Awareness of primary immunodeficiency diseases at a national pediatric reference center in Peru

Conscientização sobre imunodeficiências primárias em um centro nacional de referência pediátrica no Peru

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DOI: 10.31744/einstein_journal/2021AO6289

ABSTRACT

Objective: To investigate the level of awareness of primary immunodeficiency diseases among physicians working at Instituto Nacional de Salud del Niño. Methods: Cross-sectional study including pediatric residents and pediatricians working at the Instituto Nacional de Salud del Niño during the study period (2017-2019). Physicians working at the immunology unit and surgery departments were excluded. Three aspects of awareness of primary immunodeficiency diseases were investigated: education, general knowledge, and diagnostic suspicion and actions taken in the face of suspicion. Results: This sample comprised 83 physicians with a median age of 33 years. Most physicians were women (71.1%) and half were pediatric residents. During their undergraduate studies, 43.1% had taken primary immunodeficiency disease courses, and 39.2% had attended conferences on this topic. During their residency training, 25.9% had taken primary immunodeficiency disease courses, and 60.3% had participated in conferences on this topic. Among pediatricians, 50% had taken primary immunodeficiency disease courses, and 53.1% had attended conferences on this topic. Only 39.8% of physicians reported being familiar with the list of 10 warning signs proposed by the Jeffrey Modell Foundation. More than half of physicians considered the lack of access to laboratory tests the major challenge in making diagnosis of primary immunodeficiency diseases. Conclusion: This study revealed limited awareness of primary immunodeficiency diseases among physicians working at Instituto Nacional de Salud del Niño. Although most physicians suspected primary immunodeficiency diseases in patients with a history of recurrent infections and frequent use of antibiotics, not all of them were familiar with the list of 10 warning signs proposed by the Jeffrey Modell Foundation, nor were they able to describe ancillary tests requested in suspected cases.

Keywords: Awareness; Education, medical; Primary immunodeficiency diseases/diagnosis; Peru

RESUMO

Objetivo: Investigar o nível de conscientização sobre imunodeficiências primárias entre os médicos do Instituto Nacional de Salud del Niño. Métodos: Estudo transversal com todos os residentes de pediatria e pediatras que faziam parte do corpo clínico do Instituto Nacional de Salud del Niño quando o estudo foi realizado (2017-2019). Médicos atuantes na unidade de imunologia e nos setores de cirurgia foram excluídos. Foram estudados três aspectos da conscientização sobre imunodeficiências primárias: educação, conhecimento geral e suspeita diagnóstica e ações

Keywords: Conscientização; Educação, médica; Imunodeficiências primárias/diagnóstico; Peru
Primary immunodeficiency diseases (PIDD) are a heterogeneous group of disorders of the immune system. The most common presentations include severe recurrent infections, neoplasms, atopy and autoimmune conditions, with high mortality, especially in patients with severe combined immunodeficiency. Approximately 6 million people worldwide suffer from PIDD. However, the number of reported cases is lower.

In August 2020, the Latin American Society for Immunodeficiencies (LASID) registered 8,383 cases of PIDD. Peru contributed with 213 cases (2.5% of total caseload), of which 33.8% were reported by Unidad Funcional de Alergia, Asma e Imunologia (UFAAI), of the Instituto Nacional de Salud del Niño (INSN) - Breña, LIM, Peru the most important Peruvian health center for training in pediatrics. In 2015, the Jeffrey Modell Foundation recognized the UFAAI and two other immunology centers as Jeffrey Modell Foundation Diagnostic and Research Centers, a crucial step in establishing international collaborations for the benefit of Peruvian PIDD patients. The number of registered cases in Latin America has been on the rise year after year due to improved diagnostic techniques and enhanced awareness. However, many challenges must still be overcome in order to guarantee coverage for a higher number of PIDD patients.

Different studies suggest low awareness of PIDD among physicians may delay diagnosis and treatment of PIDD patients. According to a study performed in the United States, awareness of PIDD was limited to 32% of physicians and was greater among pediatricians. A Brazilian study revealed that, although 80% of physicians admitted recurrent infections may be related to PIDD, only 40% evaluated these patients. Likewise, only 32% of physicians approved a survey of PIDD awareness in Iran. Even though the highest scores were attributed to treatment, 86% of physicians reported having problems in managing these patients.

Knowledge and awareness have different meanings, the latter being mainly related to attitude and action. In that sense, lack of awareness among physicians may explain the limited number of reported cases of PIDD, and the delayed diagnosis in Latin American countries, such as Peru. This study aimed to investigate the level of awareness of PIDD among physicians working at a national pediatric reference center in Peru. Findings of this study may inform the development of strategies aimed to increase awareness of PIDD, which may contribute to early diagnosis and timely treatment provision for affected patients.

**INTRODUCTION**

Primary immunodeficiency diseases (PIDD) are a heterogeneous group of disorders of the immune system. The most common presentations include severe recurrent infections, neoplasms, atopy and autoimmune conditions, with high mortality, especially in patients with severe combined immunodeficiency. Approximately 6 million people worldwide suffer from PIDD. However, the number of reported cases is lower.

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**OBJECTIVE**

To investigate the level of awareness of primary immunodeficiency diseases among physicians working at Instituto Nacional de Salud del Niño.

**METHODS**

**Study design and population**

Cross-sectional study conducted at INSN. The study population comprised all physicians working at INSN during the study period (October 2017- March 2019). Pediatric residents and pediatricians working at pediatric inpatient units were included. Physicians working at UFAAI were excluded given their formal training in PIDD. Surgeons were also excluded due to limited access to such specialists.

**Procedures**

Initially, random sampling stratified by level of specialization (pediatric resident or pediatrician) was used. The population comprised 148 physicians (105 residents and 43 pediatricians). According to estimations obtained using Epidat V. 4.0 software, a sample size of 106 (75 residents and 31 pediatricians) would be required to yield 40.3% of physicians who had already examined one patient with PIDD with 5% accuracy and a level of significance of 5%.
A list including all physicians working at INSN at the beginning of this study was used to identify potential participants. Selected physicians were visited twice and invited to participate. However, several potential participants refused to answer the survey due to lack of knowledge about the topic, while others were difficult to contact or locate. For these reasons, convenience sampling was used and physicians were selected during five visits to the hospital complex.

**Study variables**

Three aspects related to awareness of PIDD were investigated: education, general knowledge and diagnostic suspicion and actions taken in the face of suspicion.

Educational aspects included questions about PIDD-related courses, conferences, and rotations during undergraduate studies and residency training, or following residency completion.

General knowledge was assessed using the following questions: “Are you aware that patients who often take antibiotics may have primary immunodeficiency diseases?” , “Do you think primary immunodeficiency diseases are amenable to treatment?” , and “Do you think patients with primary immunodeficiency diseases suffer from a severe disease?”. Response alternatives were “No, never,” “Yes, in some cases,” “Yes, in approximately half of cases,” and “Yes, always.”

In order to assess the ability to suspect PIDD, physicians were asked to list the 10 warning signs of PIDD developed by the Jeffrey Modell Foundation. Infection-related signs were the most commonly described, with 33.7% (n=28) of physicians identifying other signs, including recurrent and opportunistic infections (78.6%, n=22), unspecified gastrointestinal disease (35.7%, n=10) and hematologic diseases, such as immune-mediated cytopenia (21.4%, n=6). Furthermore, 94.9% (n=74) of physicians declared live vaccines should be avoided in PIDD patients, and 92.6% (n=75) thought inactivated vaccines were safe.

**Instrument**

An ad hoc questionnaire including sociodemographic variable- and PIDD-related questions (education, general knowledge and diagnostic suspicion, and actions taken in the face of suspicion) was developed. The questionnaire was validated by four PIDD specialists and one statistician, and tested through interviews with four Peruvian physicians (pediatric residents and pediatricians) who did not participate in the study, and whose suggestions were considered in the development of the final version (Appendix 1).

**Data analysis plan**

Categorical variables were described as absolute and relative frequencies. Quantitative variables were described using measures of central tendency and dispersion. Statistical analyses were performed using Stata v14 software (StataCorp LP, 2015, College Station, Texas, USA), with a level of significance of 5%.

**Ethical aspects**

This study was reviewed and approved by the Institutional Review Board of INSN number 0287-2018. Participants received an informed consent form explaining the objectives of the study when invited to participate. Information collected was kept confidential.

**RESULTS**

This sample comprised 83 physicians with median age of 33 years. Most physicians (71.1%) were females and half of them were pediatric residents. With regard to education at the undergraduate level, 43.1% reported having taken PIDD-specific courses, 39.2% reported having attended PIDD conferences, and only 2% reported having completed a rotation in an immunology unit. With regard to education during the residency training program, 25.9% reported having taken PIDD-specific courses, 60.3% reported having attended PIDD conference, and only 3.5% reported having completed a rotation in an immunology unit.

Pediatricians were questioned about continuing education (i.e., education after completion of residency training in pediatrics). In this group, 50% reported having taken PIDD-specific courses, 53.1% reported having attended PIDD conferences, and only 3.1% reported having completed a rotation in an immunology unit. General knowledge about PIDD among physicians is described in table 1.

In this sample, 39.8% (n=33) of physicians reported being familiar with the 10 warning signs proposed by Jeffrey Modell Foundation (Table 2). Infection-related signs were the most commonly described, with 33.7% (n=28) of physicians identifying other signs, including recurrent and opportunistic infections (78.6%, n=22), unspecified gastrointestinal disease (35.7%, n=10) and hematologic diseases, such as immune-mediated cytopenia (21.4%, n=6). Furthermore, 94.9% (n=74) of physicians declared live vaccines should be avoided in PIDD patients, and 92.6% (n=75) thought inactivated vaccines were safe.
Most physicians reported having seen patients with a history of recurrent infections (96.4%, n=80) and frequent use of antibiotics (92.8%, n=77) (Table 3). More than half of physicians (64.6%, n=53) reported having suspected PIDD and requested ancillary tests. However, only 69.8% (n=37) were able to describe the tests ordered (Table 4). With regard to actions taken in the face of suspicion of PIDD, 74.7% (n=62) of physicians reported having referred patients to a specialist or specialized organization. In all cases, UFAAI was the referral unit of choice, followed by other hospitals (9.7%, n=6) and other specialists (11.3%, n=7).

When questioned about challenges involved in diagnosis of PIDD, physicians ranked first the lack of access to laboratory tests (57.7%), followed by high test costs (32.1%), and shortage of immunology specialists (5.1%).

### DISCUSSION

In this sample, less than half of participants had taken courses, attended conferences or completed a rotation in an immunology unit during their undergraduate education studies. The number of physicians who attended PIDD-related meetings increased during and after residency. Overall, the number of rotations in immunology units was low. Conversely, a prior study involving 27 general hospitals in Brazil reported pediatricians learned about PIDD throughout their residency training or thereafter (72.2% and 75.9%, respectively). The fact that immunology is a new medical specialty in Peru and that the UFAAI was inaugurated recently, in 2012, may explain this difference, since physicians trained prior to that year may not have had access to appropriate education about PIDD.

This study revealed physicians have limited knowledge about PIDD. Similar findings have been reported in previous studies assessing PIDD-specific knowledge in different countries, such as the United States, Iran, the United Arab Emirates, and Mexico. These studies have shown low levels of information among general practitioners, primary care physicians and pediatricians, including residents. Interestingly, the fact that these studies have been conducted 5 to 10 years prior to this analysis suggests this is a persistent problem in many countries, regardless of socioeconomic status.
As to warning signs, those associated with infections, which are typical of PIDD, were identified more frequently.\(^{(1)}\) However, many concerns about the 10 warning signs proposed by the Jeffrey Modell Foundation have been raised, given signs pertaining to PIDD, such as sporadic infections, autoimmunity, autoinflammation and malignancy, are not accounted for.\(^{(17-20)}\) In this sample, signs associated with the immune dysregulation syndrome class of PIDD, other than those included in the Jeffrey Modell Foundation list were reported,\(^{(21)}\) such as cytopenia and gastrointestinal diseases. Some authors have proposed the inclusion of “autoimmunity” in the list of 10 warning signs developed by the Jeffrey Modell Foundation,\(^{(22)}\) based on findings of a retrospective study, in which this sign was associated with increased sensitivity regarding suspicion of PIDD in pediatric patients, although not in adults.\(^{(18)}\) 

As in a prior Brazilian study,\(^{(10)}\) most physicians in this sample reported having managed patients with a history of recurrent infections and frequent use of antibiotics. Also, more than half reported having suspected PIDD, a higher percentage relative to a previous national report (42%).\(^{(23)}\) In this study, 44.6% of physicians reported having ordered ancillary tests when dealing with PIDD patients, the most common being laboratory tests, such as serum immunoglobulin levels differential lymphocyte count. This finding is somewhat different from those of a study conducted with pediatricians in the United Arab Emirates. In that study, complete blood count and serum immunoglobulin levels were the most commonly reported tests (96%), followed by IgG subclass levels, and chest X-ray (76.5%).\(^{(15)}\) The recent introduction of immunology as a specialty training program may explain discrepant findings.

In this study, lack of access to laboratory tests was the most critical barrier to PIDD diagnosis. This finding is congruent with previous Latin American data.\(^{(8,10)}\) Other less common challenges reported were higher test costs and shortage of specialists, which were rated higher in other studies.\(^{(10)}\) Overall, the number of specialists and reference centers has increased worldwide. However, specialized laboratories have not followed this trend.\(^{(8)}\) 

Antibody deficiency has been singled out as the most common PIDD in several studies\(^{(6,12,23-25)}\) and the diagnosis of this condition does not require complex laboratory infrastructure.\(^{(26)}\) Nevertheless, a Peruvian report including 13 national hospitals reported limited access to immunological tests, such as immunoglobulin levels (56.5%).\(^{(22)}\) Moreover, only four centers in Peru perform simple lymphocyte population analysis for PIDD. Although the INSN is the primary national pediatric reference center in Peru, research and private collaboration initiatives are the only settings where flow cytometry analyses can be conducted.\(^{(27)}\) Therefore, advanced flow cytometry studies, genomic analysis and other tests can only be carried out abroad.

**Limitations**

This was the first study to investigate the level of PIDD awareness in Peru, and was conducted at a national pediatric reference center, namely the most important pediatric hospital providing specialized training to Peruvian pediatricians. Although more than half of physicians (residents and pediatricians) working at INSN were surveyed, convenience sampling was used instead of random sampling. Given physicians with particular interest in the topic were more likely to participate, results may have been biased towards higher levels of awareness. Therefore, it would not be surprising if actual levels of awareness were lower. Also, the type and number of courses or conferences physicians attended was not deeply investigated. Hence, the risk of memory bias must be accounted for.

**Clinical applicability**

This study revealed a need for PIDD-specific education in residency programs in Peru. Training programs may contribute to increased awareness of PIDD, suspicion and referral of patients.\(^{(26,28)}\) According to a Mexican study, 75 trained physicians are required to get one patient referred.\(^{(29)}\) Structured training programs should aim to provide general knowledge about PIDD, as treatable diseases requiring early suspicion, and to inform physicians about referral of affected patients. Regular awareness campaigns should also be organized.

In Latin America, PIDD have some specific features. Hence, locally adapted warning signs have been proposed in Brazil.\(^{(50)}\) Physicians in Peru should be aware of endemic infectious diseases such as bartonellosis and dengue fever. The inclusion of bacillus Calmette-Guerin and oral poliomyelitis vaccines in the national immunization schedule introduces some clinical and laboratory features which are not shared by other cohorts.\(^{(8)}\) Hence, the development of PIDD warning signs adapted to the Peruvian reality is suggested.
CONCLUSION
This study revealed limited awareness of primary immunodeficiency, diseases among physicians working at Instituto Nacional de Salud del Niño. Although most physicians suspected primary immunodeficiency diseases in patients with a history of recurrent infections and frequent use of antibiotics, not all of them were familiar with the 10 warning signs proposer by the Jeffrey Modell Foundation, nor were they able to describe the ancillary tests ordered in suspected cases. Enhanced training on primary immunodeficiency diseases, and improved structuring of residency programs is suggested to increase awareness of these disorders.

ACKNOWLEDGMENTS
We thank Drs. Javier Pérez, Immunology Unit, Hospital Nacional Guillermo Almenara Irigoyen; Juan Carlos Aldave, Primary Immunodeficiency Unit, Hospital Nacional Edgardo Rebagliati Martins; Cesar Galvan, Unidad Funcional de Alergia, Asma e Imunologia, Instituto Nacional de Salud del Niño; Jeanett Carrillo, Allergy Unit, Hospital Central de la Policía Nacional del Peru; and Cesar Loza, Clinical Epidemiology Unit, Universidad Peruana Cayetano Heredia, for the validation of the questionnaire.

AUTHORS’ CONTRIBUTION
All authors contributed to the conception and design of the work. Jessica Hanae Zafra-Tanaka, Christian Toribio-Dionicio and Mariella R. Huamán: contributed to the data acquisition and analysis. Wilmer Córdova-Calderón: supervised the work. All authors contributed to data interpretation, provided critical comments, writing of the manuscript and approved the final version.

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Appendix 1. Questionnaire about awareness of primary immunodeficiency diseases in pediatric residents and pediatricians

Introduction:
The following survey is aimed to examine the level of awareness of primary immunodeficiency diseases among physicians working at Instituto Nacional de Salud del Niño (INSN) - Breña, Lima, Peru. This survey comprises two sections: sociodemographic data and data on awareness of primary immunodeficiency diseases. This survey is individualized, and will take a maximum of 10 minutes to complete.

Instructions:
Please read the questions carefully and select the answer you think is correct.

Section 1: Sociodemographic data
1. How old are you? _________
2. What is your gender? 
   ____ Female
   ____ Male
3. What is the highest academic level you have achieved? 
   ____ Resident
   ____ Specialist
4. In which area are you doing or have you done your residency? 
   ____ Clinical
   ____ Surgical
5. At each of the following academic levels, how many years have you worked in that area? 
   General practitioner: _____ years
   Resident: _____ years
   Specialist: _____ years
6. a) Have you completed any rotations in immunology units (either during your residency, or as complementary training thereafter)? 
   ____ No (go to question 7)
   ____ Yes
6. b) In which unit did this rotation take place? 
   ____ Unidad Funcional de Alergia, Asma e Imunologia (UFAAI)
   ____ Other (specify): _______________________
   continue...
Appendix 1. Questionnaire about awareness of primary immunodeficiency diseases in pediatric residents and pediatricians

7. a) What type of training did you receive as an undergraduate student? More than one alternative may be selected

- None
- Course on primary immunodeficiency diseases
- Rotation in an immunology unit in which patients with primary immunodeficiency diseases are managed
- Presentation addressing primary immunodeficiency diseases (conference or clinical case discussion)

7. b) What type of training did you receive during your residency? More than one alternative may be selected

- None
- Course on primary immunodeficiency diseases
- Rotation in an immunology unit in which patients with primary immunodeficiency diseases are managed
- Presentation addressing primary immunodeficiency diseases (conference or clinical case discussion)

7. c) What type of training did you receive after having completed your residency? You can select more than one option

- None
- Course on primary immunodeficiency diseases
- Rotation in an immunology unit in which patients with primary immunodeficiency diseases are managed
- Presentation addressing primary immunodeficiency diseases (conference or clinical case discussion)

Section 2. Awareness of primary immunodeficiency diseases

8. Did you know patients who frequently use antibiotics may have a primary immunodeficiency disease? Consider frequent as two or more months on antibiotics, with poor clinical response, or need of intravenous antibiotics to control infections.

- No, never
- Yes, in some cases
- Yes, in approximately half of cases
- Yes, always

9. Some physicians believe that primary immunodeficiency diseases are not treatable. Do you think primary immunodeficiency diseases are amenable to treatment?

- No, never
- Yes, in some cases
- Yes, in approximately half of cases
- Yes, always

10. Do you think patients with a primary immunodeficiency disease suffer from a severe disease?

- No, never
- Yes, in some cases
- Yes, in approximately half of cases
- Yes, always

11. a) Are you familiar with the 10 warning signs of primary immunodeficiency diseases?

- No (go to question 12)
- Yes

11. b) Which are the 10 warning signs of primary immunodeficiency diseases? List them below

12. What is the greatest challenge faced when examining patients with primary immunodeficiency diseases? Please select only one alternative.

- Lack of access to laboratory tests
- Shortage of specialists
- High test costs
- Other: ________________________________________

13. Do you see patients with a history of recurrent infections? Consider recurrent infections as ≥4 new ear infections within one year, ≥2 serious sinus infections within one year, ≥2 pneumonias within one year, recurrent deep abscesses in skin or organ (e.g., liver, lungs), or ≥2 deep-seated infections (e.g., sepsis).

- No never
- Yes, ≥1 patient per year
- Yes, ≥1 patient per month
- Yes, ≥1 patient per week
Appendix 1. Questionnaire about awareness of primary immunodeficiency diseases in pediatric residents and pediatricians

| Question                                                                 | Options                                                                 |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 14. Do you see patients who frequently take antibiotics? Consider frequent as two or more months on antibiotics with poor response or need of intravenous antibiotics to control infections | ```
| ____________ No, never
| ____________ Yes, ≥ 1 patient per year
| ____________ Yes, ≥ 1 patient per month
| ____________ Yes, ≥ 1 patient per week |
| 15. a) Have you ever evaluated a patient for primary immunodeficiency diseases? | ```
| ____________ No (go to question 16)
| ____________ Yes |
| 15. b) What laboratory or imaging tests did you request? List them below: | ```
|____________________________________________________________________|
| 16. a) When evaluating patients for primary immunodeficiency diseases, do you know who to contact? | ```
| ____________ No (go to question 17)
| ____________ Yes |
| 16. b) List your contacts: | ```
| 17. Do you think it is safe to immunize patients with primary immunodeficiency diseases using the following types of vaccines? | ```
| ____________ No
| ____________ Yes |
| Live attenuated microorganisms |
| Inactivated |

Thank you for having taken the time to answer this questionnaire.