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Physicians Awareness on Primary Immunodeficiency Disorders in Iran

Keramat Nourijelyani¹, Asghar Aghamohammadi², Mohammad Salehi Sadaghiani², Nasrin Behniafard², Hassan Abolhassani^{1,3}, Sarvenaz Pourjabar², Alireza Rezvanizadeh², Joobin Khadamy², Amir Imanzaeh², Mojtaba Sedaghat³, and Nima Rezaei^{2,4}

¹ Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran

² Research Center for Immunodeficiency, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

³ Community Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁴ Department of Immunology, Molecular Immunology Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Primary immunodeficiency diseases (PIDs) consist of a group of genetic disorders that predispose the patients to immune-mediated complications. The aim of this study was to assess the knowledge of Iranian general practitioners and pediatricians about PIDs.

A questionnaire consisting 52 closed questions on clinical symptoms, laboratory data, associated syndromes and management of PIDs patients was made valid and reliable by a pair pilot study. Then the questionnaire was filled by pediatricians, general practitioners and pediatric residents from different regions of Iran.

Totally, 333 physicians (50 general practitioners, 52 pediatric residents, 182 pediatric specialists, and 49 pediatric sub specialists) participated in this study. 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 correctly more than two third of all questions. In order to qualitatively compare the groups a ranking system was used. Total scores was significantly different between physicians groups ($p < 0.01$). Pediatric subspecialties gained the highest rank, which was significantly over the other participants ($p < 0.05$).

This study showed that there is a considerable lack of awareness on PIDs in physicians. This may be one of the major reasons in late diagnosis and the delay in adequate treatment deteriorating patients' morbidity and mortality. Retraining classes and reconsidered educating schedules are needed as an efficient strategies and improving physicians' knowledge about PIDs.

Keywords: Awareness; Pediatricians; Primary immunodeficiency diseases

Corresponding Author: Asghar Aghamohammadi, MD, PhD;
Children's Medical Center Hospital, 62 Qarib St., Keshavarz Blvd.,
Tehran 14194, Iran. Tel: (+98 21) 6642 8998, Fax: (+98 21) 6692
3054, E-mail: aghamohammadi@sina.tums.ac.ir

INTRODUCTION

Primary immunodeficiency diseases (PIDs) consist of a group of genetic disorders that affect components

of the immune system, which predispose patients to both infectious and non-infectious immune-mediated complications.¹⁻⁴

Originally, PIDs were thought to be rare, but nowadays it has become clear that they are much more common.⁵ Among all physicians, primary care physicians and pediatricians are more likely to visit patients with PIDs in their practice; therefore, they should be familiar with these life-threatening disorders.⁶

The most significant clinical presentations in PIDs are infection,^{3,7} although the rate of autoimmune diseases and malignancies are also considerable among them.^{2,8} The consequent complications may lead to decrease in quality of life and even death in PIDs patients.⁹⁻¹³ The delay in diagnosis of PIDs patients is one of the important reason in occurrence of the permanent sequels.^{14,15}

Therefore, better quality of life, longer life saving therapy and precautions sequels establishment mainly depends on early diagnosis.¹⁵⁻²⁰

Unfortunately, the diagnosis of patients with PIDs is associated with a considerable delay.²¹ One of the responsible major problems is the lack of physicians awareness about PIDs, which was particularly pertinent to developing countries.²²⁻²⁵

The aim of this study was to evaluate the knowledge and practice of Iranian physicians about PIDs.

MATERIALS AND METHODS

Study Population

Population of this study was pediatricians (specialties and subspecialties), pediatric residents and general practitioners from different parts of Iran who participated in the 21st International Pediatrics Congress, October 2009 in Tehran, Iran.

Prior to data collection the study was approved in the ethic committee of the Ministry of Health in Tehran University of Medical Sciences. Demographic data, university certificate, duration of medical practice, place of medical practice, history of previous encounter with suspected or documented primary immunodeficient patients and overall score of awareness about PIDs were evaluated for each

participant. The survey was done before the initiating date of immunologic conferences.

Survey Approach

To assess a score of awareness of physician about PIDs, a prototype questionnaire was prepared based on questionnaire from a similar survey in Kuwait²⁵ which translated and modified by consulting professionals in PIDs and a professional in questionnaire making. A pilot study was performed to make the questionnaire reliable and valid (alpha koronbach= 0.7961, kappa=0.8127)

The final version of questionnaire with 52 closed questions was ready containing 26 questions on the clinical presentation of PIDs, 10 questions on associated diseases and syndromes, 14 questions were on laboratory investigations (Table 1). The last two questions were on the problems of physicians in managing PIDs patients and their needs to reeducation classes. The overall score of each participant was computed by adding the correct answers to these 52 questions. Passing the exam was defined as answering more than 2/3 of the questions.²⁵ Also in order to assess qualitatively, ten 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).

Data Analysis

The awareness scores transformed to a common 0–100 scale and the primary analyses included 333 physicians (The non-responder rate to single items was very low in total, 0.31%) who were fully compliant with the study protocol. Correlation analyses were done using Pearson's product moment correlation coefficients; statistical tests were two-tailed intra group. Pearson chi-square from crosstab was used to compare especial category with other ranks. Moreover, to handle many observations as possible, missing data for repeated measurements were imputed using an explicit regression model (i.e., repeated measure model with unstructured covariance matrix) that included previously observed scores of the participants as well as the important covariates.

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Table 1. The questions and scores*

Question	Correct answer	%
I-Clinical features		
What is the most important feature in a child with PID		
Malignancy		1.5
Recurrent Infections	Yes	85.9
Autoimmune disease		2.7
Growth failure		3.9
Not answered		6
Which of the following can be a clue to PID disease		
Lymphoid hypoplasia	Yes	73.6
Torticollis	No	41.1
Hypophyseal failure	No	28.2
Eosinophilia with erythrodermia	Yes	58.3
Polydactylia	No	31.8
Frequent common colds	No	18.6
Frequent oral candidiasis at the age of two	Yes	91
More than 3 weeks delay in umbilical cord separation	Yes	81.1
Angioedema	Yes	47.1
Delay in shedding the deciduous teeth	Yes	41.7
Simultaneous existence of two internal infections	Yes	85
Lymphoid hyperplasia	Yes	56.2
Wilms tumor	No	33.9
Hypoparathyroidism	Yes	43.8
Pneumocystis jiroveci pneumonia	Yes	76
Neonatal botulism	No	39
Poliomyelitis after receiving oral polio vaccine (OPV)	Yes	70.6
Failure to thrive	Yes	82.3
History of 3 otitis media during childhood	No	29.1
Partial albinism	Yes	47.4
Eczema and subcutaneous bleeding	Yes	63.1
Bronchiectasia	Yes	75
True or false		
The signs or symptoms of PID patients can emerge after the 6 months of age, when the maternal antibodies are diminished	Yes	80.8
The signs or symptoms of PID patients can emerge during the third decade of life	Yes	43.8
The signs or symptoms of PID patients can emerge from the time of birth	Yes	66.7
II- Associated symptoms and diseases		
Which of the following is associated with PID		
Ehler-Danlos syndrome	No	34.5
Wiskott-Aldrich syndrome	Yes	77.8
Ataxia-Telangiectasia	Yes	72.4
Hypomelanosis of ito	No	17.4
Sturge-Weber syndrome	No	29.1
Kostman syndrome	Yes	46.5
Bardet-Biedle syndrome	No	20.7
Job's syndrome	Yes	57.7
Turner syndrome	No	48
Chediak-Higashi syndrome	Yes	82.6

III- Laboratory findings**Which of the following directly helps us in diagnosis a PID patients**

Lymphocyte stimulation tests	Yes	77.2
Fecal occult blood test	No	42.3
Antibacterial antibody response to previous vaccines	Yes	71.2
Blood urea nitrogen, creatinine	No	48.3
Determining superficial markers of lymphocytes	Yes	82.3
Anemia panel	No	26.1
Complete blood count and differential	Yes	78.1
Serum isohemagglutinins	Yes	57.4
Hepatic function panel	No	31.8
Candida and tetanus skin test	Yes	73.3

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 equals to 15,500	Yes	58
Small platelets and thrombocytopenia	Yes	61
Serum IgG concentration in an infant with 7 months of age equals to 420 mg/dl	No	18.6
Large granules in neutrophils	Yes	70.9

IV -Managing PID patients**Which of the following vaccines should not be administered in a child with PID**

Influenza A vaccine		
BCG	Yes	74.2
IPV		
Hepatitis B vaccine		

Which of the following medications decreases rate of infections in child with common variable immunodeficiency

Immunoglobulin replacement therapy	Yes	63.7
Recombinant interferon		
Recurrent blood transfusion		
Plasmapheresis		

Do you have difficulties in managing patients with PID	Yes	86.2
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Is retraining classes regarding the PID syndromes necessary for general practitioners and specialists	Yes	95.8
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* The score of each question is 100/52

RESULTS

A total of 333 pediatricians (50 general practitioners, 52 pediatric residents, 182 pediatric specialists, and 49 pediatric sub specialists) were included in the study which 61% of them were male. The median age of participants was 44 (range 26-88) years; the median years of practicing medicine was 16 (1-48) years.

Most of the participants (55.8%) worked in the state hospitals; 20.1% worked in their private clinics; 6.6% worked in non-state hospitals; Remaining participants (17.5%) worked in more than one center and had overlap between state, non-state hospitals and clinics. Nineteen percent of them were also academic staff in medical Universities. Most of the participants (252

persons=75.7%) had visited at least one suspected or documented PIDs case during their practice.

The mean total knowledge score was 55.9 with a standard deviation of 14.3. One hundred and five participants (31.9%) answered correctly more than 2/3 of all questions and passed the exam. The best scores were documented in management of PIDs (68.9±1.32%), which followed by laboratory findings (56.9±5.4%), clinical symptoms (57.3±9.78%) and associated syndromes (48.7±5.3%) respectively. Total scores of physicians were 46.4 ± 13.7 for general practitioners, 54.8±14.8 for pediatric specialties, 61.5±18.4 for pediatric residents, and 63.8±14.5 for pediatric subspecialties. The scores were found to be independent of gender ($p=0.54$).

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According to the mentioned qualitative ranking system, the performance of the groups involved in this study is demonstrated in table 2. Based upon the qualitative assessment, the rank between different groups of physicians was significantly different ($p<0.01$). General practitioner perceived the lowest rank as "low- medium", pediatric residents along with pediatric specialists remained in the "high-medium" group and sub-specialist gained the "high" rank. The subspecialists' rank significantly was above practitioners ($p<0.01$) and pediatric specialists

($p<0.05$). Moreover the rank of residents was significantly more than general practitioners ($p< 0.01$). Furthermore, visiting 6 or more than 6 patients significantly increased the rank from low-medium to high ($p<0.05$). Moreover, working at state hospitals significantly was associated with higher rank ($p<0.05$). The period of time passed from graduation of physician had reverse association with their scores ($r=-0.26$, $p <0.001$) especially in the scores of associated syndromes ($r=-0.75$, $p <0.001$) (Table 2)."

Table 2. Comparison of awareness score in different groups of 333 Iranian physician

Age group	Number (%)	Mean of scores (±SD)	Qualitative ranking	Post Hoc P value	P value
≤29 years old	32 (9.6%)	56.5± 10.3	High-medium	-	<0.001
30-39 years old	97 (29.1%)	63.7± 8.9	High	(with more than 60<0.001)	
40-49 years old	112 (33.6%)	59.8 ± 8.8	High-medium	-	
50-59 years old	46 (13.8%)	53.3± 9.8	High -medium	-	
≥60 years old	46 (13%)	50.2 ± 6.5	High -medium	(with 30-39<0.001)	
Sex					
Male	204(61.3%)	56.2 ±10.0	High-medium	-	0.54
Female	129(38.7%)	55.4 ± 9.2	High-medium	-	
Place of medical practice					
A (Only in Governmental hospital)	188(55.8%)	62.4± 9.0	High-medium	(with G<0.001)	<0.001
B (Only in Private hospital)	22(6.6%)	54.3±10.3	High-medium	-	
C (Only in Private office)	67(20.1%)	53.6±9.6	High-medium	-	
D (Governmental hospital and Private hospital)	8(2.4%)	64.7±5.6	High	(with G<0.001)	
E (Governmental hospital and Private office)	23(9.4%)	63.0±10.0	High	(with G<0.001)	
F (Private hospital and Private office)	14(4.2%)	50.6±8.8	High-medium	-	
G (Governmental hospital and Private hospital and Private office)	5(1.5%)	42.4±3.8	Low-medium	(with A<0.001) (with D<0.001) (with E<0.001)	
University certificate					
General practitioner	50(15%)	46.4 ±13.7	Low-medium	(with resident<0.01) (with SS= 0.001)	<0.01
Pediatric specialist	182(54.7%)	54.8± 14.8	High-medium	(with SS<0.05)	
Sub-specialists	49(14.7%)	63.8± 14.5	High	(with GP*=0.001) (with specialist<0.05)	
Pediatric resident	52(15.6%)	61.5±18.4	High-medium	(with GP<0.01)	
Being faculty member					
Yes	63(18.9%)	56.52±18.6	High-medium	-	0.78
No	270(81.1%)	54.1±18.1	High-medium	-	
Previous encounter with suspected or documented primary immunodeficient patients					
<6 patients	206 (61.8%)	43.1±17.5	Low-medium	-	0.01
>6 patients	46 (13.8%)	69.2±15.1	High	-	

GP: General Practitioner; SS: Sub-specialists

DISCUSSION

PIDs are a group of inherited primarily disorders of the immune component system.^{8,26,27} Among 180 distinct PIDs, knowledge about 20 most prevalent diseases can account for >90% of cases. The disorders vary in the severity and spectrum of symptoms, but without effective and early treatments, they can be fatal. A high index of suspicion and prompt diagnosis can lead to lifesaving treatment and substantial improvement in quality of life for persons with PIDs.

Despite advances in new molecular techniques on human genomics for identification of the responsible gene defects and in development of new therapeutic methods such as gene therapy,^{16,18,28-30} there are many lack in the public health intervention for this group of diseases.

However, appropriate defining characteristics of PIDs by common feature of increased susceptibility to chronic and recurrent infections make them candidates for a more public health attention. Prompt diagnosis and treatment of PIDs patients can be lifesaving and result in marked improvements in the quality and length of life. Therefore the foundation for a public health intervention to improve the health status of persons with PIDs is increase in accuracy of diagnostic methods; and the efficacy of early interventions. Additional obstacles include the difficulty of diagnosis in the absence of a high index of suspicion and the lack of awareness among health-care providers, which impedes the timely recognition of affected persons.

To address these impediments and improve health outcomes among patients with PIDs, Centers for Disease Control and Prevention (CDC) and associates have adapted a population-based public health framework developed as part of CDC's strategic plan for genomics and public health, for the problem of PIDs (Available at <http://www.cdc.gov/genomics/about/strategic.htm>).

In November 2001, CDC convened a multidisciplinary panel of specialists to identify and discuss public health strategies that can be applied to PIDs (Available at <http://www.cdc.gov/genomics/info/conference/PIsynop.htm>).

During the meeting, specialists in clinical immunology, public health, genetics, pediatrics, health communication, and ethics from state and federal agencies, academic centers, professional organizations, and advocacy foundations discussed the public health

framework relating to PIDs. The framework has four components as follows: 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;³¹ 3- Evaluation of screening and diagnostic tools to ensure their quality and appropriateness for identification of patients with PIDs; and 4- Communication with health-care providers and the public to facilitate prompt and appropriate diagnosis and intervention.

CDC has begun to apply this framework in the context of ethical, legal, and social considerations in different conditions.³²⁻³⁴ However, educational efforts have the first priority because of the role of education on each four mentioned components. Targets of education are three major subsets of PIDs as priorities for a systematic public health assessment; include profound T-cell defects, because of their resulting high mortality in the absence of interventions; antibody deficiencies, and due to the substantial number of persons affected and the high burden of morbidity; and Chronic granulomatous disease (CGD), because of the existence of an established data set.

All these framework components need to trained and reevaluate in physicians especially pediatrics, and clinical immunologists.

Review of data obtained from National Primary Immunodeficiency Registry of Iran has shown that the mean delay in diagnosis of PIDs was almost 4 years.^{35,36}

According to basis lack of knowledge in target physicians in this study, educations of primary-care physicians group must be considered to achieve early clinical recognition by following items: lessons on the effect of early interventions on morbidity and mortality associated with PIDs, identification of a group of diseases that can benefit from using an early clinical recognition algorithm include Severe combined immunodeficiency, X-Linked Agammaglobulinemia, Common variable immunodeficiency, CGD, evaluate the usefulness and accuracy of family history, early clinical signs and symptoms and initial laboratory tests for early recognition of PIDs. Then a national system for early clinical recognition of PIDs and conduct

collaborative studies among clinical centers in selected PIDs should be established.

Although these educational efforts have been ongoing for years in our country, outcomes have not been formally evaluated which led us to perform this study. Among the Iranian pediatricians who participated in this survey, awareness about the PIDs was in high-medium qualitative rank.

In this study the main cause of low knowledge in target group was general deficit in both the knowledge and practice of pediatricians in the field of PIDs which recently has also been reported in another study in Kuwait.²⁵ Although clinical manifestations of PIDs were the most important items for diagnosis; this did not appear to be well in the knowledge of Iranian pediatricians.

Most of our pediatricians did not have enough knowledge about application of para-clinical tests for their patients, but they had in desirable level of knowledge about treatment of PIDs patients.

Although those with previous PIDs patients are more likely to have high knowledge, the proportion of these physicians who had performing well interventions remains at or below 50%.

The exact limitation of this study was due to non-responders and also who did not attend the congress which may lead to selection bias.

Amazingly, knowledge of PIDs among more experienced pediatricians with higher qualification and higher ranking was not different significantly when compared to less experienced ones. This may be related to limited availability or awareness of the pediatricians about PIDs programs. We therefore recommend implementation of strategies to improve the awareness of pediatricians about PIDs to early interventions with intravenous immunoglobulins.

These strategies may include comprehensive under- and post-graduated education, organizing educational courses, and publishing educational materials. Pediatricians should also be educated about the warning signs of PIDs.

Despite rapid developments in the science of PIDs, these diseases have still a significant impact into the health system. Continuing medical education after graduation can increase the knowledge of physicians especially in younger physicians. An understanding of the reasons for lack of awareness can help us to decrease the number of mismanaged PIDs patients. With this information about pediatricians' PIDs care

practices, perceptions, and beliefs; it may be possible to conduct targeted interventions to improve primary care for PIDs in Iran

REFERENCES

1. Lee PP, Lau YL. Primary immunodeficiencies: "new" disease in an old country. *Cell Mol Immunol* 2009; 6(6):397-406.
2. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999; 92(1):34-48.
3. Stiehm ER, Chin TW, Haas A, Peerless AG. Infectious complications of the primary immunodeficiencies. *Clin Immunol Immunopathol* 1986; 40(1):69-86.
4. 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.
5. Casanova JL, Fieschi C, Bustamante J, Reichenbach J, Remus N, von Bernuth H, et al. From idiopathic infectious diseases to novel primary immunodeficiencies. *J Allergy Clin Immunol* 2005; 116(2):426-30.
6. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol* 2007; 27(5):497-502.
7. Eades-Perner AM, Gathmann B, Knerr V, Guzman D, Veit D, Kindle G, et al. The European internet-based patient and research database for primary immunodeficiencies: results 2004-06. *Clin Exp Immunol* 2007; 147(2):306-12.
8. Chapel H, Geha R, Rosen F. Primary immunodeficiency diseases: an update. *Clin Exp Immunol* 2003; 132(1):9-15.
9. Sigstad HM, Stray-Pedersen A, Froland SS. Coping, quality of life, and hope in adults with primary antibody deficiencies. *Health Qual Life Outcomes* 2005; 3:31.
10. Zebracki K, Palermo TM, Hostoffer R, Duff K, Drotar D. Health-related quality of life of children with primary immunodeficiency disease: a comparison study. *Ann Allergy Asthma Immunol* 2004; 93(6):557-61.
11. Nicolay U, Haag S, Eichmann F, Herget S, Spruck D, Gardulf A. Measuring treatment satisfaction in patients with primary immunodeficiency diseases receiving lifelong immunoglobulin replacement therapy. *Qual Life Res* 2005; 14(7):1683-91.
12. Mozaffari H, Pourpak Z, Pourseyed S, Moin M, Farhoodi A, Aghamohammadi A, et al. Health-related quality of life in primary immune deficient patients. *Iran J Allergy Asthma Immunol* 2006; 5(1):23-7.

13. Dinakar C. Alleviating disease burden in primary immunodeficiency diseases. *Ann Allergy Asthma Immunol* 2006; 96(2):260-2.
14. Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J Med* 1993; 86(1):31-42.
15. Champi C. Primary immunodeficiency disorders in children: prompt diagnosis can lead to lifesaving treatment. *J Pediatr Health Care* 2002; 16(1):16-21.
16. Buckley RH. Primary immunodeficiency diseases due to defects in lymphocytes. *N Engl J Med* 2000; 343(18):1313-24.
17. Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999; 134(5):589-96.
18. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. *Blood* 2002; 99(3):872-8.
19. Antoine C, Muller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, et al. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968-99. *Lancet* 2003; 361(9357):553-60.
20. 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.
21. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. *J Clin Pathol* 2005; 58(5):546-7.
22. 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.
23. 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.
24. Al-Herz W, Naguib KK, Notarangelo LD, Geha RS, Alwadaani A. Parental Consanguinity and the Risk of Primary Immunodeficiency Disorders: Report from the Kuwait National Primary Immunodeficiency Disorders Registry. *Int Arch Allergy Immunol*; 154(1):76-80.
25. 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.
26. Puck JM. Primary immunodeficiency diseases. *Jama* 1997; 278(22):1835-41.
27. Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. *Clin Exp Immunol* 1999; 118 Suppl 1:1-28.
28. Aiuti A, Slavin S, Aker M, Ficara F, Deola S, Mortellaro A, et al. Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. *Science* 2002; 296(5577):2410-3.
29. Buckley RH. Advances in the understanding and treatment of human severe combined immunodeficiency. *Immunol Res* 2000; 22(2-3):237-51.
30. Cavazzana-Calvo M, Hacein-Bey S, Yates F, de Villartay JP, Le Deist F, Fischer A. Gene therapy of severe combined immunodeficiencies. *J Gene Med* 2001; 3(3):201-6.
31. 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.
32. 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.
33. McDonnell SM, Witte DL, Cogswell ME, McIntyre R. Strategies to increase detection of hemochromatosis. *Ann Intern Med* 1998; 129(11):987-92.
34. Wetterhall SF, Cogswell ME, Kowdley KV. Public health surveillance for hereditary hemochromatosis. *Ann Intern Med* 1998; 129(11):980-6.
35. Mir Saeid Ghazi B, Aghamohammadi A, Kouhi A, Farhoudi A, Moin M, Rezaei N, et al. Mortality in Primary Immunodeficient Patients, Registered in Iranian Primary Immunodeficiency Registry. *Iran J Allergy Asthma Immunol* 2004; 3(1):31-6.
36. 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.