Awareness Concerning Primary Immunodeficiencies Among Physicians in Turkey

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ABSTRACT

Objective: In many countries worldwide, medical knowledge of PIDs remains insufficient, which leads to late diagnosis, higher morbidity, a shorter life span, and worse quality of life. This study aims to assess the level of awareness and knowledge of physicians working in Turkey about PIDs.

Materials and Methods: Between June and September 2019, a questionnaire regarding the findings, diagnosis, and treatment of PIDs was sent via social media to physicians from various medical specialties. The research was conducted using the data collected from physicians who agreed to participate in the study and completed the questionnaire.

Results: The results of 661 participants (50.8%) who completed the entire survey were evaluated. While the majority of the questions in the general information section about PIDs were correctly answered by more than 80% of the physicians, knowledge about warning signs, laboratory findings, and treatment methods was less robust. Remarkably, pediatricians' knowledge was slightly higher than that of other specialties. Only a small part of family physicians and internists felt competent; 29.7% of pediatricians, 8.2% of family physicians, and 19% of internists felt worried; and half of the family physicians and internists stated they referred these patients directly without performing any evaluation.

Conclusion: It may be possible to perform intervention programs to enhance primary care for PIDs in Turkey using this information regarding physicians' PID management approaches, views, and beliefs.

Keywords: Primary immunodeficiency, awareness, warning signs, knowledge

INTRODUCTION

Primary immunodeficiencies (PID) are genetic diseases caused by mutations affecting one or more immune system components. More than 450 diseases and syndromes have been identified to date (1,2).

Although the diseases seem to be rare when considered individually, the overall prevalence of PID diseases varies between 1 in 200 and 1 in 100,000. It is estimated that the frequency is higher in countries where consanguineous marriages are more common, like Turkey. The PID prevalence has been reported as 30.5/100,000 in the study, including two centers in Turkey, conducted by Kılıc et al. (3). The prevalence of severe combined immunodeficiency (SCID) was detected at 1/58,000 according to the findings from neonatal screening programs in the United States (4). In a retrospective study in our country and an ongoing neonatal screening study (unpublished data), the frequency of SCID was reported as 1/10,000 (5).

With the advances in genetic diagnostic methods, more patients will be identified, and the number of genes linked to PID will increase. PIDs may present with a predisposition to infections, autoimmune diseases, allergies, autoinflammatory diseases, lymphoproliferation, hemophagocytosis, and malignancies (1). In recent years, approaches for genetic diagnosis and functional research on defective genes have made significant progress not only in disease diagnosis but also in the development of rational...
and targeted strategies for treatment. However, the major difficulty in characterizing PID cases is the occurrence at different age groups and very diverse clinical pictures. Though diagnosing immunodeficiencies with more severe presentations is more straightforward than milder cases, certain cases cannot be detected until severe sequelae develop.

In many countries worldwide, medical knowledge of PIDs remains insufficient. Physicians’ lack of awareness and experience results in the patients being diagnosed late or not at all. Late diagnosis of PIDs leads to complications, higher morbidity, a shorter life span, and worse quality of life (6).

This study aims to assess the level of awareness and knowledge about PIDs among physicians from Turkey and identify possible factors affecting the knowledge and issues that need to be addressed for timely diagnosis and effective treatment.

MATERIAL and METHODS

Between June and September 2019, a questionnaire regarding the findings, diagnosis, and treatment of PIDs was sent via social media to a total of 1300 physicians from various medical specialities working in a variety of workplaces around Turkey; no one province or region was chosen. The research was conducted using the data collected from physicians who agreed to participate to the study and completed the questionnaire (Supplementary file). The questionnaire was first provided to 15 physicians working at the same hospital, and the responses of the physicians included in the pilot application were not included.

The first section of the questionnaire was about the participants’ age, sex, area of specialization, professional experience, workplace, and level of education in the immune system and immunodeficiencies. The categorization regarding the age values included ≤ 30, 31-35, 36-50, and ≥ 51 years. Specializations were divided into three categories: basic medical sciences, internal sciences, and surgical sciences. Additionally, each participant identified their departments specifically. The experience was classified as 1-5 years, 6-10 years, 11-15 years, and 16 years and over according to duration of work. Each participant identified their affiliations as a primary health care clinic, a university hospital, a training and research hospital, or a state hospital.

The second section of the questionnaire included information about PIDs; the third section included warning signs for children and adults (7); the fourth section included laboratory findings for PIDs and the fifth section examined therapeutic methods for PIDs. The questionnaire’s final section asked participants how they felt when they examined a patient with immunodeficiency during their daily clinical practice.

The study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine, under approval number GO-19/562.

Statistical Analysis

The descriptive data was presented in the form of percentages. If the numerical variables were normally distributed, they were represented as mean and standard deviation; if they were not normally distributed, they were expressed as median and interquartile range. The chi-square test was used to compare the frequencies between groups. P <0.05 was found significant. The statistical analysis was performed using the SPSS 22.0 software.

RESULTS

Demographical Findings

The questionnaire was sent to 1300 physicians, and the results of 661 participants (50.8%) who completed the entire survey were evaluated. 71% of the participants were female. Table I shows the distribution of participants by age categories, medical specialty, level of education about the immune system and immunodeficiencies, and the institution.

General Information on Primary Immunodeficiencies

According to the second part of the questionnaire, 82.5% of participants were aware that PIDs do not occur exclusively in childhood; 90.8% were aware that PIDs do not occur exclusively in families with consanguineous marriage. 95.2% of participants indicated that PIDs are treatable. 96.4% of participants agreed that it is critical to select which vaccinations should be administered in PIDs and which should not. 57.3% of participants indicated that PIDs are rare diseases.

Just 11.8% of participants were aware that severe combined immunodeficiencies, which present with the
most serious clinical manifestations and require urgent care, can be screened in the neonatal period. 87.3% of participants believed that people with PID would not only have severe symptoms, but may also experience mild clinical signs. When questioned about the initial signs of PIDs, 99.8% of participants reported that infections; 92.4% malignancies; 83.1% autoinflammation; and 83.1% allergic diseases; and 82.9% autoimmunity may be the initial presentation finding of a PID. Figures 1 and 2 show the responses to the general information asked about PIDs. In terms of general knowledge, pediatricians scored slightly higher than other specialties in 13 of 15 items (p<0.005). There were more pediatricians than internists who answered 9 of the 15 items correctly (p<0.005).

Warning Signs of PID in Children

Regarding the warning signs of PID in children, the three most often cited responses were a family history of PID (88.9%), persistent oral moniliasis and fungal infections (86.3%), and persistent deep tissue and organ abscess (81.3%). The least often mentioned warning signs were the need for intravenous antibiotics to treat pneumonia (35.7%), two or more sinus infections in one year (38.6%), and recurrent wheezing (48.7%). These are shown in Figure 3. 11 of the 18 warning signs in children were known by less than 70% of participants.

In terms of the warning signs of PID in children, pediatricians scored slightly higher than the other specialties in all items (p<0.005). Compared with the internists, a greater proportion of pediatricians answered 12 of the 18 items correctly (p<0.005).

Warning Signs of PID in Adults

The three most often reported warning signs for PID in adults were family history (82%), chronic deep tissue and visceral abscess (80.1%), and infection with non-tuberculous mycobacteria (79.7%). Two or more sinus infections in one year (29.3%), necessity for recurrent intravenous antibiotic therapy (33.4%), and two or ear infections in one year (37.8%) were the least often cited warning signs. They are shown in Figure 4. Less than 70% of the participants classified 8 of the 12 items as a warning sign of PID for adults.

In terms of the warning signs of PID in adults, pediatricians scored slightly higher than the other specialties on 11 of the 12 items (p<0.005). There were more pediatricians than internists who answered 5 of the 12 items correctly.

Laboratory Findings of PID

Of the laboratory findings associated with PIDs, the best-known were reduced immunoglobulin levels (86.1%), low/absent antibody titers to vaccines (82.5%), and lymphopenia (80.2%), as shown in Figure 5. Fewer than half of the participants were aware of persistent elevations in ESR and CRP, thrombocytopenia, and low MPV.

In terms of laboratory findings of PID, pediatricians scored slightly higher than other specialties on all 6 items (p<0.005). Only one of the six items was correctly answered by more pediatricians than internists.
Figure 1: Answers regarding general knowledge about PIDs (Following each item, participants were asked 'Do you agree?').

Figure 2. Answers regarding clinical presentation of PIDs (Following each item, participants were asked 'Do you agree?')
Figure 3. Answers regarding the warning signs of PID in children.

Figure 4. Answers regarding the warning signs of PID in adults.
Treatment Options for PIDs

Of the therapeutic choices for PIDs, the best-known are immunoglobulin replacement therapy (86.8%), hematopoietic stem cell transplantation (76.2%), and antibiotic prophylaxis (67.6%), as shown in Figure 6. In terms of treatment options of PID, pediatricians scored slightly higher than the other specialties on all 8 items (p<0.005). Only two of the 8 items were correctly answered by more pediatricians than internists.

Feelings and Impressions

When questioned how they feel when they see a patient with PID during daily clinical practice, the answers were as follows: 44% referred these patients to a clinical

![Figure 5. Answers regarding laboratory findings in PIDs.](image)

![Figure 6. Answers regarding treatment in PIDs.](image)
immunologist, 20% expressed discomfort and anxiety, 19% had never encountered these patients, 15% felt self-sufficient in this regard, and 1% performed the initial testing and consulted the patient afterwards. Two family physicians (2.7%) responded that they felt competent, six (8.2%) felt worried, and 41 (56.2%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seven internists (8.3%) said that they felt worried, and 43 (51.2%) referred the patient. Seven internists (8.3%) said that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient. Seventy-four pediatricians (33.3%) indicated that they felt competent, 66 (29.7%) felt worried, and 65 (29.3%) referred the patient.

DISCUSSION

This research evaluated physicians practicing in Turkey in order to assess their awareness and knowledge of the warning signs of PIDs, and to emphasize diagnosis and care. As far as we know, this is the first research in our country to analyze physicians of all medical specialties.

More than half of the participants reported that PIDs were rare. While these diseases are classified as rare when considered individually and all diagnostic categories are included, these diseases are common, particularly in countries with a high rate of consanguineous marriages, such as our country, Turkey (1). Today, PIDs constitute a large diagnostic category comprised of over 450 diseases classified into ten groups. We also know that PIDs should be considered not just in cases of infections, but also in cases of benign and malignant lymphoproliferation, autoimmunity, allergy, and autoinflammation, all of which suggest immune dysregulation (8). Although all of the study’s participants agreed that PID patients may present with infections, 20% were not aware of findings of immune dysregulation. Findings of immunodysregulation are becoming more common in individuals with PID as their life expectancy increases. Therefore, in patients with PID, and particularly in adults, a multidisciplinary approach is necessary.

The research included physicians from all specialties because PIDs have a broad spectrum of clinical results diagnosed by a physician from any department if they keep them in mind. Even for doctors who work in basic medical sciences, demonstrating an atypical, abnormal microorganism in culture or identifying pathological specimens that do not meet the criteria for a specific diagnosis, such as granuloma or inflammatory bowel disease-like, celiac-like samples, could lead to a diagnosis. To raise awareness, the primary focus will be on family physicians, who provide patients with first-line treatment, followed by internists and pediatricians. Among the physicians who participated in our study, 11% were family physicians, 11% were internists, and 33% were pediatricians. Pediatricians’ knowledge and awareness levels were significantly higher among all specialities in our study. When pediatricians were compared to internists, the greatest significant difference in terms of awareness and knowledge was on general information about PID and warning signs in children.

Pediatricians felt more competent than other departments when confronted with a patient with PID. In previous studies evaluating awareness, pediatricians or family physicians were targeted primarily (9-11). Adult patients, on the other hand, experience a greater delay in diagnosis than children (12,13), making it critical to raise awareness among physicians treating adult patients. Only small part of family physicians and internists felt competent when confronted with a patient with PID according to our study.

Indeed, while the majority of questions in the general information section about PIDs were correctly answered by more than 80% of the physicians, the lower rates of knowledge about warning signs, laboratory findings, and treatment methods for children and adults may indicate that clinical practice was insufficient. When family physicians and internists encountered these patients, half of them stated that they referred them directly without performing any evaluation. Another point to consider is that 29.7% of pediatricians, 8.2% of family physicians, and 19% of internists felt worried when they encountered a patient with PID.

In 2010, a survey of pediatricians in Turkey used a questionnaire of 71 questions to assess their level of awareness. The results of the two studies could not be compared directly since the questionnaires used in the two studies were different. About 60% of participants reported that PID was associated with a positive family history, premature death in the family, persistent diarrhea due to giardiasis, frequent oral aphthous stomatitis, the absence of tonsils, and delayed weight and height gain (9). Concerning the PID warning signs in children and adults, the majority of participants (>70%) were aware of more than half of the warning signs. The most significant warning sign for both child and adult age groups was found to be a positive family history of PID. However, the patient’s family history may be negative, or the patient may be the
first case in the family. It is essential to collect a complete family history from patients with suspected PID, including consanguineous marriage, sibling illness and death, and a family history for similar disease. The presence of a family member with PID is one of the factors that prompts an early visit to the doctor to determine whether the newborn child is sick following birth. Genetic counseling and rationales of preimplantation genetic diagnosis methods should be provided to individuals with a family history of PID. Our goal, however, should be to prevent organ damage, disability, disease-related morbidity, and early mortality in all patients with PID through early diagnosis. Noticeably, little was known about the early detection of severe combined immunodeficiency using TREC screening. When patients with severe combined immunodeficiency, which has a severe and urgent clinical picture, are diagnosed early, they can recover with HSCT, which is a curative therapy, and the success rate with HSCT without live vaccines or viral infections such as CMV is higher (14, 15). Regrettably, since TREC screening is not yet routine in our country, only a limited number of participants may have been aware of it.

The most often reported laboratory findings were low immunoglobulin levels and lack of antibody responses, which are findings of antibody deficiency, the most prevalent PID group in Europe and also our country (12, 16). Likewise, the best-known treatment choices included immunoglobulin replacement therapy and antibiotic prophylaxis. Although persistent ESR and CRP levels may suggest chronic granulomatous disease, autoinflammatory diseases, or an emergence of malignancy, less than half of participants considered these to be PID laboratory findings. Thrombocytopenia and low MPV levels, which are typical findings of Wiskott-Aldrich syndrome, were both mentioned by fewer than half of the participants.

The limitations of the study included the survey used not being validated and its use in this investigation for the first time. Participation may have remained at 50% because the survey was conducted on a voluntary basis via social media over a three-month period.

This study demonstrated that physicians have a general lack of awareness about PIDs, especially about the warning signs. Remarkably, pediatricians’ knowledge of PIDs was slightly higher than that of other specialties. This is also consistent with the fact that adult patients experience a longer diagnostic delay. Adult PIDs need significant awareness-raising programs. By identifying the causes of the lack of awareness, we may be able to reduce the number of PID patients who are mishandled. It may be possible to establish intervention programs in Turkey to enhance primary care for PIDs using this data regarding physicians’ PID management approaches, perspectives, and beliefs. Therefore, their education and ability to diagnose diseases at an earlier stage are crucial. Both the education provided in medical school and post-graduate education and meetings can enable increased physician awareness regarding PIDs.

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Author Contributions
All authors contributed to the study’s conception and design. Melike Ocak, Hacer Neslihan Bildik, Elif Soyak Aytekin, Ayşegül Akarsu collected the data. Saliha Esenboğa performed the analysis and wrote the first draft of the manuscript. Deniz Çağdaş, and Feyzi İlhan Tezcan commented on the document and improved the discussion.

All authors read and approved the final manuscript.

Data Availability
On reasonable request, the data supporting the findings of the study are available from the corresponding author.

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

Ethical Approval
This study was approved by the Ethics Committee of Hacettepe University.

Consent to Participate
Informed consent was taken from all participants.

REFERENCES


