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Primary Immunodeficiency Disorders: Awareness Survey of Physicians in Iran

Mohammad Hossein Asgardoon[1,2*], Mohamad Mehdi Rezwanifar[2], Bahar Ataeinia[1], Yasser Bagheri[3,1,4]

[1] Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[2] Iranian Student Society for Immunodeficiencies, Student's Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

[3] Clinical Research Development Unit (CRDU), 5 azar Hospital, Golestan University of Medical Sciences, Gorgan, Iran

[4] Department Immunology, School Medicine, Iran University of Medical Sciences, Tehran, Iran

Abstract

Background/objectives: Primary immunodeficiency disorders (PID) are a group of hereditary disorders characterized by various complications. Many patients with PID are undiagnosed, underdiagnosed, or misdiagnosed due to lack of physicians' awareness, which culminates in increased rates of morbidity and mortality.

Method: Nine states of Iran were chosen for evaluating physicians' awareness of PID. The population study consisted of pediatricians (specialties and subspecialties), pediatric residents, and general practitioners. A valid and reliable questionnaire was prepared for awareness scoring assessment. We provided physicians with continuing medical education (CME) and evaluated the effect on physicians' awareness of PID.

Results: Among 794 physicians, 466 general practitioners (GP), 90 pediatric residents, 124 pediatric specialists, and 20 pediatric subspecialists were included in this study. The mean age of participants was 40.96±10.63 years. The mean period of practicing medicine was 12±9.53 years. The mean total knowledge score of participants was 51.30 with a standard deviation of 18.76. Only 161 participants (20.4%) answered more than 2/3 of all questions correctly. The mean scores in the management of PIDs was 66.25±54.55, followed by laboratory findings as 49.57±25.07, clinical symptoms as 54.42 ± 17.85, and associated syndromes as 42.32 ± 28.57. Only 207 physicians completed the CME curricula. Significant improvements were observed in physician's knowledge after the programs ($P < 0.0001$).

Conclusion: This survey demonstrated that there is a lack of both the knowledge and practice of pediatricians in the field of PID in Iran. Implementation of strategies to raise pediatricians' awareness and assure the earliest diagnosis, appropriate treatment, and proper care management is critical.

Keywords: Primary immunodeficiency, Physician, Survey, Awareness

***Corresponding Author:** Mohammad Hossein Asgardoon
1. Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
E-mail: mh_asgardoon@yahoo.com

Introduction

Primary immunodeficiency diseases (PIDs) consist of a group of inherited disorders that affect components of the immune system and raise the susceptibility to both infectious and non-infectious complications (1-3). Since the original description of X-linked agammaglobulinemia in 1952, the number of independent PIDs has expanded to more than 300 entities. In April 2014, the International Union of Immunological Societies (IUIS) Expert Committee updated the classification of primary immunodeficiencies. In this classification, the major groups of PIDs have been represented in nine different tables including Combined immunodeficiencies, Combined immunodeficiencies with associated or syndromic features, Predominantly antibody deficiencies, Diseases of immune dysregulation, Congenital defects of phagocyte number, function or both, Defects in innate immunity, Autoinflammatory disorders, Complement deficiencies, and Phenocopies of PID (4).

PIDs patients are mainly characterized by increased susceptibility to infections as there are defects in neutrophils, macrophages (5), dendritic cells, complement proteins, natural killer cells, as well as T and B-lymphocytes (6). Although PIDs are commonly categorized in genetic diseases, some PIDs are clinically manifested only after imperative environmental exposures. Hence, they are generally associated with malignancies, allergies, inflammations, and a variety of other autoimmune manifestations (7).

Primary antibody deficiencies (PAD) is the most common type of PIDs (8-10) followed by T cell. The majority of patients with antibody deficiency present with recurrent infections mainly in respiratory and gastrointestinal tracts (11, 12), autoimmune diseases (13), and malignancies (14) causing irreversible complications. All these eventually lead to increased morbidity and decreased quality of life of the patients (15, 16). So, early diagnosis of the patients is extremely important to prevent these complications (17) and may increase their quality of life (18).

Unfortunately, delayed diagnosis of patients with PIDs is substantial, especially in developing countries which has an adverse effect on the patients' prognosis (8, 19-22). Meanwhile, lack of physicians' awareness of PIDs leads to increased delay in diagnosis. However, diagnosis of PID patients can be improved by raising the physician awareness in this field (19). It seems that PIDs are more common nowadays. Therefore, the number of referral patients to primary care physicians and pediatricians with the impression of PIDs is growing and it is necessary for them to be familiar with these potentially life-threatening disorders (18). It is necessary for any country's health authorities to evaluate their physicians' awareness on PIDs, for designing proper education programs to raise the physicians' awareness about PIDs. In this study, our aim was to evaluate Iranian physician's awareness regarding PIDs.

Methods

Program sites, participants, and recruitment

In this study, we chose nine highly populated cit-

ies with of Iran, including Mashhad, Shiraz, Isfahan, Ahvaz, Zahedan, Tehran, Gorgan, Rasht, and Tabriz to evaluate the awareness of physicians about PIDs. This study was conducted randomly on pediatricians (specialties and subspecialties), pediatric residents, and general practitioners of the mentioned states. Ethical approval was obtained from Research Ethics Committee of Tehran University of medical sciences.

Program evaluation and data collection

Demographic data, university certificate, duration of medical practice, place of medical practice, and history of the previous encounter with suspected or documented PID patients were documented for each participant. We used a validated and reliable questionnaire to calculate PIDs awareness score for physicians (21, 22). This questionnaire had previously been used and tested in Tehran city (Cronbach's alpha=0.7961, kappa=0.8127) with 66 closed questions, containing 28 questions on the clinical presentation of PIDs, 10 questions on associated diseases and syndromes, 14 questions on laboratory investigations, and 4 questions on its management (**Table 1**). The last two questions were about the problems of physicians in managing PIDs patients and their needs to re-education classes. The overall score for each participant was computed by adding the correct answers to these 66 questions. Further, for qualitative assessment, eight different ranks were determined, including extremely low (score less than 12.5), very low (score from 12.5 to 25), low (score from 25 to 37.5), low-medium (score from 37.5 to 50), and high-medium (score from 50 to 62.5), high (score from 62.5 to 75), very high (score from 75 to 87.5), and extremely high (score more than 87.5).

Statistical analyses

Data are presented as frequency (number and percentage), mean, and median. We used the Fisher's exact test and chi-square tests to compare categorical variables, while t-tests and one-way ANOVA were employed to compare numerical variables. To assess the correlation between quantitative and qualitative variables, Pearson's and Spearman correlation coefficient were calculated, respectively. Statistical analyses were carried out using the SPSS software package, version 20 (SPSS Inc., Chicago, IL, USA). A P-value<0.05 was considered statistically statistically significant.

Table 1. The questions and scores

Question	Correct answer	%
I-Clinical features		
What is the most important feature in a child with PID		
Malignancy		16.5
Recurrent infections	Yes	83.5
Autoimmune disease		0.0
Growth failure		0.0
Not answered		0.0
How many of children with recurrent infection have PID?		
10%	Yes	53.0
30%		47.0
60%		0.0
80%		0.0
Not answered		0.0
Which of the following can be a clue to PID disease		
Lymphoid hypoplasia	Yes	69.5

Question	Correct answer	%
Malar rash	No	69.0
Hypophyseal insufficiency	No	69.0
Eosinophilia with erythroderma	Yes	59.6
Polydactyly	No	66.6
Recurrent common colds	No	83.1
Recurrent oral candidiasis at the age of two	Yes	87.0
Delayed separation of umbilical cord beyond 3 weeks	Yes	69.9
Angioedema	Yes	46.5
Delay in shedding the deciduous teeth	Yes	42.4
Two simultaneous deep infections	Yes	82.7
Lymphoid hyperplasia	Yes	54.3
Wilms tumor	No	70.4
Hypoparathyroidism	Yes	35.6
Pneumocystis jiroveci pneumonia	Yes	78.2
Neonatal botulism	No	60.6
Poliomyelitis after receiving oral polio vaccine (OPV)	Yes	68.2
Failure to thrive	Yes	73.3
History of 3 otitis media during childhood	No	71.2
Partial albinism	Yes	44.0
Eczema and subcutaneous bleeding	Yes	58.7
Bronchiectasis	Yes	68.3
Malar rash	No	69.0
True or false		
The signs or symptoms of PID patients can emerge after 6 months of age, when the maternal antibodies are diminished	Yes	85.1
The signs or symptoms of PID patients can emerge during the third decade of life	Yes	43.2
The signs or symptoms of PID patients can emerge from the time of birth	Yes	60.1
II- Associated symptoms and diseases Which of the following is associated with PID		
Ehler-Danlos syndrome	No	69.0
Wiskott-Aldrich syndrome	Yes	68.4
Ataxia-Telangiectasia	Yes	63.1
Hypomelanosis of Ito	No	80.7
Sturge-Weber syndrome	No	75.1
Kostman syndrome	Yes	31.4
Bardet-Biedl syndrome	No	80.9
Job's syndrome	Yes	47.0
Turner syndrome	No	58.3
Chediak–Higashi syndrome	Yes	66.6
III- Laboratory findings Which of the following directly helps us in diagnosis a PID patient		
Lymphocyte stimulation tests	Yes	64.2
Fecal occult blood test	No	53.8
Antibacterial antibody response to previous vaccines	Yes	66.5
Blood urea nitrogen, creatinine	No	48.4
Determining superficial markers of lymphocytes	Yes	73.2
Anemia panel	No	71.4

Question	Correct answer	%
Complete blood count and differential	Yes	74.4
Serum isohemagglutinins	Yes	55.8
Hepatic function panel	No	65.0
Candida and tetanus skin test	Yes	63.4
Which of the following can be a clue in diagnosing a PID patient		
The count of blood eosinophils in a child with one and a half years of age being equal to 15,500	Yes	24.9
Small platelets and thrombocytopenia	Yes	39.4
Serum IgG concentration in an infant with 7 months of age being equal to 420 mg/dl	No	84.9
Large granules in neutrophils	Yes	55.5
IV -Managing PID patients		
Which of the following vaccines should not be administered in a child with PID		
Influenza A vaccine		40.1
BCG	Yes	58.3
IPV		1.2
Hepatitis B vaccine		0.0
Not answered		0.1
Which of the following medications decreases the rate of infections in children with common variable Immunodeficiency		
Immunoglobulin replacement therapy	Yes	57.6
Recombinant interferon		0.0
Recurrent blood transfusion		0.0
Plasmapheresis		2.0
Not answered		40.4
Do you have difficulties in managing patients with PID	Yes	25.1
	No	74.9
	Not answered	0.0
Is retraining classes regarding the PID syndromes necessary for general practitioners and specialists	Yes	80.5
	No	19.5
	Not answered	0.0

Results

Participant attendance and characteristics

The questionnaire was filled by 794 physicians from 9 states of Iran among whom, 466 general practitioners (GP), 90 pediatric residents, 124 pediatric specialists, and 20 pediatric subspecialists were included. The number of male and female participants was 393 (51.4%) and 372 (48.6%) respectively. The mean age of participants in this study was 40.96 (24-91) years and with a standard deviation (SD) of 10.63. The mean duration of practicing medicine was 12 years with a standard deviation of 9.53 years.

The participants were divided into 5 age groups, as shown in **Figure 1**. A total of 44.2% of study population worked in state hospitals while 17.1% worked in their private clinics and 6.7% worked in non-state hospitals. Further, 9.7% of them were also an academic staff in medical universities. Our data showed that 51.8% of participants had visited at least one suspected or documented PIDs' case during their practice.

Survey approach

The mean total knowledge score of participants was 51.30±18.76 (maximum and minimum attainable scores were 100 and 0, respectively). Only

161 participants (20.4%) answered more than 2/3 of all questions correctly. The mean scores in the management of PIDs was 66.25±54.55, followed by laboratory findings as 49.57±25.07, clinical symptoms as 54.42±17.85, and associated syndromes as 42.32 ± 28.57.

Correlation between demographic data and knowledge score of physicians

Comparison of awareness score in different groups of physicians is summarized in **Table 2**. The total knowledge score was significantly higher in females than in males (*P*=0.018). The total knowledge score of physicians who practiced medicine less than 12 years was significantly higher than in physicians with a longer medicine practice duration (*P*<0.001). Further, the total knowledge score of physicians who were faculty member was significantly higher than that of physicians who were not (*P*=0.002).

Based upon the qualitative assessment and using ANOVA test, the rank between each position level group of physicians had a statistically significant difference (P<0.001). General practitioners showed the lowest rank as "medium-low" while pediatric specialists and subspecialist achieved "medium-high" rank. The general practitioner's knowledge score was significantly lower than the score of the other groups (*P*<0.001) (**Figure 2**), while the data showed that other groups' scores were comparable. Furthermore, visiting 6 or more than 6 suspected or documented primary immunodeficient patients did not significantly increase the knowledge score of physicians (*P*=0.52). In addition, the participants who worked at state hospitals had a higher overall score (P<0.001, r=0.6). The mean total score of each state has been shown in **Figure 3.**

Table 2. Comparison of awareness score in different groups of 794 Iranian physicians

Variable	Number	Scores (Mean±SD)	P value of each group
State			
State 1	164	50.28(20.48)	
State 2	104	51.34(19.37)	
State 3	41	54.03(19.03)	
State 4	206	48.69(19.19)	
State 5	100	46.02(14.31)	
State 6	50	53.13(17.76)	
State 7	50	58.94(18.59)	<0.001
State 8	46	62.59(14.74)	
State 9	33	55.06(13.08)	
Age group			
_29 years old	116	53.97(16.18)	
30-39 years old	265	56.15(18.63)	
40-49 years old	265	52.09(17.49)	
50-59 years old	97	42.75(17.28)	<0.001
_60 years old	51	37.13(20.91)	
Sex			
Male	408	49.87(19.47)	0.018
Female	386	53.08(17.88)	
Place of medical practice			
A (Only in Governmental hospital)	407	55.14(18.51)	
B (Only in Private hospital)	62	44.82(15.37)	
C (Only in Private office)	158	45.50(17.76)	
D (more than one center)	167	51.13(18.58)	<0.001

Variable	Number	Scores (Mean±SD)	P value of each group
University certificate (position level)			
General practitioner	528	47.55(17.64)	<0.001
Pediatric specialist	141	61.11(19.26)	
Sub-specialists	23	62.8(19.55)	
Pediatric resident	102	58.16(15.36)	
Being faculty member			
Yes	87	58.56(19.83)	0.002
No	707	51.15(18.52)	
Previous encounter with suspected or documented primary immunodeficient patients			
<6 patients	498	55.58(16.68)	0.525
>6 patients	296	54.40(19.07)	

State 1 = Shiraz State 2 = Mashhad State 3 = Ahvaz State 4 = Esfahan State 5 = Zahedan State 6 = Tabriz State 7 = Tehran State 8 = Gorgan State 9 = Rasht

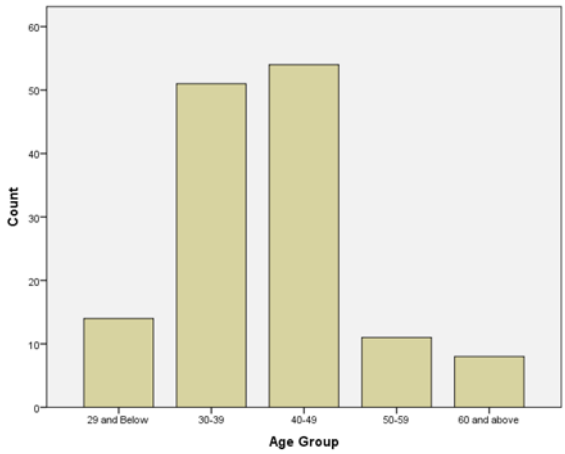

Figure 1. Frequency of five age groups of participants

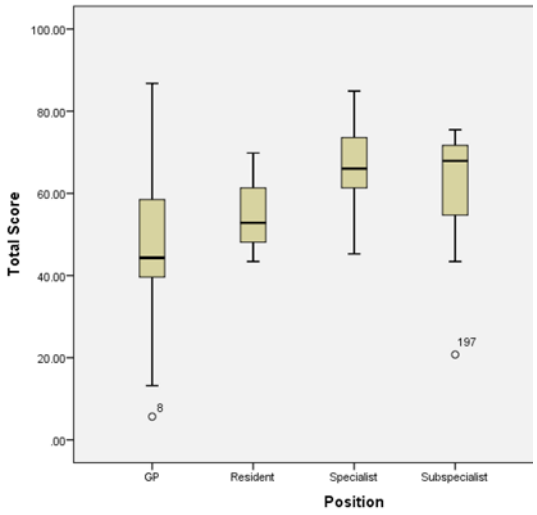

Figure 2. Mean total score of different position levels

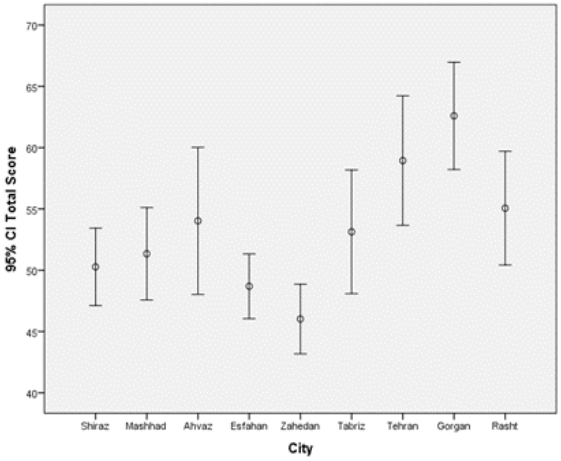

Figure 3. Mean total score of each state

Table 3. Comparison of awareness scores in different groups of 207 Iranian physicians before and after training (CME) program

Variable	Number	Mean of Scores in pre-test (±SD)	Mean of Scores in post-test (±SD)	Comparison of pre and post test scores (±SD)	P value of Comparison of pre and post test scores	P value of each group
State						
State 1	48	52.83(19.24)	62.78(16.08)	9.95(4.07)	0.01	0.208
State 2	29	53.48(18.61)	57.83(18.29)	4.35(4.84)	0.37	
State 3	22	47.94(19.56)	61.07(16.14)	13.13(5.57)	0.02	
State 4	74	46.71(16.72)	55.61(16.50)	8.9(3.25)	0.00	
State 5	7	40.43(16.18)	41.50(17.45)	1.07(9.39)	0.91	
State 6	27	51.29(15.37)	61.13(14.20)	9.84(4.34)	0.02	
Age group						
_29 years old	16	51.57(15.87)	55.81(19.09)	4.24(6.87)	0.543	0.001
30-39 years old	77	53.98(17.54)	64.43(15.04)	10.45(3.01)	0.001	
40-49 years old	74	49.79(16.31)	59(18.36)	9.21(3.29)	0.006	
50-59 years old	26	39.62(17.34)	46.34(13.41)	6.72(4.87)	0.176	
_60 years old	14	38.02(14.22)	51.25(16.11)	13.23(7.67)	0.120	
Sex						
Male	117	47.81(18.10)	58.98(16.65)	11.17(2.55)	<0.0001	0.137
Female	90	51.55(16.72)	57.91(17.73)	6.36(2.92)	0.032	
Place of medical practice						
A (only in governmental hospital)	85	52.47(18.66)	62.71(16.34)	10.24(3.36)	0.003	0.008
B (only in private hospital)	9	46.63(14.76)	46.63(7.83)	0(6.31)	1	
C (only in private office)	53	42.45(13.95)	56.24(16.33)	13.79(3.83)	0.001	
D (more than one center)	60	53.29(17.45)	56.73(17.91)	3.44(3.69)	0.354	
University certificate						
General practitioner	157	45.93(15.61)	56.68(15.38)	10.75(2.08)	<0.0001	<0.0001
Pediatric specialist	41	62.10(17)	72.37(12.21)	10.27(13.81)	0.368	
Sub-specialists	4	49.68(26.77)	-	-	-	
Pediatric resident	5	54.24(12.36)	-	-	-	
Being faculty member						
Yes	12	70.15(17.08)	62.68(20.18)	-7.47(8.47)	0.391	<0.0001
No	195	48.60(16.56)	58.66(16.84)	10.06(1.99)	<0.0001	
Previous encounter with suspected or documented primary immunodeficient patients						<0.0001
<6 patients	166	48.11(17.37)	56.75(16.81)	8.64(2.03)	<0.0001	
>6 patients	41	55.59(18.65)	68.10(13.47)	12.51(4.13)	0.004	

Physician participation in CME activities and learner knowledge scores

A total of 207 physicians completed the CME curricula. Before CME program, the mean total knowledge score of physicians was 49.59 with a standard deviation of 17.83. The maximum and minimum attainable scores were 100 and 0 respectively. Specifically, 43 participants (20.77%) answered more than 2/3 of all questions correctly. The mean scores in the management of PIDs were 76.57 ±62.85, followed by laboratory findings as 48.13 ± 26.49, clinical symptoms as 53.14 ± 16.97, and associated syndromes as 36.66 ± 28.52. The mean total score of participants after the CME program was 58.42 (SD = 16.81). The mean scores in the management of PIDs were 73.07±47.38, followed by laboratory findings as 56.14 ± 22.85, clinical symptoms as 62.08 ± 16.05, and associated syndromes as 48.81 ± 26.94.

CME assessment

Comparison of pre- and post-CME knowledge scores revealed a significant increase in the total score of participants (P<0.0001), suggesting a growth in their awareness and efficacy of the CME program. The survey scores are displayed in Figure 4. The maximum score elevation belonged to associated syndromes with 12.15. Based on comparison of awareness score in different groups of 207 Iranian physicians before and after the training class (CME), according to **Table 3**, the maximum awareness growth in each group belonged to state 3 (13.13), age group "more than 60 years old" (13.23), male (11.17), those working in their private office (13.79), General practitioner (10.75), those who were not faculty member (10.06), and whose who visited more than 6 immunodeficient patients (12.51).

Discussion

PIDs are a heterogeneous group of disorders predisposing patients to serious complications, where early interventions can be lifesaving. Therapy of PID has changed significantly over the last 20 years and almost normal life can be expected for most patients if the diagnosis is made correctly and therapy measures are established timely enough. Despite significant developments in the entire process of diagnosis to management of PID patients, there is still a significant impact on the health expenditure and health system imposed by these disorders world-.wide, particularly in Iran

In our study, in order to control information bias, the population study was asked to answer the questions based on their current knowledge and avoid searching to find the correct answer. In order to avoid selection bias, we used cluster sampling for our study. Nine states of Iran were chosen as clusters; different groups of physicians including GP, pediatric residents, pediatric specialists, and pediatric subspecialists were included in our study. Our findings revealed that the associations found are plausi-.ble with the current knowledge

Similar results have been obtained through several studies. Our analysis showed that there is a dose-response relationship between lack of awareness in PIDs and increased delay in diagnosis, burden of health expenditure, and complications for the patients, their family, and the health system in general.

According to PID inheritance classification done by Notarangelo et al. (23), 78 out of 118 PIDs are inherited as autosomal recessive traits. Given the high rate of consanguineous marriages in developing countries, pediatricians working in such countries should have a high awareness of PID. In this study, knowledge of PID among general practitioners was significantly lower than that of pediatric residents, pediatric specialists, and subspecialists.

Our study is congruent with a limited number of studies evaluating PID knowledge and practice. In the previous Iranian study conducted in 2012, the mean total score was 55.9±14.3 (i.e. about 29 correct answers out of 52 questions). One hundred and five participants (31.9%) answered more than two thirds of all questions correctly. In order to qualitatively compare the groups, a ranking system was used. Total scores were significantly different between physicians'

groups (P<0.01). Pediatric subspecialties' scores were significantly higher than those of the other participants (P<0.05). It was found that there are deficiencies in both the knowledge and practice of pediatricians in the field of PID (22). In a study conducted in Kuwait, 26% of the pediatricians correctly answered ≥ 67% of the questions. The mean overall score was 60% (95% CI=58% to 61%), the clinical presentation score was 63%, the syndromes associated with immunodeficiency score was 58%, and the laboratory investigation score was 51%. It was uncertain whether these results are applicable to other countries or further studies are warranted (21). Pediatricians' awareness of important PID indicators was evaluated in a Turkish study. They concluded that more comprehensive pre/postgraduate education in PID is necessary for physicians in Turkey (24).

In Iran, a combination of medical history, physical examination, and laboratory investigations all together plus ruling out common probable diagnoses leads to final diagnosis of PIDs.

In November 2001, a multidisciplinary panel of specialists was set by CDC to identify and discuss public health strategies to apply for PIDs (25) . Its components are as follow: 1-Application of traditional public health methods to assess the impact of PIDs on community health; 2-Development, implementation, and evaluation of screening tests administered to newborns and clinical algorithms for early recognition of symptomatic persons to facilitate the earliest possible diagnosis and treatment for PIDs surveillance systems. 3-Evaluation of screening and diagnostic tools to ensure their quality and appropriateness for identification of patients with PIDs; and 4-Communication with healthcare providers and the public to facilitate prompt and appropriate diagnosis and intervention (26-29).

The CME program conducted in this study, compared with a previous study conducted in 2012, demonstrated the reversibility principle of one of Hill's criteria; it states that educating physicians through different programs including CME accreditations, improves their awareness and knowledge of diagnosis as well as management of PID patients, which brings its own benefits for the patient, their families, and the health system in general. It also confirms the four components of CDC strategies for PIDs mentioned above.

Conclusions

We conclude that there is a lack of medical awareness concerning PID among pediatricians in Iran. Since there are no screening tests for PID, early diagnosis can only be achieved by increasing the index of suspicion of physicians about these disorders. We, therefore, recommend implementation of strategies to improve the awareness of pediatricians about PID so that early interventions with immunoglobulin therapy and immune reconstitution would be used in order to prevent significant tissue damage, morbidity, and mortality; all of these culminate in economic savings. These strategies may include comprehensive under- and post-graduated education, organizing continuing medical education (CME) courses, and publishing educational materials (posters, booklets, articles). Pediatricians should also be educated about the ten warning signs of PIDs. We observed that the increase in awareness was greater in groups with a lower score than among those with a higher score. Therefore, training classes are more efficient in groups with lower awareness compared to groups of physicians with higher awareness. Although the survey was conducted at a national level in Iran, the implementation of strategies to improve the awareness of pediatricians about PID should seriously be considered by other countries too.

Conflict of interest: The authors declare that they have no conflict of interest.

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References

1. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34-48.
2. Aghamohammadi A, Farhoudi A, Moin M, Rezaei N, Kouhi A, Pourpak Z, et al. Clinical and immunological features of 65 Iranian patients with common variable immunodeficiency. Clin Diagn Lab Immunol. 2005;12(7):825-32.
3. Yazdani R, Abolhassani H, Asgardoon M, Shaghaghi M, Modaresi M, Azizi G, et al. Infectious and Noninfectious Pulmonary Complications in Patients With Primary Immunodeficiency Disorders. J Investig Allergol Clin Immunol. 2017;27(4):213-24.
4. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol. 2014;5:162
5. Sharifi L, Mirshafiey A, Rezaei N, Azizi G, Magaji Hamid K, Amirzargar AA, et al. The role of toll-like receptors in B-cell development and immunopathogenesis of common variable immunodeficiency. Expert Rev Clin Immunol. 2016;12(2):195-207.
6. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol. 2007;120(4):776-94.
7. Kumar A, Teuber SS, Gershwin ME. Current perspectives on primary immunodeficiency diseases. Clin Dev Immunol. 2006;13(2-4):223-59.
8. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol. 2002;22(6):375-80.
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. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. J Clin Immunol. 2014;34(4):478-90.
11. Aghamohammadi A, Allahverdi A, Abolhassani H, Moazzami K, Alizadeh H, Gharagozlou M, et al. Comparison of pulmonary diseases in common variable immunodeficiency and X-linked agammaglobulinaemia. Respirology. 2010;15(2):289-95.
12. Khodadad A, Aghamohammadi A, Parvaneh N, Rezaei N, Mahjoob F, Bashashati M, et al. Gastrointestinal manifestations in patients with common variable immunodeficiency. Dig Dis Sci. 2007;52(11):2977-83.
13. Abolhassani H, Amirkashani D, Parvaneh N, Mohammadinejad P, Gharib B, Shahinpour S, et al. Autoimmune phenotype in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol. 2013;23(5):323-9.
14. Abolhassani H, Aghamohammadi A, Imanzadeh A, Mohammadinejad P, Sadeghi B, Rezaei N. Malignancy phenotype in common variable immunodeficiency. J Investig Allergol Clin Immunol. 2012;22(2):133-4.
15. Aghamohammadi A, Pouladi N, Parvaneh N, Yeganeh M, Movahedi M, Gharagolou M, et al. Mortality and morbidity in common variable immunodeficiency. J Trop Pediatr. 2007;53(1):32-8.
16. Aghamohammadi A, Montazeri A, Abolhassani H, Saroukhani S, Pourjabbar S, Tavassoli

M, et al. Health-related quality of life in primary antibody deficiency. Iran J Allergy Asthma Immunol. 2011;10(1):47-51.
17. Abolhassani H, Asgardoon MH, Rezaei N, Hammarstrom L, Aghamohammadi A. Different brands of intravenous immunoglobulin for primary immunodeficiencies: how to choose the best option for the patient? Expert Rev Clin Immunol. 2015;11(11):1229-43.
18. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27(5):497-502.
19. Lee PP, Lau YL. Endemic infections in Southeast Asia provide new insights to the phenotypic spectrum of primary immunodeficiency disorders. Asian Pac J Allergy Immunol. 2013;31(3):217-26.
20. Matamoros Flori N, Mila Llambi J, Espanol Boren T, Raga Borja S, Fontan Casariego G. Primary immunodeficiency syndrome in Spain: first report of the National Registry in Children and Adults. J Clin Immunol. 1997;17(4):333-9.
21. Al-Herz W, Zainal ME, Salama M, Al-Ateeqi W, Husain K, Abdul-Rasoul M, et al. Primary immunodeficiency disorders: survey of pediatricians in Kuwait. J Clin Immunol. 2008;28(4):379-83.
22. Nourijelyani K, Aghamohammadi A, Salehi Sadaghiani M, Behniafard N, Abolhassani H, Pourjabar S, et al. Physicians awareness on primary immunodeficiency disorders in Iran. Iran J Allergy Asthma Immunol. 2012;11(1):57-64.
23. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol. 2006;117(4):883-96.
24. Yuksek M, Ikinciogullari A, Dogu F, Elhan A, Yuksek N, Reisli I, et al. Primary immune deficiency disease awareness among a group of Turkish physicians. Turkish J Pediatr. 2010;52(4):372-7.
25. Available from: http://www.cdc.gov/genomics/info/conference/PIsynop.htm.
26. Thacker SB, Stroup DF. Future directions for comprehensive public health surveillance and health information systems in the United States. Am J Epidemiol. 1994;140(5):383-97.
27. Brown AS, Gwinn M, Cogswell ME, Khoury MJ. Hemochromatosis-associated morbidity in the United States: an analysis of the National Hospital Discharge Survey, 1979-1997. Genet Med. 2001;3(2):109-11
28. McDonnell SM, Witte DL, Cogswell ME, McIntyre R. Strategies to increase detection of hemochromatosis. Ann Intern Med. 1998;129(11):987-92.
29. Wetterhall SF, Cogswell ME, Kowdley KV. Public health surveillance for hereditary hemochromatosis. Ann Intern Med. 1998;129(11):980-6.