about PID among general internal medicine, infectious disease, and family physicians. Despite recent rapid advances in the pathophysiology of PID, the delay in diagnosis of these diseases is still a major problem within the healthcare system. In PID, prompt diagnosis and treatment can be life-saving, and improve the quality of life of patients. An understanding of the causes of lack of awareness about PID will help in the correct management of these patients. According to this information, revising PID warning signs and organizing comprehensive training programs and courses on PID seem to be important factors in increasing physicians' awareness of PID.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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