Review Article

Iran J Pediatr
Mar 2010; Vol 20 (No 1), Pp:16-34

History of Primary Immunodeficiency Diseases in Iran

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Received: *Sep 25, 2009*; Accepted: *Dec 30, 2009*

Abstract

Pediatric immunology came into sight in the second half of 20th century, when pediatricians and basic immunologists began to give attention to diagnosis and treatment of children with primary immunodeficiency diseases (PIDs). Understanding the genetic and mechanistic basis of PIDs provides unique insight into the functioning of the immune system. By progress in basic and clinical immunology, many infrastructural organizations and academic centers have been established in many countries worldwide to focus on training and research on the immune system and related disorders. Along with progress in basic and clinical immunology in the world, pediatric immunology had a good progress in Iran during the last 33-year period. Now, patients with PIDs can benefit from multidisciplinary comprehensive care, which is provided by clinical immunologists in collaboration with other specialists. Patients with history of recurrent and/or chronic infections suggestive of PIDs are evaluated by standard and research-based testing and receive appropriate treatment. The progress in PIDs can be described in three periods. Development of training program for clinical fellowship in allergy and immunology, multidisciplinary and international collaborative projects, primary immunodeficiency diseases textbooks, meetings on immunodeficiency disorders, improvement in diagnosis and treatment, and construction of Iranian primary immunodeficiency association, Students' research group for immunodeficiencies, Iranian primary immunodeficiency registry, and the immunological societies and centers were the main activities on PIDs during these years. In this article, we review the growth of modern pediatric immunology and PIDs status in Iran.

Iranian Journal of Pediatrics, Volume 20 (Number 1), March 2010, Pages: 16-34

Key Words: Iran; Immunodeficiency diseases; Registries; Research

Introduction

Inherited defects in the development/function of the immune system result in primary immunodeficiency diseases (PIDs). PIDs are a diverse group of genetic disorders that affect the development and/or function of the immune system. Affected individuals with PIDs are

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predisposed to a variety of infectious diseases as well as autoimmunity and malignancy. The infections in PIDs can occur repeatedly, severely and atypically damaging the organs and reducing quality of life[1-3].

Primary immunodeficiency diseases were originally felt to be rare, occur only in infants and young children and associated with severe clinical symptoms. However, as clinical experiences with the PIDs have grown, it has become clear that they are much more common than originally thought. The diseases can be present in older children, adolescents and adults, and they can be associated with relatively mild clinical disease in some patients. Increase in the knowledge of basic immunology and human genetics has led to recognition of several distinct immunodeficiency disorders and their underlying genetic causes during the last decade and more than 180 different PIDs are classified by the International Union of Immunological Societies (IUIS)[2,4], with about 20 new ones per year[5]. The overall frequency of PIDs has been estimated about 1:10,000 individuals[6].

Early diagnosis and adequate therapy are the keys to survival and a better quality of life, while delays in diagnosis and/or inadequate management may lead to permanent organ damage and shortening lifespan[7,8].

Understanding the genetic and mechanistic basis of PIDs provides unique insight into the functioning of the immune system. These progresses lead to translational research to provide better care for affected individuals. By progress in basic and clinical immunology, many institutions and academic departments have been organized to focus on research and educational resources to provide training and encourage collaborative research on the immune system and related disorders. Along with this progress, clinical immunology and activities on PIDs has good progress in Iran since 33 years ago. In this review, we try to introduce the situation of PIDs in Iran.

Brief History of Immunology and Primary Immunodeficiency Diseases

The first concept of immunology is believed dated to 9th century, when Zakariya Razi (Rhazes, 864-930 C.E.)[9], a Persian physician, described first clinical observation of immunity, arisen from a specific disease causing organism.

Although some descriptions resembling smallpox had been appeared in the earliest Egyptian, Indian and Chinese writings, the first clear description and distinction between smallpox and measles was provided by Zakariya Razi[9-12].

Louis Pasteur (1822–1895) and Robert Koch (1843–1910) established the germ theory of disease. Pasteur developed attenuated germs to vaccinate against fowl cholera, anthrax, and rabies; whereas Koch showed that passive transfer of tuberculin sensitivity could be accomplished with cells. In 1884, Elie Metchnikoff proposed the concept of cellular immune defense as the principal way that animals are protected against infectious disease agents[13]; and in 1890, Behring and Kitasato described specific humoral factor or antibody in the serum of animals which had received sub lethal doses of tetanus toxins[14].

Since beginning of 20th century, much attention focused on explanation of various types of antibody and their use in diagnosis and therapy. Although during first half of 20th century, several patients with characteristic clinical manifestations of immunodeficiency disorders such as complement deficiency (1919)[15], neutropenia (1922)[16], ataxia-telangiectasia (1926)[17], mucocutaneous candidiasis (1929)[18], Wiskott-Aldrich syndrome (1937)[19] had been reported, the birth of immunodeficiency is usually given as 1952, when Odgen Bruton reported the first case of agammaglobulinemia[20].

Pediatric immunology and clinical immunology, in global, came into sight in the early 1950s, when pediatricians and basic immunologists began to give attention to clinical and basic research related to normal and defective immune system.

Since first report of X-linked agammaglobulinemia in 1952, more than 150 different types of PIDs have been identified[2].

The discovery of PIDs and characterization of these diseases led to crucial contributions to understanding the functional organization of the immune system and molecular biology. Thus, the study of PIDs has contributed to progress in

immunological and molecular diagnostic techniques[3]. As a result of these advances and a major biotechnology breakthrough, new therapeutic strategies such as hematopoietic stem cell transplantation and gene therapy have been devised leading to better care of infants and new therapeutic approaches to PIDs.

Highlights of Primary Immunodeficiency Diseases in Iran

Along with progress in medical sciences in Iran, knowledge and activities in the field of PIDs have developed during last three decades. This progress can be described in three periods as follow:

First period (1978-1988): First period began in 1970s when Professor Abolhasan Farhoudi returned to Iran after training in the field of pediatric immunology and allergy in the United Kingdom. He established the division of Clinical Immunology and Allergy at Children's Medical Center.

Second period (1988-1997): In the second period that starts in 1988, the training program for clinical fellowship in the field of Pediatric Allergy and Immunology was established. Subsequently the clinics for affected patients with PIDs were extended and a unit for patients, who needed intravenous immunoglobulin infusion, was also established.

Third period (1997-2009): In 1997, a group of junior doctors and students joined seniors in this filed to establish Iranian Primary Immunodeficiency Registry (IPIDR). Their scientific activities were focused on many areas of modern PIDs, both basic and disease oriented.

Several research collaborations with national and international centers and lots of publications were part of activities in this period, while improving the diagnosis of PIDs by developing molecular methods, construction of Iranian Primary Immunodeficiency Association (IPIA), and establishment of Immunology, Asthma and Allergy Research Institute (IAARI) were other activities which led to better management of the patients with PIDs. First International Congress on Immunodeficiencies was organized in Tehran in this period, whilst a number of Iranian scientists had active participation in other international congresses as well.

Increasing knowledge of physicians and patients using different media was also considered as a priority in this period.

Although several progresses occurred during these three periods, some significant and important events will be described in the following sections with more details.

Training Program for Clinical Fellowship in Allergy and Immunology

Professor Abolhasan Farhoudi (1924-2006)[21], well-known pediatrician and pioneer in pediatric immunology and allergy in Iran is the first physician who worked in the field of pediatric immunology in Iran. He was trained in the United Kingdom by Late Professor Soothill at Great Ormond Street Hospital. Upon returning to Iran in 1977, he established the division of Clinical Immunology and Allergy as well as Immunology Laboratory in Children's Medical Center affiliated to Tehran University of Medical Sciences. In addition to presenting lectures on clinical immunology, he was interested in training and encouraging pediatric residents to continue their carrier in the field of clinical immunology[22,23].

In 1988, Professor Farhoudi and his colleagues, including Reza Farid Hosseini, Reza Amin and Naser Javahertarash established the training program for clinical fellowship in the field of Pediatric Allergy and Immunology. The goals of the educational program for fellowship were to provide a comprehensive training milieu for better understanding of the basic immunology principles and their application to the clinical immunology. Since the beginning of training program for clinical fellowship in immunology and allergy, more than 35 pediatric immunologists have been trained in four Universities in Iran, including Tehran, Mashhad, Shiraz, and Iran Universities of Medical Sciences.

Although there is a wide variation of clinical immunologists per capita in different countries in the world[24], 1 clinical immunologist per 500,000 population is considered the required sub-specialists for Iran, based on incidence of allergy in the country, high rate of consanguineous marriages and geographical location. Therefore considering the current population of Iran, more than 100 additional clinical

immunologists should be trained in future.

Establishment of Intravenous Immunoglobulin Infusion Unit

Many patients with PIDs require regular immunoglobulin replacement therapy[3]. Intravenous immunoglobulin (IVIG), a blood product prepared from the serum of human, is the treatment of choice for patients with antibody deficiency diseases. IVIG is used at a replacement dose of 400–500 mg/kg, given approximately every 3-4 weeks[25]. Decision about the use of IVIG replacement in the management of patients with PIDs is critical.

IVIG therapy is important to reduce mortality from life-threatening invasive infections. Timely institution of IVIG prevents the development of end-organ damage such as bronchiectasis, which causes significant morbidity and increased mortality for these patients. Because of the risk of adverse reactions during IVIG infusion, it should be administered under supervision of physicians and trained nurses who are aware of these reactions. In 1995, the immunoglobulin infusion unit was established in the Children's Medical Center. This unit serves twice weekly; all patients with hypogammaglobulinemia, including antibody deficiency and combined immunodeficiency, who receive IVIG in this unit are monitored by trained nurses and clinical fellows.

Since establishment of this unit, regular monitoring of the patients who receive IVIG has been performed and efficacy of this treatment was studied[26-28], while adverse reactions of this treatment were regularly recorded[29,30].

Our preliminary results indicated that the incidence of pneumonia in patients with agammaglobulinemia significantly decreased from 0.82 per patient per year before diagnosis to 0.12 per patient per year after IVIG administration. Hospitalization due to pneumonia also significantly decreased from 0.58 to 0.05 per patient per year[26]. The incidence of pneumonia in the patient with common variable immunodeficiency also significantly decreased from 3.4 per patient per year before diagnosis to 0.7 per patient per year after IVIG therapy. These data can show importance of early diagnosis and appropriate treatment with IVIG in this group of patients, which could prevent further complications and improve quality of life of the patients.

However, a number of patients experience some adverse events in the course of their therapy. In order to manage and prevent adverse events in these patients, IVIG should be administered under supervision of physicians and trained nurses who are aware of these reactions. Our recent report on a total of 3004 infusions during 13-year period showed that about 7% of infusions were associated with adverse reactions, while these reactions are usually mild and only 3 severe reactions were recorded in this period[30].

Students' Research Group for Immunodeficiencies

In 1997, a group of interested medical students from Student Scientific Research Center (SSRC) affiliated to Tehran University of Medical Sciences started their activities in the field of PIDs under supervision of pediatric immunologists in Children's Medical Center to construct a database for registration of Iranian patients with PIDs. They established the Iranian Primary Immunodeficiency Registry (IPIDR) in 1999; and substantially the number of interested people has risen and this expansion has been commensurate with a growth in the complexity of the group, necessitating a clearer definition of the purposes and activities. Each year, a number of medical students join the Students Research Group for Immunodeficiencies (SRGID) to focus their activities in the field of PIDs. Some junior members find a number of achievements during their activities. Being a member of some international societies such as European Academy of Allergology and Clinical Immunology (as an EAACI affiliate junior member) and European Society for Immunodeficiencies (as an ESID junior member) helped some to have better interactions with other scientists around the world, whilst some had a chance to get travel grants to attend the international congresses to present their studies. The members of SRGID, which is currently considered as a Real Research Experience (RRE) in SSRC, usually start their work by presenting some lectures among the group and learning some basic and clinical

immunology as well as methodology of research and scientific writing. However, a number of these members continue their activities by doing specific research projects. They consequently have active contribution in preparing scientific papers and active attendance of international congresses.

Iranian Primary Immunodeficiency Association (IPIA)

As discussed, it has been shown that patients with PIDs are often diagnosed with a substantial delay[7,8]. It has also been demonstrated that shortage of awareness among family physicians and general practitioners contribute greatly to this delay. Therefore, it is expected to increase the knowledge on PIDs among medical professionals. At the same time the community needs to be aware of these disorders for an on time medical consultation.

In order to achieve aforementioned goals, the working groups and NGOs must convince the authorities, governmental bureaus and profitable organizations to sponsor programs and research in the field of PIDs. This necessitates a comprehensive project to make needed materials available to target groups. In order to support the patients with PIDs, The Iranian Primary Immunodeficiency Association (IPIA) as a national non-profit organization was founded in 1998. It is dedicated to improving the diagnosis and treatment of patients with PIDs through research and education. IPIA is governed by an active Medical Advisory Committee comprised of prominent clinical immunologists, a nationwide volunteer support network.

In this regard the IPIA made periodical meetings and reunions with authorities as consultants of related ministries, assembly members and other governmental organizations as well as commercial units. This is an attempt to inform them about the importance of research and activity for patients with PIDs.

The goal of the IPIA is to develop a program to help individuals overcome these difficulties and live a healthy and productive life in the following areas:

1. To increase the understanding of PIDs among the medical community, patients and families of patients.
2. To introduce the concept of immunity and its primary defects in human to the general population.
3. To catch the attention of authorities to take the significance of PIDs into account when making health national policies.
4. To support research into safe and effective treatments and ultimately a cure for these conditions.

IPIA had several activities to promote awareness among the medical community as well as the general public about PIDs. A poster showing 10 Warning Signs of PIDs was designed in Farsi language (Fig. 1), which is the modified version of the poster that was originally prepared by Jeffrey Modell Foundation (JMF). This poster was distributed to all medical university hospitals to increase the awareness of medical personnel in this regard.

Fig. 1: Ten warning signs of primary immunodeficiency diseases, prepared by Iranian Primary Immunodeficiency Association (in Farsi language)

Fig. 2: Patients' organizations in the world that are part of the International Patient Association for Primary Immunodeficiencies

The IPIA, which has been recognized as a global organization working to improve the quality of patients with PIDs, is currently a voting member of the International Patient Association for Primary Immunodeficiencies (IPOPI) (www.ipopi.org) (Fig. 2).

Iranian Primary Immunodeficiency Registry (IPIDR)

Epidemiological studies have shown wide geographical and racial variations in terms of prevalence and pattern of PIDs. Many countries worldwide have developed registries to estimate the prevalence and characteristics of different PIDs phenotypes among their population[31-40].

In order to determine the frequency and characteristic features of various PIDs in Iran, we established the Iranian Primary Immunodeficiency Registry (IPIDR) in August 1999. In this registry, which is located in the Children's Medical Center[41], the main referral center for immunodeficiency diseases, the clinical files of all patients were reviewed in the past 20 years and afterward. This registry covered major University Hospitals in Iran, where immunodeficiency clinics and immunological laboratories were available. The main goals of registry were to determine the frequency of different types of PIDs in Iran, to stress the importance of teaching the clinical immunology in the medical curriculum, to enhance the knowledge about these diseases among general practitioners and pediatricians, and to promote research about PIDs in our country.

The process of patients' registration in IPIDR consisted of following steps: The preliminary one-page questionnaires had been sent to all participating centers. After making definite diagnosis by clinical immunologists, the centers were asked for sending additional information using four-page questionnaires. Then patients were registered in our database[42].

The preliminary results in the year 2002 revealed that 440 patients with PIDs had been registered[43]; however, this number was

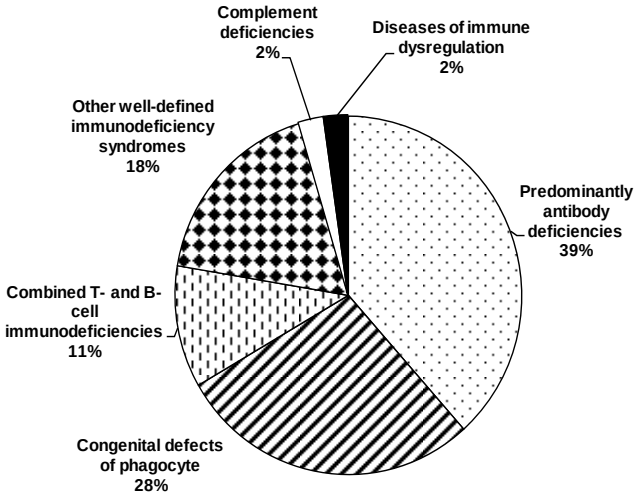

Fig 3: Frequency of different types of PIDs, based on the second report of the national registry in Iran[43]

increased to 930 patients in the year 2006, when the second report of our registry was published, which represented all registered patients in the country registered during three decades[42]. Among them, predominantly antibody deficiencies were the most common, followed by congenital defects of phagocyte, other well-defined immunodeficiency syndromes, combined T- and B-cell immunodeficiencies, complement deficiencies, and diseases of immune dysregulation[42] (Fig 3). Overall, consanguinity rate among parents of PIDs patients was estimated around 65%, which was higher than in normal population[42,44].

Research Projects

Several basic and clinical research projects on PIDs were designed and completed during last decade. Some descriptive studies on series of children and adult patients with specific disorders from this region were reported in early 21st century[42,43,45]. Clinical and laboratory characteristics of patients with common variable immunodeficiency (CVID)[46], X-linked agamma-globulinemia (XLA)[47], selective IgA deficiency [48], severe combined immunodeficiency (SCID) [49], ataxia-telangiectasia syndrome [50], chronic mucocutaneous candidiasis[51], severe congenital neutropenia (SCN)[52], cyclic neutropenia[53], chronic granulo-matous disease (CGD)[54], hyper IgE syndrome (HIES)[55], leukocyte adhesion defects (LADs)[56], Chediak-Higashi syndrome (CHS)[52,57], and Shwachman-Diamond syndrome (SDS)[52] were well described. However, after developing molecular diagnosis, recent studies on XLA[58,59], hyper IgM syndromes[60], Griscelli syndrome type 2 [61] CGD[62,63] and SCN[64] provided the results of mutation analysis of the patients as well (Table 1). In addition to several original papers as results of research projects published during last decade, some other case series and several interesting case reports are also published[28,65-90].

Different aspects of patients with different types of PIDs were investigated; here, a brief report on what has been done on CVID, one of these disorders, is given as an example: 65 patients with diagnosis of CVID who suffered from recurrent infections, mainly in the respiratory[91] and gastrointestinal systems[92,93], were described in an original paper in the year 2005[46]. Although bronchiectasis is the major complication of the disease[94], autoimmune disorders [95] and malignancies[96,97] could also be seen in this group of patients, which increase morbidity and mortality of the patients[94].

Although the underlying cause of CVID still remains unknown, several investigations in this patient group showed a number of humoral and cellular defects, including switched memory B

Table 1: Published papers on specific primary immunodeficiency diseases

Disease	No of studied patients	Year of report	Reference
Chediak-Higashi syndrome	6	2003	[57]
Chronic granulomatous disease	41	2004	[54]
Cyclic neutropenia	7	2004	[53]
Common variable immunodeficiency	65	2005	[46]
Chronic mucocutaneous candidiasis	3	2005	[51]
Shwachman-Diamond syndrome	7	2005	[52]
X-linked agammaglobulinemia	37	2006	[58]
Hyper IgE syndrome	22	2006	[55]
Ataxia-Telangiectasia syndrome	104	2007	[50]
Severe congenital neutropenia	18	2007	[64]
Leukocyte adhesion defects	15	2007	[56]
Severe combined immunodeficiency	40	2008	[49]
Griscelli syndrome type 2	9	2008	[61]
Hyper IgM syndromes	23	2009	[60]
Selective IgA deficiency	37	2009	[48]

cells, T cell function and cytokine production, and dendritic cells[98-104]. Cytokine gene polymorphisms and mannose-binding lectin (MBL) polymorphisms were investigated in this group of patients, which showed an association between specific polymorphisms and disease[105-108].

Furthermore a group of CVID pediatric patients with parental consanguinity had chromosomal radiosensitivity[109], which may suggest an autosomal recessive pattern of inheritance in this heterogeneous group of disorders[110]. Further molecular studies in collaboration with international centers revealed some novel mutations in the TACI (TNFRSF13B) gene[111].

Multidisciplinary Projects

Due to different organs involvement in individuals with PIDs, designing multi-disciplinary projects was a priority in the recent years. Evaluation of different systems were performed in the patients with PIDs, particularly, respiratory system, gastrointestinal tract and ear, nose and throat (ENT)[91,92,112-115].

ENT evaluation of more than 100 patients with primary antibody deficiencies revealed that about 75% of patients experienced ENT infections during the course of the disease[112].

Moreover evaluation of the immune system in those with specific symptoms referred to other setting could lead to early diagnosis of affected patients. The study on more than 100 patients with history of recurrent or chronic ENT infections revealed that about 15% of cases have some defects in antibody-mediated immunity including CVID, IgA deficiency, IgG subclass deficiency and specific antibody deficiency[116]. Indeed study of humoral immune function in 40 bronchiectatic patients revealed that more than 35% of patients had defects in antibody mediated immunity including CVID, IgA deficiency, IgG subclass deficiency and specific antibody deficiency[117].

International Collaborative Projects

International collaborative studies had a significant effect on quality of ongoing projects in the region. Although some projects were performed with help and comments from international well-known PID experts[64,69,70,74,104,118-122], contribution to inter-national projects, especially those that led to discovering specific phenotypes and genetic defects had a major impact in improving the science in this field[123-129].

Reporting four cases from Iran, Sweden and Spain with IgA deficiency that progressed to CVID could suggest that these diseases may have share phenotype and underlying genetic defect, which is not limited to a country[118].

Consequently, further genetic studies on patients with IgA deficiency and CVID were designed[111,130].

Reporting some patients with hyper IgM syndromes with no mutation in CD40, CD40L, AID and UNG genes[60,73,131] encourage scientists for more studies in this group of patients for identification of new gene defect(s).

A number of international scientists participated in the regional projects, whilst Iranian scientists were also involved in some international projects. Study in the field of congenital neutropenia is a good example: While descriptive studies on SCN in Iran provided an update on status of disease in the country[52,132], identification of mutations in the HAX1 gene that lead to autosomal recessive form of severe congenital neutropenia[123] and discovering a new syndrome with congenital neutropenia associated with cardiac and urogenital malformations due to mutations in the G6PC3 gene[124] were the key publications that highlights this issue. Although mutations in the ELA2 gene can also lead to SCN[74], frequency of HAX1 deficiency in our region seems to be more common than previously expected[64], due to high rate of consanguineous marriages[44]. Some complications in the patients with HAX1 deficiency were further described such as fungal infections[66], and neurodevelopmental delay and convulsions[70]. Association of neurological disorders with HAX1 deficiency was first described in an Iranian patient with SCN who had R86X mutation in the HAX1 gene, which was consequently confirmed by further studies[133-135]. It seems that HAX1 isoforms may play a distinctive role in the neuronal system[127]. An update on SCN and other PIDs associated with neutropenia is published in a collaborative review paper[136].

Determination of mutation in the CARD9 gene in an Iranian family with susceptibility to fungal infections[125], contribution to the paper on patients with Mendelian susceptibility to mycobacterial disease who had mutations in IFNGR2 gene[129], and contribution to the paper on DOCK8 mutations in hyper-IgE syndrome[128] are some other achievements which were made based on an international collaboration.

Scientific Output

Contribution of Iranian scientists to the scientific output of the world has increased since 1970, particularly at the threshold of the 21st century[137]. Based on performed research projects in the field of PIDs, more than 150 articles and some books have been published.

The number of published papers in the field of PIDs in international journals which are indexed in the major databases, including ISI Web of Knowledge, MedLine (Pubmed) and Scopus was significantly increased during last decade. Using ISI Web of Science with search strategy of using keywords "primary immunodeficiency", some other specific immunodeficiencies and combination with address "Iran" indicated that more than 100 papers have been published in the field of PIDs since the year 2000 showing that the scientific output of the country has increased in the meantime. While only 1-2 papers per year had been published in this field at the beginning of 21st century from Iran, the number of publication increased to about 40 in the year 2008 (Fig. 4). Comparing with other Universities of Medical Sciences in Iran, Tehran University of Medical Sciences is the most prolific in such scientific output, while about 75% of these publications were as of active contribution of the scientists in this University. Shaheed Beheshti and Shiraz Universities of Medical Sciences had second and third roles in respect to PIDs publications. Among the international universities/institutes that had co-publication with the centers in Iran, the following centers could be named: Karolinska University Hospital (Sweden)), Hannover Medical School (Germany), Freiburg University Hospital (Germany), National Institute of Health (USA), University College of London (UK), University of Washington (USA), Toyama Medical and Pharmaceutical University (Japan), University of Brescia (Italy), and University of Sheffield (UK).

In order to see the current position of the country in the world in scientific output of PIDs the keyword "primary immunodeficiency" was searched in combination with some common immunodeficiencies such as "common variable immunodeficiency" or "agammaglobulinemia" or "IgA deficiency" or "combined immunodeficiency" or "Ataxia-Telangiectasia" or "chronic mucocutaneous candidiasis" or "congenital neutropenia" or "chronic granulomatous disease" or "hyper IgE" or " leukocyte adhesion

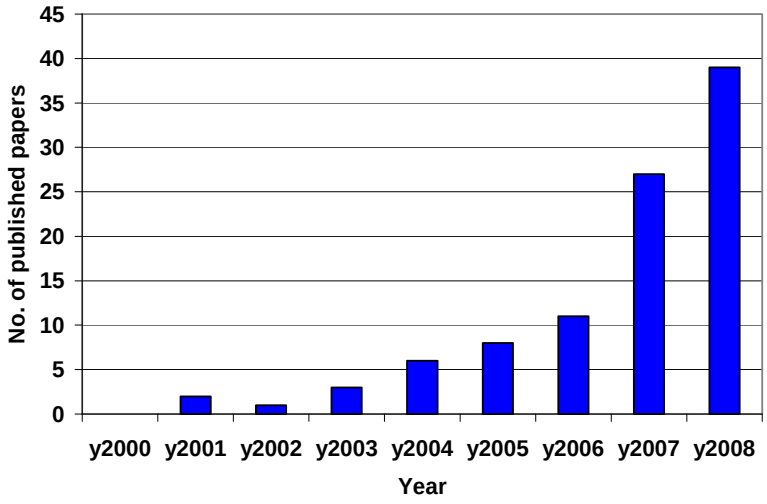

Fig. 4: Scientific output in the field of PIDs from Iran, using ISI Web of Science

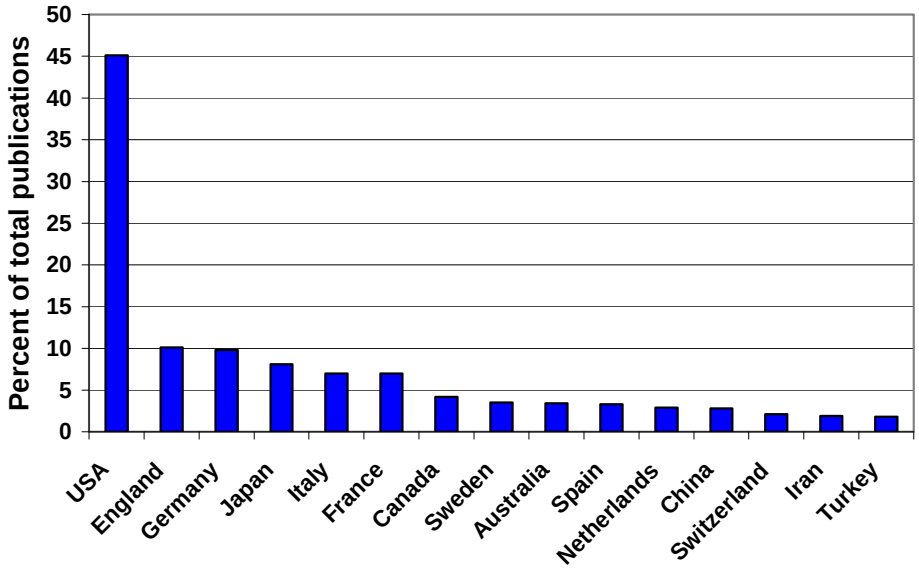

Fig. 5: Scientific output in the field of PIDs in different countries, using ISI Web of Science since 2006

defect" or "hyper IgM". Although more than 17,000 documents were found, approximately one fourth of the papers were published during the last 3 years (after the year 2005).

Using this search strategy, in general, Iran is placed at the 25th place considering the publications in the field of PIDs. However, in respect to rapid progress in scientific output of the country, Iran is currently located among top 15 countries that have a role in scientific output in the field of PIDs with about 2% of total publications during the last 3 years (Figure 5). Among the worldwide universities/institutes, Harvard University is the top institute in this field, whereas Tehran University of Medical Sciences is currently ranked as 10th center worldwide based on the 3-year scientific output in the field of PIDs. Although such kind of search has a number of limitations considering more than 150 types of PIDs and several genetic defects, it can emphasize the trend of scientific output in different countries.

Participation of Iranian scientists in international congresses was also prominent during last decade, while it is estimated that more than 200 abstracts in the field of PIDs were presented in the International congresses as either oral or poster.

Primary Immunodeficiency Diseases Text-Books

In order to increase knowledge and understanding of physicians, pediatricians, medical students, and patients and their families, five books have been edited and published.

"Primary Immunodeficiency Disorders in Iran" (Edited by Farhoudi A) is one of the first books in the field of PIDs in Iran, which is published in 2002 in collaboration with other clinical immunologists in Iran. "Immune System and Microorganisms" (Edited by Rezaei N, Aghamohammadi A, Pourpak Z, Mahmoudi M) is an interesting book, which was published by UNESCO Chair in Health Education, Tehran University of Medical Sciences in 2005. The book was dedicated to all patients with PIDs and their families. In the foreword of the book by a PID expert (from National Institutes of Health, USA), it was noted that "knowledge will allow patients and their family to understand, accept and even predict the natural evolution of the disease, which will give them control and the will to persevere. For this reason, the book accomplishes a function of critical importance as it helps bridging the gap between general medicine and rare diseases and provides physicians and family important tools that will

improve the quality of clinical management of patients with primary immunodeficiencies." Subsequently, two other books "Primary Immunodeficiency Disorders in Iran" (Edited by Aghamohammadi A, Pourpak Z, Rezaei N, Farhoudi A, Moin M) and "Treatment in Primary Antibody Deficiencies" (Edited by Aghamohammadi A, Parvaneh N, Yeganeh M) have been published and a new book entitled "Diagnosis and Treatment in Primary Immunodeficiency Disorders" (Edited by Aghamohammadi A, Khazaei HA, Rezaei N) is edited and to be published soon. Another title "Clinical Cases in Primary Immunodeficiency Diseases: A Problem-Solving Approach" is also agreed with Springer to be published in 2010.

"Primary Immunodeficiency Diseases: Definition, Diagnosis, and Management" (Edited by Rezaei N, Aghamohammadi A, Notarangelo LD) is a new text in PIDs which was published by Springer in 2008, as of main role of Iranian scientists with contribution of more than 40 senior and junior scientists in this field from more than 30 universities worldwide[3] (Fig. 6).

This book which is currently considered as a reference book for fellows of clinical immunology and allergy in the country was very welcomed by scientists all around the world. The book is an attempt to gather the most recent advances in this field, and tries to provide a concise and structured review of hitherto known PID. Although the ultimate orientation of the book is toward practical diagnosis and management, the pathophysiology of diseases is also discussed. An overview and update classification of PIDs is presented in the first chapter, whilst etiology, clinical manifestations, diagnosis, and management of each disease are discussed separately in other chapters. In the foreword of the book by PID experts (from Oxford [UK] Boston [USA] and Seattle [USA]), it is noted that "The recent appreciation of these conditions in Iran and the flood of papers describing patients with primary immune-deficiency diseases make it timely that many chapters in this volume should be authored by an Iranian investigator in combination with a recognized authority in the subject. It is a tribute to the rapid establishment of facilities in Tehran to both diagnose and treat such patients that this book could be written in record time thus ensuring that it is up-to-date as well as practical." and continued "The wide coverage of all aspects of primary immunodeficiency diseases provides a comprehensive text and will serve as a tool for experts who care for these patients in other geographical areas and who wish to spread awareness and understanding of this rapidly expanding field." Two reviews on this book have also been published in the Immunology News of British Society of Immunology (BSI)[138] and Journal of the American Medical Association (JAMA)[139].

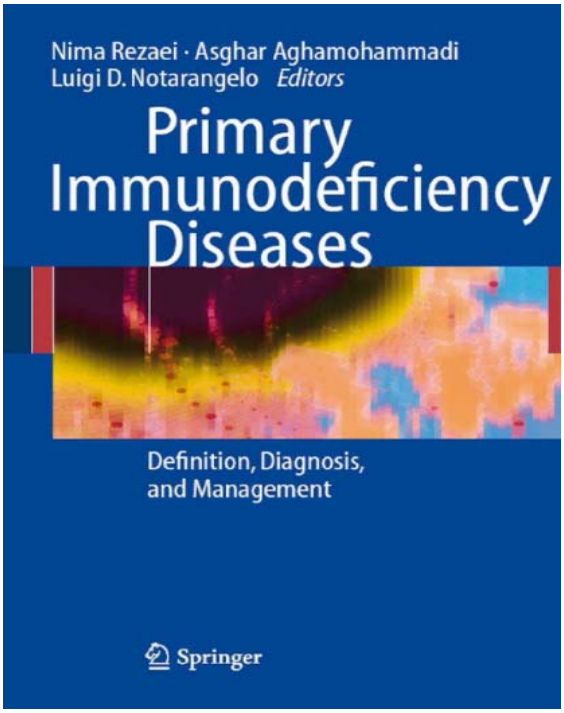

Fig. 6: The cover of the book "Primary Immuno-deficiency Diseases: Definition, Diagnosis, and Management". Springer Berlin and Heidelberg GmbH & Co. K. August 2008. ISBN: 978-3-540-78537-8

Meetings on Immunodeficiency Disorders

Several PID experts attended scientific congresses, especially International Congress of Pediatrics, in Iran during last decade to present an update on PIDs. In 2005 (28 February - 2 March), the first International Congress on Immunodeficiency Disorders (ICID) was organized in Tehran. A number of PIDs experts

from different countries (USA, UK, Germany, France, Italy, Sweden, Spain, Japan, and Turkey) attended the congress to present an update in this field, whereas many scientists and researchers took part in this congress to increase their knowledge. This congress was a great venue to have bilateral scientific exchange of Iranian scientists with other researchers of the world. The congress focused on the linkages of fundamental sciences and patient-oriented research under the main themes of immunodeficiencies, immunogenetics, immunodiagnosis and infections in six main sessions including immunodeficiency disorders, general aspects; B-cell deficiencies; T-cell deficiencies; Deficiencies of innate immunity, phagocytic cells and complement; secondary immunodeficiencies; and treatment in immunodeficiency disorders and other topics. Organizing several workshops along with the congress was part of the activities, including immunogenetic diagnosis in immunodeficiencies (PCR HLA-typing); immunodeficiency and nursing; molecular diagnosis of immunodeficiency; cancer in immunodeficiencies; vaccination and immunodeficiency disorders; and acquired immunodeficiency syndrome. A meeting for the patients with PIDs was also arranged at that time in collaboration with the IPIA. Contribution of all scientists, research workers and students in the field of basic and clinical immunology, genetics, infectious diseases and other related specialties contributed to the success of this congress.

Four years after this congress, the Primary Immunodeficiency Meeting was organized in Tehran, Iran as a J Project meeting. Each year an International Congress on Pediatrics, which is organized by the Department of Pediatrics in Tehran University of Medical Sciences, takes place in Tehran. On 11-12 October, 2009, alongside the 21st congress, a joint meeting on Immunodeficiency Diseases was established. This J Project meeting is planned to be repeated in 2010 in Tehran.

Improvement in Diagnosis and Treatment

The overall activities in the field of PIDs led to an increased trend in recognition of more patients in the recent years. It is estimated that more than 75% of the Iranian patients with PIDs were diagnosed in the recent decade, whilst the approximate number of diagnosed patients has increased from 7 patients per year in the 1980s to 30 patients per year during the early 1990s and 58 patients per year since 2000[42].

This rapid progress in identification of the patients with PIDs is important not only as of epidemiological aspect, but also as of timely diagnosis and appropriate treatment of the patients. It is well-understood that delay in diagnosis leads to several complications and even death in the patients with PIDs, whilst early diagnosis and proper management can prevent irreversible complications. It has been shown that the diagnosis of patients with PIDs has been made at an earlier age in more recent years. The diagnostic delay has been decreased from 7 years in the 1980s to 2.5 years in the 1990s, and 6 months since the year 2000[42].

While all activities related to awareness of medical personnel had main roles in this achievement, development of diagnostic techniques and greater access to more sophisticated molecular diagnoses had also great impact in precise diagnosis of patients.

Construction of DNA banking for the patients with PIDs[140] and transformation of B cell line[141] provide an opportunity to save genetic information of patients with PIDs for further molecular studies.

Availability of several therapeutic modalities and expanding management strategies for the patients with PIDs during last decade has led to better survival of affected individuals.

However, some optimal treatments such as bone marrow transplantation for patients with PIDs[142-144] are at the beginning which needs more experiences, especially for the pediatric patients.

Immunological Societies and Centers

Although this review focused on the activities related to PIDs, the role of immunological research centers and non-governmental organizations (NGOs) cannot be neglected, whilst they had major roles in improving the immunology science in the country in all these years. Therefore the main ones are briefly named here:

The “Immunology, Asthma and Allergy Research Institute (IAARI)”, affiliated to Tehran University of Medical Sciences, was approved in 1999, and officially began its scientific activities at the hospital of the Children's Medical Center on January 2001 (http://iaari.tums.ac.ir). Other centers that can be named are as follow: Mashhad Immunology Research Center (http://www.mums.ac.ir/immunology), Shiraz Institute for Cancer Research (http://www.icr.ir/), Hematology-Oncology Research Center and Stem Cell Transplantation (HORCSCT) (http://horcsct.tums.ac.ir), Growth and Development Research Center, Molecular Immunology Research Center, Iran Immunology Research Center, Infectious Disease Research Center, and Pediatric Infectious Disease Research Center.

The "Iranian Society of Immunology and Allergy (ISIA)" (http://www.isiairan.net) and the "Iranian Society of Asthma and Allergy (ISAA)" (http://www.isaa.hbi.ir) are two main active NGOs that had significant impact in the field of immunology by wide range of activities such as organizing bi-annually meeting and publications of two well-known journals "Iranian Journal of Allergy, Asthma and Immunology" (http://ijaai.tums.ac.ir) by the ISAA and "Iranian Journal of Immunology" (http://www.iji.ir) by the ISIA. Iranian Basic and Clinical Immunology Network (IBCIN) (http://www.ibcin.net) is also a new network in the country, which is constructed to develop collaboration between basic and clinical scientists.

Current Problems

In spite of considerable progress in the field of PIDs in the country there are still some problems that need further consideration. The current problems can be listed as follow:

1. Lack of awareness on PIDs amongst the medical community and general public.
2. Misunderstanding of the impact of PIDs and differences between primary (PIDs) and acquired (AIDS) immunodeficiencies and Delay in diagnosis of PIDs.
3. Lack of training program in clinical immunology for medical and nursing schools
4. Lack of epidemiological data on PIDs in the country.
5. Lack of facilities for accurate diagnosis and treatment in some centers.
6. Lack of screening tests for early diagnosis of severe forms of PIDs.
7. Lack of national guidelines for diagnosis and management of PIDs.
8. Access difficulties (availability and costs) to appropriate treatments (eg, immunoglobulin, GCSF, IFN-gamma) for patients with PIDs.
9. Lack of organizations to well support all patients with PIDs in the country.
10. Lack of a specific bone marrow transplantation center dedicated to PIDs.
11. Lack of national plan for follow-up of the patients with PIDs.
12. Lack of a specific center dedicated to PIDs.
13. Lack of joint collaboration and defined integration between basic scientists and clinicians.
14. Budget deficit for research in PIDs in some centers.

Suggested Plan for Future

In order to improve situation of PIDs in Iran several issues should be undertaken in four key areas, including awareness and education, diagnosis and prevention, treatment, and infrastructural facilities and research.

Awareness and education

1. Training program for more clinical fellowships in Allergy and Immunology, based on distribution of population in different regions of Iran.
2. Integrating basic and applied immunology teaching, particularly for general practitioners, general pediatricians, and other specialists in internal medicine, rheumatology, respiratory medicine, and infectious diseases.
3. Basic and applied immunology training in the core content for medical and nursing schools, with particular emphasis on PIDs.
4. Designing education programs targeting the general public and healthcare policy makers to raise awareness of PIDs.
5. Publication of specific magazines and/or journals about PIDs.

Diagnosis and prevention

1. Availability of practical tools for efficient diagnosis of PIDs in all major University of Medical Sciences in country.
2. Development of appropriate screening tests for identification of PIDs.
3. Development of genetic laboratories as part of prenatal, newborn and carrier screening programs.
4. Designing specific programs for those who are planning relative marriages.

Treatment

1. Development of national guidelines to provide equal access to treatment.
2. Providing appropriate supply of treatment, specifically immunoglobulins, for patients with PIDs requiring this life saving therapy.
3. Strengthening of the current supporting patients' organization in the country.
4. Encouraging other organizations to support patients with PIDs.
5. Developing center(s) for bone marrow transplantation for PIDs.
6. Identifying ways of improving existing therapies and discovery of new therapies.
7. More supporting the cost of treatment by insurance companies.

Infrastructural facilities and research

1. Establishment of national networks to determine disease outcomes through the country improves the quality of life of the patients with PID, and progress research in the country.
2. Construction of a research center focusing on PIDs.
3. Establishment of defined program to train new investigators.
4. Strengthening and encouraging the current research centers in the country to develop research groups for PIDs.
5. Establishment of specific scientific society in the field of PIDs.
6. Studying the molecular, cellular and clinical characteristics of genetically determined PID and identifying the genetic bases of newly defined PIDs.
7. Collection and storage of cell and tissue samples from patients with PIDs.
8. Increasing resources for research in PIDs.
9. More professional research collaboration with integration between basic scientists and clinical researchers and more collaboration with international PIDs research centers.
10. Encouraging selected medical students and PhD candidates, enabling them to spend time at medical centers which are specialized in the study of one or more aspects of PIDs.

We hope by improvement in education, infrastructural facilities and real translational research, we will be able to reach our main goal to help PIDs children to lead a healthy life.

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