Immunology and Genetics Journal (2018) 1:1-23
Doi: 10.22034/igj.2018.69304

Review

Recent Advances and Current Status of Primary Immunodeficiency Disease in Iran

Hassan Abolhassani, Nima Rezaei, Asghar Aghamohammadi*

Received: 19 April 2018 /Accepted: 22 August 2018 /Published online: 22 September 2018

Abstract

Although comprehension of the molecular basis of primary immunodeficiency diseases (PID) provides unique insight into the functioning of the immune system, translational research is also needed to provide better care to affected individuals. Many institutions and academic departments have been established to provide training and encourage collaborative research on the immune system and related disorders. In Iran, one of the frontiers of PIDs in the Middle Eastern region, considerable progress in basic and clinical immunology has been achieved during the last three decades. During this period, massive improvements have revolutionized the management of PIDs in the country, from educational and research related aspects to diagnostic procedures and treatments available to Iranian PID patients. In this review, we seek to elucidate the current status of PIDs in Iran from different angles and to speculate upon the opportunities that the future may bring.

*** Corresponding author:** Asghar Aghamohammadi
aghamohammadi@tums.ac.ir

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

Keywords Iran, Immunodeficiency diseases, Registry, Research, Education, National network

Introduction

Primary immune deficiency (PID) diseases are characterized by a wide spectrum of inherited disorders caused by intrinsic defects in one or more components of the immune system (1-3). Individuals affected with a PID present with increased susceptibility to infections in the vast majority of cases; however sometimes they are associated with autoimmunity, immune dysregulation, allergic diseases, auto-inflammatory disorders, and malignant tumors (4-7). Infections in PIDs can occur repeatedly and severely. Atypically they can locally or systematically damage different organs and reduce quality of life (8, 9). PIDs were previously thought to be rare and exclusively present in infants and young children who manifest severe clinical infections. However, observations report the boundaries of such complicated disorders with widely divergent pathologies among

adolescents and adults and varying phenotypes and symptoms along with a broad spectrum, from very mild to potentially life-threatening.

The first case of PID was described in 1952 (10). Subsequently, through continued progress in both basic and clinical immunology, the availability of different methods such as complementing traditional linkage analysis and homozygosity mapping, and after successful completion of the Human Genome Project (HGP) and the availability of next generation sequencing as a more efficient and invaluable method, more than 350 PIDs have been described with about 20 new entities per year (1). The overall frequency of PIDs has been estimated at about 1:10,000 individuals; however, this rate is an underestimation particularly in countries with a higher rate of consanguineous marriages (11). Early diagnosis and adequate therapies 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 a shortened lifespan (9, 12, 13).

The history of clinical immunology refers to the study of resistance to smallpox and measles that was performed by the 9th-century Persian physician, Zakariya al-Razi (880-932 A.D). In (1843–1910), the germ theory of contagious disease was described by the German physician Robert Koch, and later, Louis Pasteur discovered how to make vaccines from attenuated microbes. Pasteur developed the earliest vaccines to prevent against fowl cholera, anthrax, and rabies, while Koch demonstrated that tuberculin sensitivity can be transferred passively through cells but not by serum.

Understanding the genetic and mechanistic basis of PIDs provides a unique insight into the functioning of the immune system. Such progress leads to translational research to provide better care for affected individuals. Focused approach on the immunologic and genetic bases of PIDs provides a unique opportunity for research into immune disorders, particularly those severely attacking host defense mechanisms. A number of medical schools and organizations in the world have focused on basic and clinical-based research and developed into specialized centers of clinical immunology for research on the immune system and related disorders. The evidence demonstrates that our country has made appropriate progress in basic and clinical immunology in the past 30 years. In this review, we try to describe the current status of PIDs in Iran and the country's strengths and weaknesses as well as challenges and opportunities in facing them.

A brief history of clinical immunology and PID in the world

Elie Metchnikoff (1884) described phagocytosis as phagocyte cells digesting foreign materials to destroy them and to protect the host against infectious agents (2). In 1890, Behring and Kitasato showed that the transfer of antibodies from animals immunized against diphtheria to animals suffering from it could cure the infected animals. Later in 1900, Paul Ehrlich suggested the side-chain theory and hypothesized that side chain receptors on cells are bound to a given pathogen. In the early twentieth century, much attention was focused on the various types of antibodies as well as their use

in diagnosis and treatment. Afterwards, Dr. John Enders and Dr. Hugh Ward described "opsonization" and demonstrated that the optimal process needs the antibodies (3). Although several patients with immunodeficiency disorders such as complement deficiency (1919) (4), neutropenia (1922) (5), ataxia telangiectasia (AT) (1926) (6), or Wiskott-Aldrich syndrome (WAS) (1937) (7) had been reported by signs/symptoms in the early 1950s, the birth of the PID field is related to 1952, when the first case of agammaglobulinemia was reported by Dr. Ogden Bruton (8). Since that time more than 350 different PIDs have been identified (1, 9). The discovery of PIDs and the 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 (10). As a result of these advances and major biotechnology breakthroughs, new screening methods as well as therapeutic strategies have been devised, leading to the better care of individuals affected by PIDs.

PIDs in Iran: history at a glance

Progress and activities in the field of PIDs have developed during last three decades, and as one of the frontiers of PIDs diagnosis and treatment in the Middle Eastern region, Iran has achieved much progress in the fields of both clinical and molecular immunology during the last three decades in the four periods described below (**Table 1**).

Improvements in treating PIDs were initiated in Iran in the 1970s, when the Division of Clinical Immunology and Allergy at the Children's Medical Center in Tehran was established. Then, in 1988, a training program for fellowship in the field of clinical immunology and allergy established, followed by a unit for patients requiring treatment with intravenous immunoglobulin infusion. The third period of progress began in 1998 with the development of a national registry for PID. Finally, in 2009, the Research Center for Immunodeficiencies (RCID) was established and subsequent events were synchronized by this research center. Each event is described in more detail in the following sections.

Table1. Progress and activities in the field of PIDs in Iran over the last three decades

Period	Years	Events
First period	1978–1988	Professor Abolhasan Farhoudi returns to Iran after allergy training in the United Kingdom. Clinics for patients affected with PIDs are established.
Third period	1997–2009	Training program for clinical fellowship in the field of Allergy and Immunology is established. Clinics for PID patients requiring intravenous immunoglobulin infusion are established.
Third period	1997–2009	Iranian Primary Immunodeficiency Registry (IPIDR) is established. Iranian Primary Immunodeficiency Association (IPIA) is established.
Fourth period	2009-2018	Research Center for Immunodeficiencies (RCID) is established. Training program for Ph.D. by research student in the field of PID is established. Training program for clinical researcher in the field of PID is established. Iranian PID network is established. Immunology and Genetics Journal is established.

Establishment of clinics for patients affected with PIDs

Among the countries located in the Middle Eastern region, Iran has established itself as a front runner in treating PID patients during the last three decades. Improvements began in the 1970s when Professor Abolhasan Farhoudi (11), who trained in pediatric immunology and allergy in the United Kingdom, returned to Iran and established the Division of Clinical Immunology and Allergy as well as the Immunology Laboratory in the Children's Medical Center affiliated with Tehran University of Medical Sciences (TUMS) (12, 13).

Establishment of clinics for PID patients needing treatment with intravenous immunoglobulin infusionMost patients with a PID require regular immunoglobulin replacement therapy (14). Intravenous immunoglobulin (IVIG), a blood product obtained from human serum, is the treatment of choice for the majority of patients with antibody deficiencies, and it has been used since the 1970s. IVIG is used at a replacement dose of 400–600 mg/kg given approximately every 3 to 4 weeks (15, 16). Deciding on IVIG replacement in the management of patients associated with hypogammaglobulinemia is critical. IVIG therapy is vital in reducing the burdens of PIDs, including the affected patient’s quality of life (17) and mortality due to life-threatening invasive infections and complications (18). Timely and regular administration of IVIG at the correct dosage can also prevent the development of many end organ damages (such as bronchiectasis), which cause significant morbidity and increased mortality for PID patients (19). Our preliminary results indicated that the incidences of pneumonia and hospitalization in patients with agammaglobulinemia were significantly decreased after IVIG administration. The data showed the importance of early diagnosis and appropriate treatment with IVIG in this group of patients (20, 21). Because of the risk of adverse reactions, IVIG infusion should be administered under the supervision of trained physicians and nurses who are aware of the possible complications (14, 22, 23). In 1995, the Immunoglobulin Infusion Unit was established in the Children's Medical Center. This unit serves four times a week; all patients with hypogammaglobulinemia, including those with antibody deficiency or combined immunodeficiency, who receive IVIG in this unit are monitored by trained nurses and clinical fellows. Since the establishment of this unit, regular monthly follow-up of patients who require IVIG has been performed and the efficacy of this treatment was studied. Furthermore, adverse reactions of this treatment were regularly recorded. A recent report on a total of 3004 infusions during a 13-year period showed that less than 10% of patients receiving infusions faced adverse reactions, and most of those cases were as mild as chills and a low fever. Only 3 severe reactions were ever recorded during this period. To the best of our knowledge, there are currently at least 4 special units for IVIG administration in the country and other patients also receive their medications. In line with the improvement seen in specialized centers, there are three IVIG brands available with costs of approximately $80 per gram. The plasma

fractionated for the production of IVIG used in Iran is obtained from the blood of Iranian donors, which commonly contains antibodies against the endemic pathogens of the country. IVIG is administered mainly to patients suffering from different forms of antibody production impairment, including common variable immunodeficiency (CVID), combined immunodeficiency (CID), X-linked agammaglobulinemia (XLA), undefined hypogammaglobulinemias, AT, WAS, and hyper IgM syndrome (HIgM). The number of patients affected by these conditions is estimated to be 4000, of which currently about 40% are covered.

Students' research group for immunodeficiencies

In 1997, some academic members of TUMS and medical students started to investigate the frequency of PID in Iran. In recent years, the number of interested researchers has risen substantially, resulting in an increase in the complexity of the group, and this situation has brought about the requirement for a clearer definition of the group's purposes and activities. Meanwhile, an informal research group with a specific interest in the field of PID got the opportunity to design several national and international research projects with outstanding scientific output in this field. In 2009, a proposal for the establishment of Research Center for Immunodeficiencies (RCID, http://rcid.tums.ac.ir) was submitted to TUMS by this group and was accepted by the Ministry of Health Organization. The RCID is located in the Pediatrics Center of Excellence, Children's Medical Center Hospital in Tehran, Iran and is directed by Professor Asghar Aghamohammadi.

Iranian PID association for diagnostic and therapeutic aims

In more developed countries, thousands of people with PID still do not have access to their treatment of choice due to misdiagnosis of their underlying condition. Early diagnosis can be lifesaving and prevent permanent organ damage. Therefore, it is expected that by increasing the current level of knowledge of PIDs among first line physicians, the number of PID patients identified will rise consistently. To achieve the aforementioned goals, physicians and researches should work in close harmony with non-governmental organizations (NGOs) to convince the authorities and for-profit organizations to sponsor training programs, treatment, and research in the field of PIDs. A successful attempt was made in 1998 to support PID patients by establishing the Iranian Primary Immunodeficiency Association (IPIA) as a national non-profit organization. The IPIA held a significant number of meetings and reunions with authorities as consultants of the related ministries in an attempt to inform them of the dangers of delayed diagnosis of PIDs. This NGO has highlighted the importance of research for PID patients during its lifetime. IPIA modified and translated into Persian a poster showing 10 Warning Signs of PIDs and distributed it to all medical university hospitals in hopes that it will help increase awareness of PIDs among medical personnel and improve the diagnosis and

treatment of PID patients. Full details of the application and all supporting documentation can be found on the website for the International Patient Association for Primary Immunodeficiencies (IPOPI). The IPIA, which has been recognized as a global organization working to improve diagnosis and management of PID through research, advocacy, and education, was accepted as a member of IPOPI in 2002. (www.ipopi.org).

Iranian PID registry (IPIDR)

Epidemiological studies have shown wide geographical and racial variations in terms of prevalence and patterns of PIDs. Many countries worldwide have developed registries to estimate the prevalence and characteristics of different PID phenotypes among their populations (24). In order to determine the frequency and characteristic features of various PIDs in Iran, the IPIDR was established in August 1999 (25). The main goals of this national registry were to determine the frequency of different types of PIDs in Iran, follow the importance of treatment procedures of patients, encourage physicians to record secondary complications and their consequences experienced by patients, and to subsequently enhance advanced molecular/clinical research on PIDs in our country (26). The patient registration process in IPIDR initially consisted of different steps. First, a preliminary one-page questionnaire was sent to all participating centers. Then, after confirmation of definite diagnoses by clinical immunologists, the centers were asked to send complementary information. Recently, an online registry system has become available to all participating centers which facilitates and accelerates data entry. Each center is provided with a specific password and can update its own data by visiting the registry website at http://rcid.tums.ac.ir. Currently, data is collected from 42 different centers and distributed in 25 major cities of Iran where patients with PID are treated and immunologic laboratories are available for the diagnosis of PID patients. Patients from peripheral states are usually referred to central centers in order to be managed under advanced immunologic evaluation and genetic analysis. IPIDR is currently the only center from Iran accepted as a documenting center of the European Society for Immunodeficiencies (ESID, https://esid.org/Working-Parties/Registry-Working-Party/Documenting-centers/Iran-Iranian-Primary-Immunodeficiency-Registry-IPIDR). It is also a well-known Jeffrey Modell foundation collaborating on the global study of PID; it is the only Iranian center among 358 institutions from 86 countries spanning 6 continents, www.info4pi.org.

Establishment of the Research Center for Immunodeficiencies (RCID)

In 2009, a proposal to establish the Research Center for Immunodeficiencies (RCID, http://rcid.tums.ac.ir) was submitted to Tehran University of Medical Sciences (TUMS) by Dr. Aghamohammadi, Dr. Nima Rezaei, and Dr. Nima Parvaneh and was accepted by TUMS and the Ministry of Health Organization. The RCID is located in the Pediatrics Center of Excellence, Children's Medical Center Hospital in Tehran, Iran and is directed by Professor Asghar

Aghamohammadi. It is the first established specific PID research center in Iran. It has published more than 300 publications since its establishment, and three members of this research center (Dr. Aghamohammadi, Dr. Nima Rezaei, and Dr. Hassan Abolhassani) have been honored as the top 1% of the most cited scientists in the category of immunology according to Thomson Scientific's Essential Science Indicators (ESI).

Education and meetings on PID

World PID Week in Iran

World PID Week (WPIW, http://worldpiweek.org/) is part of the global campaign aimed at improving knowledge, diagnosis, and treatment of PID through the participating of different centers around the world in this theme. It has been taking place in Iran since 2011 after WPIW events entitled "Awareness Raising in Iran" were organized and held on the 22nd of April 2011. In these annual meetings, participants mostly comprise general practitioners and pediatricians, nurses and paramedic staff, and patients and their families. Discussions have been centered on "PID warning signs" and experiences sharing among groups of general practitioners, expert pediatricians, and clinical immunologists. The second annual WPIW included Immunodeficiency Day in Iran on the 22nd of April 2013, organized by the RCID and Children's Medical Center of TUMS. Case discussions, an expert PID meeting, a junior scientists' meeting, a panel discussion, and interviews with the media were all part of this event. From 2014 through 2018, the RCID has harmonized its international conferences with WPIW by inviting all pediatricians as well as basic and clinical immunology scientists to join and commemorate this global event. Expert PID meetings, PID morning reports and case discussions, special panels and expert discussions with the subject of each year's PID slang suggested by the Jeffrey Modell Foundation were planned and held.

J-Project meetings

The mission of the J-Project is to be the forum in Eastern European countries for increasing awareness and improving diagnostic facilities and the complex management of PIDs. The main aims of the J-Project are to organize professional meetings on PID and related diseases in several developing countries that have a low number of registered PID patients and limited budgets, discuss diagnostic and therapeutic practices and problems, define specific areas to be improved and to generate support by other developed Western countries, institutions, companies, and foundations. Other goals of the J-Project include updating national PID registries, establishing PID professional working groups, and forming a group for PID patients. Iran has been selected as the pioneer country in Central Asia, and the RCID has aimed to spread its valuable knowledge in Persian-speaking countries including Afghanistan and Tajikistan through its project titled J-Persia.

Continuing medical education programs for targeted physicians (Awareness of PID)

Among all healthcare providers, general practitioners and pediatricians are the most likely to

visit PID patients at the onset of the disease, so their up-to-date knowledge in this field could prevent most delayed diagnoses, disease complications, and life-threatening challenges. As the most common type of clinical presentations is an infection, PIDs are very likely to be missed by first line physicians, especially general practitioners. There are only about 20 PIDs the diagnosis of which can help save lives. This indicates the importance of education in preventing life-threatening side effects. In 2001, the Center for Disease Control and Prevention (CDC) began a program aimed at improving the health outcomes of PID patients. It was concluded that educational efforts have top priority because of the role of education in every aspect of improving the health outcomes of PID patients. According to a 2011 article on an Iranian physician's awareness of PID, about half of general practitioners and one third of pediatric specialists lacked basic knowledge about PIDs. Hence, educating primary care physicians must be considered to achieve early clinical recognition. This can be achieved through continuing medical education (CME) programs containing special lessons such as approaches to recurrent infections (27), the effect of early diagnosis and appropriate treatment on morbidity and mortality of PIDs, the identification of most common PID diseases, the evaluation of the usefulness and accuracy of family history, the recognition of early clinical signs and symptoms, and the role of initial laboratory tests in diagnosing PIDs (18, 28). In the past 5 years, 6 different local CME projects have been held in different states with higher PID prevalence rates. Recently, non-infectious complications of PIDs, including autoimmunity, allergic diseases, syndromic features, malignancies, and angioedema, were integrated into the CME programs.

Establishment of a program to train Ph.D. candidates by a research student in the field of PID

The education and training of doctoral students are highly important activities of a research center. The program of training special Ph.D. students in the field of PID aims to train scholars who will go on to conduct original research as faculty members of leading global institutions. The RCID is trying to improve healthcare services and train skilled researchers in the field of immunodeficiency. In 2012, with the goals of having a Ph.D. by research course for specialists who are surrounded by scientific literature in the PID-specific field and who know about advanced research methods and accessing the latest basics of education, the RCID launched a training program promoting knowledge in the field of PIDs. The RCID is now educating 2 post-doctoral and 2 Ph.D. students of clinical immunology. Three individuals have graduated with a Ph.D. by research, and more than 20 medical students are collaborating on PID projects.

Establishment of a program to train clinician-researchers in the field of PID

The clinician-researcher program focuses on clinical and research knowledge and skills, targeted simultaneously in a particular domain of medical science. Volunteers are selected on the basis of their potential abilities in leadership, innovation, analytic and critical thinking, quality and quantity of

research output, national interest and commitment, university and research center needs, quality of the intended project, and available facilities. All rules of specialty or sub-specialty courses as well as Ph.D. by research courses are applied in the clinician-researcher curriculum.

Establishment of a specialized PID referral laboratory

The list of specific immunologic laboratories in different provinces of Iran was acquired and analyzed with the help of Iran's Ministry of Health, the portal for Iran's medical research (http://labs.research.ac.ir). The search method was based on two keywords, "pathobiology" and "immunology", under the name field of the list of specific laboratories. Overall, a total of 250 laboratories all around the country were assigned to specific immunological tests (3.6 labs per 1 million people). Well more than one third of these are centered in Tehran (seven labs per 1 million people), and 85% of provinces provide more than one lab per 1 million people (**Table 2**). Although most of these labs can provide the basic tests necessary for making a clinical diagnosis of PID according to the ESID criteria, the RCID has decided to establish a central lab professionally designed for molecular and advanced experiments which need more skilled and research-based technology, which is currently located in the Children's Medical Center affiliated with TUMS.

Table 2. Number of specific immunologic labs per million population in different provinces of Iran

Province	Capital	Area km^2	Population	Labs	Labs/One Million Population	Density (population/km^2)
Alborz	Karaj	5833	1375450	17	12.4	235.8
Golestan	Gorgan	20195	1637063	17	10.4	81.1
Qom	Qom	11526	1064456	8	7.5	92.4
Tehran	Tehran	18814	13530742	94	6.9	645.8
Bushehr	Bushehr	22743	887115	6	6.8	35.9
Gilan	Rasht	14042	2410523	16	6.6	171.7
Kerman	Kerman	180836	2660927	17	6.4	13.5
Khorasan, South	Birjand	69555	640218	4	6.2	7.3
Lorestan	Khorramabad	28294	1758628	9	5.1	62.2
Mazandaran	Sari	23701	2940831	14	4.8	118.9
Kermanshah	Kermanshah	24998	1938060	9	4.6	77.5
Khorasan, North	Bojnourd	28434	820918	3	3.7	27.7
Semnan	Semnan	97491	590512	2	3.4	6
Ardabil	Ardabil	17800	1257624	4	3.2	70.7
Markazi	Arak	29130	1361394	4	2.9	46.7
Fars	Shiraz	122608	4385869	9	2.1	35.8
Azerbaijan, West	Urmia	37437	2949426	6	2.0	78.8
Yazd	Yazd	129285	992318	2	2.0	7.4
Ilam	Ilam	20133	545093	1	1.8	27.1
Hamadan	Hamadan	19368	1790770	3	1.7	91
Kohgiluyeh and Boyer-Ahmad	Yasuj	15504	695099	1	1.4	44.8

Sistan and Baluchestan	Zahedan	181785	2410076	3	1.2	12.6
Zanjan	Zanjan	21773	970946	1	1.0	44.6
Hormozgān	Bandar Abbas	70669	1410667	1	0.7	18.6
Isfahan	Isfahan	107029	4590595	3	0.7	41.6
Kurdistan	Sanandaj	29137	1574118	1	0.6	54
Khuzestan	Ahvaz	64055	4345607	2	0.5	67.8
Azerbaijan, East	Tabriz	45650	3620183	NI	NI	76.7
Chahar Mahaal and Bakhtiari	Shahrekord	16332	842002	NI	NI	51.6
Khorasan, Razavi	Mashhad	144681	5620770	NI	NI	36
Qazvin	Qazvin	15549	1166861	NI	NI	75
Iran (Total)	**Tehran**	**1628554**	**71767413**	**257**	**3.6**	**44**

lishment of Iranian PID network

One delay in the timely diagnosis and treatment of PIDs in Iran is caused by deficient physician-physician interactions. It has been demonstrated that poor communication among physicians could significantly impede the timely diagnosis and treatment of patients and waste time and resources (29). In addition, the absence of appropriate diagnostic laboratories in endemic regions in Iran leaves some patients undiagnosed for years, despite recognizable symptoms. Thus, the Iranian PID Network (IPIN), a multidisciplinary organization dedicated to PID disorders, was established in 2016. All clinical immunologists, subspecialists, scientists, and medical practitioners who are working on PID were invited to be members of IPIN. This network has several aims, including to increase physicians' awareness, increase collaboration between centers for clinical education, develop consensus statements and clinical guidelines for the diagnosis and therapy of PID patients, balance the quality of care for PID patients, and facilitate the registration of diagnosed patients (http://ipin.tums.ac.ir).

Research Projects

Targeted research at the national level based on community requests

In the last decade, many projects focusing on PIDs have been designed and completed based on the frequency of the disease in the country. A number of descriptive studies on series of children and adults with specific disorders from this region were reported initially. More clinical and laboratory characteristics of patients with high regional prevalence such as CVID (30-32), XLA (33-35), HIgM (36, 37), selective IgA deficiency (SIgAD) (38-40), CID (41-43), AT (44, 45), chronic mucocutaneous candidiasis (CMCC) (46, 47), and Chediak–Higashi syndrome (48), were well described in detail. Moreover, the characteristics of less common diseases, such as severe congenital neutropenia (SCN) (49-51), cyclic neutropenia (52, 53), hyper-IgE syndrome (HIES) (54, 55),

leukocyte adhesion defects (LADs) (56-58), Griscelli syndrome type 2 (59), and Shwachman-Diamond syndrome (SDS) have also been acceptably investigated.

International Collaborative Projects

International cooperative studies have had a significant effect on the quality of current projects in the field of PID (60, 61). Universities/Institutes that have published in collaboration with centers in Iran are the Karolinska University Hospital (Sweden); Hannover Medical School, Freiburg University Hospital Department of Pediatric Oncology, Hematology and Immunology, Heinrich Heine University Medical Center, Dusseldorf (Germany); National Institute of Health, University of Washington, Division of Immunology, Boston Children's Hospital, Harvard Medical (USA); University College of London and University of Sheffield(UK),Toyama Medical and Pharmaceutical University (Japan); University of Brescia (Italy); and Inserm Institutet and Unit of Pediatric Immunology-Hematology, Necker-Enfants Malades Hospital, Assistance Publique Hoˆpitaux de Paris (France).

Discovery of new genes and new PID diseases

Although comments and assistance from internationally well-known PID experts have led to effective projects, contributing to international projects, especially those that culminated in the discovery of specific phenotypes and genetic defects, has greatly refined science in this field. Findings on mutations in the *HAX1* gene (severe congenital neutropenia), the *G6PC3* gene (congenital neutropenia), the *ELA2* gene (severe congenital neutropenia), the *JAGN1* gene (severe congenital neutropenia), the *CARD9* gene (susceptibility to fungal infections), the *IFNGR2* gene (susceptibility to mycobacterial disease), and *DOCK8* (susceptibility to HIES), which were described as a new PID disease in the last IUIS classification, are additional achievements stemming from international collaborations. New investigations have also revealed the roles of the *STK4*, *LRBA*, and *CD70* genes in CVID and autoimmune disorders (62-69).

Scientific Outputs

Published articles

Since 2000, approximately 300 papers have been published in the field of PIDs, representing Iran's significant advancement in this field (42, 70-73). At the beginning of the third millennium, only 1 to 2 papers were published annually from Iran; this number reached 40 in 2008, around 60 by 2018, and still rising (**Figure 1**). More than 80% of these publications are based on research performed by TUMS scientists, but Shaheed Beheshti University and Shiraz University of Medical Sciences rank second and third in respect to PIDs publications. This accelerated rate of investigation and research keeps Iran among the 14 leading countries in the field of PID (**Figure 1**). During the last decade, the participation of Iranian scientists in international congresses was also noticeable; more than 250 abstracts in the field of PIDs were presented by

Iranian experts, either orally or as a poster, in international congresses.

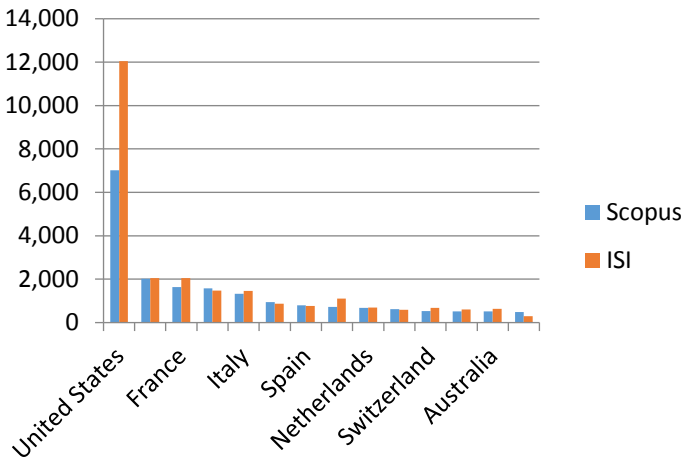

Figure 1. International ranking of first 14 countries on scientific publications in the field of primary immunodeficiency according to the indexed articles in the Thomson Reuters (formerly ISI) Web of Knowledge and Scopus.

Published PID Textbooks

To date, 8 textbooks (in Persian and English) on PID have been published by member of RCID in order to improve the knowledge of healthcare providers, students, patients and their families, and the public. "Primary Immunodeficiency Disorders in Iran" (edited by A. Farhoudi, 2002) is one of the first published books and resulted from collaboration with other clinical immunologists. "Immune System and Microorganisms" (edited by N. Rezaei, A. Aghamohammadi, Z. Pourpak, and M. Mahmoudi), affiliated with TUMS, is a remarkable book published by the United Nations Educational, Scientific and Cultural Organization (UNESCO) Chair in Health Education, in 2005, and was dedicated to all PID patients and their families. This book helps to bridge the gap between physicians and families and is an important tool for improving the quality of clinical management of patients with PID. Three other published books are titled: "Primary Immunodeficiency Disorders in Iran" (edited by A. Aghamohammadi, Z. Pourpak, N. Rezaei, A. Farhoudi, and M. Moin), "Treatment in Primary Antibody Deficiencies" (edited by A. Aghamohammadi, N. Parvaneh, and M. Yeganeh), and "Diagnosis and Treatment in Primary Immunodeficiency Disorders" (Edited by A. Aghamohammadi, HA Khazaei, and N. Rezaei). As references for the course of clinical immunology, three books titled "Primary Immunodeficiency Diseases: Definition, Diagnosis, and Management" (two editions, both edited by N. Rezaei, A. Aghamohammadi, and LD Notarangelo), “Clinical Cases in Primary Immunodeficiency Diseases: A Problem Solving Approach" (edited by A. Aghamohammadi and N. Rezaei), and" Cancer Immunology: A Translational Medicine Context" were published by Springer and included the contributions of international senior and junior scientists in this field from more than 30 universities worldwide.

Immunology and Genetics Journal

Immunology and Genetics Journal is a peer-reviewed journal published every four months that publishes original articles on the molecular, cellular and genetic bases of immunological disorders. In addition to original articles, the journal publishes interesting reviews and case reports. This publication is the official journal of the RCID, and contributor authors will receive both reviews of heir submissions and the editors' decision within six to eight weeks of receipt of their manuscripts by the journal office (http://www.igjournal.ir).

Improvements in diagnosis and treatment

Diagnosis of PID patients in Iran

The high prevalence of PID can be explained by the high rate of consanguineous marriages in the Middle East (ME) compared with Western countries (74, 75). Indeed, many defective genes with autosomal recessive patterns of inheritance that underlie PIDs were first described in patients originating from this region (76, 77). Hence, the abovementioned activities in recent years have led to considerable improvements in the diagnosis of PIDs, considering that more than half of the currently diagnosed Iranian PID patients were recognized in the last 5 years. The estimated diagnostic rate has increased from 7 patients per year in the 1980s to 30 patients per year during the early 1990s, 58 patients per year from 2000 to 2006, and 104 per year from 2006 till March of 2012. This rapid progress, which recently brought the diagnostic rate of PIDs to 350 patients per year, is critical for improving patients' quality of life and chances for survival (78). In recent years, PIDs have been diagnosed at earlier ages, reducing delays in diagnosis from 7 years in the 1980s to 2.5 years in the 1990s and to 6 months by the year 2000. The current diagnostic delay is as little as 3 months. Three reports on the national registry of Iranian PID patients in 2002 (79), 2006 (80), and 2014 (81) have played important roles in determining the prevalence of various types of PID in Iran. A total of 1,661 PID patients (1,028 male and 633 female) were registered in the IPIDR before 2014; that number increased to more than 3000 in 2018. The registry reports declared that the number of patients included 930 PID patients who were diagnosed during a 30-year period ending in March of 2006, and the remaining PID cases were diagnosed and registered in the IPIDR afterwards. The cumulative incidence of PIDs in Iran during the past 10 years is estimated to be around 30 cases per 1,000,000 population. The majority of registered cases were diagnosed predominantly with antibody deficiencies (35.7%) with CVID comprising 60% of this group as the most common PID. Based on the underestimated frequency of PID (a prevalence of 1:10,000 population), there should be at least 7,500 patients with the diagnosis of PID in Iran, but only 1,661 patients have been reported (82), and fewer than 3,500 patients have been registered so far. Moreover, less than 30% of diagnosed patients have a defined molecular diagnosis (mainly patients with combined immunodefiency and autoinflammatory disorders). Many factors can influence this difference, such as a lack of awareness among the

normal population as well as widespread ignorance among first-line general practitioners about the importance of PIDs and their related complications, a lack of subspecialists in major cities which further complicates referral and follow-up systems, the absence of newborn screening and special laboratories for specific immunologic tests and molecular identification which results in ineffective tests, and finally, the early deaths of PID patients due to disease severity or secondary infections which often lead to misdiagnosis or misclassification of their conditions under disease groups other than PID (29). Despite the new reliable techniques which have facilitated the diagnosis of PIDs, delays in diagnosing PIDs is still ponderable. Examples of this phenomenon can be observed in other countries; for instance, in Japan and England, better education results in early diagnosis of many PID patients and effective treatment for them. In India or China, however, which have much larger populations and presumably more PID patients, both the number and the rate of diagnosed patients are not considerable. This correlation between education and diagnosis brings to mind that low prevalence of PIDs in some countries could be a secondary outcome of low education and diagnostic facilities, necessitating more reliable investigations.

Treatment of PID patients in Iran

Beside therapeutic and prophylactic antibiotics for infections, the most common treatment options for PID patients are immunoglobulin replacement therapy, interferon gamma (IFN-γ) therapy, granulocyte colony stimulating factor (G-CSF) injection, and hematopoietic stem cell transplantation (HSCT). Of the estimated 7,500 Iranian patients requiring these therapies, 1,282 (17.09%) are diagnosed and receiving appropriate treatment. The information regarding these treatment procedures in Iran is summarized in **Table 3**. Another technique that recently became available for the treatment of PIDs is gene therapy. This option is currently not available in Iran, although many patients could benefit from it. Another commonly employed therapy is HSCT, a useful procedure for the treatment of a variety of PIDs, including (but not limited to) CID, WAS, AT, CD40/CD40 ligand defect, neutropenia, chronic granulomatous disease (CGD), and LADs. In many instances, HSCT increases PID patients' quality and quantity of life by dramatically decreasing their various complications and, sometimes (typically in younger patients), nearly reconstructing their defective immune system. HSCT was introduced in Iran in 1991, and there are currently near 10 centers capable of running this procedure across the country. However, there are currently only two active centers for transplantation in PID cases, both affiliated with TUMS (Hematology-Oncology and Stem Cell Transplantation Research Centers in "Dr. Shariati" and "Children's Medical Center" hospitals). These centers were established officially in 1993 and 2016, respectively, and have been the greatest Iranian contributors, both scientifically and practically, to HSCT procedures. The cost of HSCT in Iran is remarkably low in comparison with European countries and the U.S., equaling between $16,000 and $40,000. Of this amount, less than $3,000 is paid by the patient, and most are supported by the Iranian Ministry of Health and

other organizations, including several NGOs. In non-PID patients, there have been nearly HSCT 4000 operations up to now, and an average of 400 are carried out every year, generally with acceptable outcomes (in more than 70% of all cases). In contrast, of the around 2,250 PID patients requiring HSCT, less than 100 patients have been transplanted, and only 32 (1.4%) are reportedly diagnosed and have undergone therapy. According to this report, 12 were diagnosed with LADs, 5 with SCID, 3 with CHS, 1 with SCN, 6 with WAS, 3 with Griscelli syndrome, 1 with primary CD4 deficiency, and another with Familial Erythrophagocytic Lymphohistiocytosis (83, 84). The third major drug for PID patients is G-CSF, and it is regularly administered to all patients suffering pathologic immunodeficiency associated with neutropenia. Important PIDs treated by G-CSF therapy include congenital and severe congenital neutropenia, cyclic neutropenia, and Kostmann syndrome. Many patients undergoing chemotherapy and HSCT or those affected by secondary neutropenia require G-CSF therapy as well. For most patients, G-CSF is administered on a daily dosage of 5-20 µg/kg of body weight by subcutaneous injection, but for some, the dosage might vary widely. This therapy is effective for increasing blood neutrophil levels but has several side effects, including skin reactions, osteoporosis, arthralgia, and alopecia. The administered G-CSF for these PID patients is a recombinant drug, and the price of each premade syringe (containing 300 µg) is between $45 for the major domestic brand and about $115 for imported types. Almost a quarter of the estimated 500 Iranian PID patients requiring G-CSF therapy have been diagnosed and are currently receiving therapy. Finally, IFN-γ is the treatment of choice for many primary phagocytic disorders, the most common of which in Iran is CGD. IFN-γ acts on macrophages and other cells and activates them in response to infection, causing an increase in the macrophage killing and antigen presenting abilities. As a potent macrophage activator, this drug has side effects such as fever, weight loss, fatigue, and gastrointestinal complications. The average required dose is 50 µg/m^2 of body surface for those with a body surface of more than 0.5 m^2 and 1.5 µg/m^2 of body surface for those with a lesser body surface. The drug is usually administrated by subcutaneous injection 3 times a week. IFN-γ exists in the form of 0.5 ml vials, each containing 100 µg of IFN-γ and costing about $95 in Iran. Of the estimated 500 CGD patients in Iran, about 250 have to date been reportedly diagnosed and are receiving IFN-γ therapy, and the coverage of these patients is ~50% accordingly. Both G-CSF and IFN-γ using patients' expenses are covered mostly by the Ministry of Health and various insurance companies.

Table 3. General status of different PID treatment procedures in Iran.

Parameters	IVIG	HSCT	IFN-γ	G-CSF
Number of covered patients	970	<100	173	75
Percentage of coverage (%)	11.32	<0.5	45.2	24.5
Cost of treatment ($)	78.9 /g	15,800 -39,600/n	94.7/100 µg	44.2- 116.9/300 µg

HSCT: Hematopoietic stem cell transplantation, G-CSF: Granulocyte colony stimulating factor, IVIG: Intravenous immunoglobulin, IFN-γ: Interferon gamma

Plan for the Future

Despite current achievements in the field of PID in Iran, there are still strong ambitions for the future. Although the RCID is already a leading center for diagnostics and treatment in Iran, a priority area for the country's main cities undergoing rapid expansion is mandatory. Our aim is to continue building our influence and reach to turn the RCID into a major national and international location for translational medicine research and become a key player in the life sciences expansion in the field of PID. Therefore, we hope in the near future to establish the Iranian Society for Immunodeficiencies (ISID) and later the Iranian Academy of Clinical Immunology. Current pilot studies into newborn screening for PID should be translated to the public routine, and the genetic diagnosis of patients will be used to expand prenatal diagnosis clinics for PID family members. Weaknesses in the donation, detection, and time-span for performing HSCT will be targeted by developing programs, and CME programs will be continued in other states of Iran. We hope to collaborate on more professional research with integration between basic scientists and clinical researchers and more collaboration with international PIDs research centers. National guidelines for the diagnosis and management of PIDs will be continually revised by expert panels, and the current patient support organization in the country will be strengthened (85, 86).

Conclusion

The anticipated road map for improving PID diagnosis and treatment in Iran requires the focus to initially be on abating current problems; these issues are categorized in 4 main areas: awareness/education, diagnosis/prevention, treatment, and infrastructural facilities, especially for research. All four areas are described as follows. Both the general population and the medical community are involved. Awareness of PIDs is lacking among the general population and healthcare providers and physicians such that primary symptoms are ignored and there is low compliance by parents, low rate of suspicion to early symptoms of PID and misunderstanding of PID by first line physicians due to a lack of education, and a lack of training programs in clinical immunology for medical and nursing schools. All these factors can lead to shortages, exposing the essential requirement of a vast investment in this area. Changing from curative- to prophylactic-based policies in the field of PID is a somewhat time-consuming process for which a variety of factors must be established. From one perspective, the need for accurate screening tests for the identification of PIDs and the development of genetic laboratories as part of prenatal, newborn, and carrier screening programs can be sensed so far. Moreover, designing specific programs for those who are planning consanguineous marriages indicates the role of education in PID prevention, as mentioned before. In order to achieve these goals, a developed referral system is needed to further

reduce the delay time of diagnosis and complications prevention. The cost and availability of life-saving treatments such as IVIG and HSCT are now major issues in the course of treatment, requiring more assistance from insurance companies and patient support organizations. The development of national guidelines for the provision of equal access to treatment seems to be vital. Currently, research in the field of PIDs suffers from the shortage of specified centers focusing on PIDs and is limited to the centers previously named. Although encouraging the current research centers to develop research groups for PIDs are important steps in this process, the establishment of a defined program to train new researchers and scientists should not be neglected. Recent developments in the area of molecular, cellular, and clinical characteristics of genetically determined PIDs have paved the way for accelerated improvement in identifying the genetic bases of newly defined PIDs.

Conflict of interest

The authors declare no conflicts of interest.

References

1.Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018 Jan;38(1):96-128.

2.Tauber AI, Chernyak L. The birth of immunology. II. Metchnikoff and his critics. Cellular immunology. 1989 Jul;121(2):447-73.

3.von Behring E, Kitasato S. [The mechanism of diphtheria immunity and tetanus immunity in animals. 1890]. Molecular immunology. 1991 Dec;28(12):1317, 9-20.

4.Alper CA, Rosen FS, editors. Inherited deficiencies of complement proteins in man. Springer seminars in immunopathology; 1984: Springer.

5.Schultz W. Ueber eigenartige halserkrankungen. Dtsch Med Wochenschr. 1922;48(1495):7.

6.Syllaba L, Henner K. Contribution an l'independence de l'athetose double idiopathique et congenitale. Rev Neurol. 1926;1(541-562):147.

7.Wiskott A. Familiarer, angeborener morbus werlhofii? Monatsschr Kinderheilkd. 1937;68:212-6

8.Bruton OC. Agammaglobulinemia. Pediatrics. 1952 Jun;9(6):722-8.

9.Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, et al. Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. Journal of clinical immunology. 2015 Nov;35(8):696-726.

10.Rezaei N, Aghamohammadi A, Notarangelo LD. Primary immunodeficiency diseases: Definition, diagnosis, and management: Springer Science & Business Media; 2008.

11.Rezaei N. Obituary: Abolhassan Farhoudi (1924-2006). Iranian Journal of Allergy, Asthma and Immunology. 2006;5(1):1-2.

12.Farhoudi A. Cell-mediated immunodeficiency after BCG vaccination. Developments in biological standardization. 1986;58 (Pt A):347-9.

13.Farhoudi AH. [Recurrent pneumococcal meningitis associated with C3 deficiency]. Presse medicale (Paris, France : 1983). 1988 Apr 16;17(14):696.

14.Dashti-Khavidaki S, Aghamohammadi A, Farshadi F, Movahedi M, Parvaneh N, Pouladi N, et al. Adverse reactions of prophylactic intravenous immunoglobulin; a 13-year experience with 3004 infusions in Iranian patients with primary immunodeficiency diseases. Journal of investigational allergology & clinical immunology. 2009;19(2):139-45.

15.Aghamohammadi A, Moin M, Farhoudi A, Rezaei N, Pourpak Z, Movahedi M, et al. Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. FEMS immunology and medical microbiology. 2004 Mar 8;40(2):113-8.

16.Rezaei N, Abolhassani H, Aghamohammadi A, Ochs HD. Indications and safety of intravenous and subcutaneous immunoglobulin therapy. Expert review of clinical immunology. 2011 May;7(3):301-16.

17.Mozaffari H, Pourpak Z, Pourseyed S, Moin M, Farhoodi A, Aghamohammadi A, et al. Health-related quality of life in primary immune deficient patients. Iranian journal of allergy, asthma, and immunology. 2006 Mar;5(1):23.

18.Aghamohammadi A, Pouladi N, Parvaneh N, Yeganeh M, Movahedi M, Gharagolou M, et al. Mortality and morbidity in common variable immunodeficiency. Journal of tropical pediatrics. 2007 Feb;53(1):32-8.

19.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. Iranian journal of allergy, asthma, and immunology. 2004 Mar;3(1):31-6.

20.Pourpak Z, Aghamohammadi A, Sedighipour L, Farhoudi A, Movahedi M, Gharagozlou M, et al. Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immunodeficiency. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2006 Apr;39(2):114-20.

21.Salehzadeh M, Aghamohammadi A, Rezaei N. Evaluation of immunoglobulin levels and infection rate in patients with common variable immunodeficiency after immunoglobulin replacement therapy. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2010 Feb;43(1):11-7.

22.Abolhassani H, Sadaghiani MS, Aghamohammadi A, Ochs HD, Rezaei N. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. Journal of clinical immunology. 2012 Dec;32(6):1180-92.

23.Aghamohammadi A, Farhoudi A, Moin M, Pourpak Z, Rezaei N, Nikzad M, et al. Adverse effects of intravenous immunoglobulin therapy in patients with antibody deficiency. Iranian journal of allergy, asthma, and immunology. 2003 Sep;2(3):121-6.

24.Abolhassani H, Aghamohammadi A, Abolhassani F, Eftekhar H, Heidarnia M, Rezaei N. Health policy for common variable

immunodeficiency: burden of the disease. Journal of investigational allergology & clinical immunology. 2011;21(6):454-8.

25.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. Journal of clinical immunology. 2006 Nov;26(6):519-32.

26.Farhoudi A, Aghamohammadi A, Moin M, Rezaei N, Pourpak Z, Movahedi M, et al. Distribution of primary immunodeficiency disorders diagnosed in the Children's Medical Center in Iran. Journal of investigational allergology & clinical immunology. 2005;15(3):177-82.

27.Aghamohammadi A, Abolhassani H, Mohammadinejad P, Rezaei N. The approach to children with recurrent infections. Iranian journal of allergy, asthma, and immunology. 2012 Jun;11(2):89-109.

28.Karimi A, Isaiyan A, Aghamohammadi A, Moin M, Zandiyeh F, Dini AT,et al. Immunological evaluation of children with recurrent ear, nose, and throat (ENT) infections. Iranian journal of pediatrics. 2007;17(Suppl 1):5-13.

29.McPhee SJ, Lo B, Saika GY, Meltzer R. How good is communication between primary care physicians and subspecialty consultants? Archives of internal medicine. 1984 Jun;144(6):1265-8.

30.Yazdani R, Heydari A, Azizi G, Abolhassani H, Aghamohammadi A. Asthma and Allergic Diseases in a Selected Group of Patients With Common Variable Immunodeficiency. Journal of investigational allergology & clinical immunology. 2016;26(3):209-11.

31.Abolhassani H, Farrokhi AS, Pourhamdi S, Mohammadinejad P, Sadeghi B, Moazzeni S-M, et al. Expression of activation-induced cytidine deaminase gene in B lymphocytes of patients with common variable immunodeficiency. Iranian journal of pediatrics. 2013;23(4):451.

32.Abolhassani H, Sagvand BT, Shokuhfar T, Mirminachi B, Rezaei N, Aghamohammadi A. A review on guidelines for management and treatment of common variable immunodeficiency. Expert review of clinical immunology. 2014.

33.Ghazi BMS, Aghamohammadi A, Kouhi A, Farhoudi A, Moin M, Rezaei N, et al. Mortality in primary immunodeficient patients, registered in Iranian primary immunodeficiency registry. Iranian Journal of Allergy, Asthma and Immunology. 2004;3(1):31-5.

34.Aghamohammadi A, Fiorini M, Moin M, Parvaneh N, Teimourian S, Yeganeh M, et al. Clinical, immunological and molecular characteristics of 37 Iranian patients with X-linked agammaglobulinemia. International archives of allergy and immunology. 2006;141(4):408-14.

35.Moin M, Aghamohammadi A, Farhoudi A, Pourpak Z, Rezaei N, Movahedi M, et al. X-linked agammaglobulinemia: a survey of 33 Iranian patients. Immunological investigations. 2004;33(1):81-93.

36.Mohammadzadeh I, Shahbaznejad L, Wang N, Farhadi E, Aghamohammadi A, Hammarström L, et al. A novel CD40 ligand mutation in a patient with

pneumonia, neutropenia, and hyperimmunoglobulin M phenotype. Journal of investigational allergology & clinical immunology. 2012;23(1):50-1.

37.Atarod L, Aghamohammadi A, Moin M, Kanegane H, Rezaei N, Kalantari KR, et al. Successful management of neutropenia in a patient with CD40 ligand deficiency by immunoglobulin replacement therapy. Iranian Journal of Allergy, Asthma and Immunology. 2007;6(1):37-41.

38.Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, et al. Progression of selective IgA deficiency to common variable immunodeficiency. International archives of allergy and immunology. 2008;147(2):87-92.

39.Nikfarjam J, Shahrabi M, Pourpak Z, Nikfarjam L, Kouhkan A, Aghamohammadi A, et al. Oral manifestations in selective IgA deficiency. International journal of dental hygiene. 2004;2(1):19-25.

40.Soheili H, Abolhassani H, Arandi N, Khazaei HA, Shahinpour S, Hirbod-Mobarakeh A, et al. Evaluation of natural regulatory T cells in subjects with selective IgA deficiency: from senior idea to novel opportunities. International archives of allergy and immunology. 2012;160(2):208-14.

41.Farhoudi A, Chavoshzadeh Z, Ghazi BMS, Aghamohammadi A, Gharagozlou M. Recurrent infections and bilateral uveitis in a patient with CD8 deficiency. receptor. 2005;3:5.

42.Yeganeh M, Heidarzade M, Pourpak Z, Parvaneh N, Rezaei N, Gharagozlou M, et al. Severe combined immunodeficiency: a cohort of 40 patients. Pediatric Allergy and Immunology. 2008;19(4):303-6.

43.Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. Journal of Infection. 2012;64(6):543-54.

44.Moin M, Aghamohammadi A, Kouhi A, Tavassoli S, Rezaei N, Ghaffari S-R, et al. Ataxia-telangiectasia in Iran: clinical and laboratory features of 104 patients. Pediatric neurology. 2007;37(1):21-8.

45.Isaian A, Bogdanova NV, Houshmand M, Movahadi M, Agamohammadi A, Rezaei N, et al. BAK, BAX, and NBK/BIK proapoptotic gene alterations in Iranian patients with Ataxia Telangiectasia. Journal of clinical immunology. 2010;30(1):132-7.

46.Moghtaderi M, Kashef S, Rezaei N. Interstitial lung disease in a patient with chronic granulomatous disease. Iranian journal of pediatrics. 2012 Mar;22(1):129-33.

47.Movahedi M, Aghamohammadi A, Rezaei N, Shahnavaz N, Babaei Jandaghi A, Farhoudi A, et al. Chronic granulomatous disease: a clinical survey of 41patients from the Iranian primary immunodeficiency registry. International archives of allergy and immunology. 2004;134(3):253-9.

48.Farhoudi A, Chavoshzadeh Z, Pourpak Z, Izadyar M, Gharagozlou M, Movahedi M, et al. Report of six cases of chediak-higashi syndrome with regard to clinical and laboratory findings. Iranian journal of allergy, asthma, and immunology. 2003 Dec;2(4):189-92.

49.Eghbali A, Eshghi P, Malek F, Rezaei N. Cardiac and renal malformations in a patient with

sepsis and severe congenital neutropenia. Iranian journal of pediatrics. 2010;20(2):225.

50.Rezaei N, Farhoudi A, Ramyar A, Pourpak Z, Aghamohammadi A, Mohammadpour B, et al. Congenital neutropenia and primary immunodeficiency disorders: a survey of 26 Iranian patients. Journal of pediatric hematology/oncology. 2005;27(7):351-6.

51.Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Moin M, Movahedi M, et al. Neutropenia in Iranian patients with primary immunodeficiency disorders. Haematologica. 2005;90(4):554-6.

52.Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Ramyar A, Moin M, et al. Clinical and laboratory findings in Iranian children with cyclic neutropenia. Iranian Journal of Allergy, Asthma and Immunology. 2004;3(1):37-40.

53. Rezaei N, Farhoudi A, Pourpak Z, Aghamohammadi A, Moin M, Gharagozlou M, et al. Neutropenia in patients with primary antibody deficiency disorders. Iranian Journal of Allergy, Asthma and Immunology. 2004;3(2):77-82.

54. Rezaei N, Aghamohammadi A. Hyper-IgE syndrome. Journal of postgraduate medicine. 2010 Apr-Jun;56(2):63-4.

55. Moin M, Farhoudi A, Movahedi M, Rezaei N, Pourpak Z, Yeganeh M, et al. The clinical and laboratory survey of Iranian patients with hyper-IgE syndrome. Scandinavian journal of infectious diseases. 2006;38(10):898-903.

56. Behmanesh F. Leukocyte Adhesion Deficiency; Case Report. Iranian journal of pediatrics. 2007;17(Suppl 2):311-3.

57. Movahedi M, Entezari N, Pourpak Z, Mamishi S, Chavoshzadeh Z, Gharagozlou M, et al. Clinical and laboratory findings in Iranian patients with leukocyte adhesion deficiency (study of 15 cases). Journal of clinical immunology. 2007;27(3):302-7.

58. Parvaneh N, Mamishi S, Rezaei A, Rezaei N, Tamizifar B, Parvaneh L, et al. Characterization of 11 new cases of leukocyte adhesion deficiency type 1 with seven novel mutations in the ITGB2 gene. Journal of clinical immunology. 2010;30(5):756-60.

59. Ashrafi MR, Mohseni M, Yazdani S, Alizadeh H, Ramyar A, Aghamohammadi A, et al. Bilateral basal ganglia involvement in a patient with Griscelli syndrome. European Journal of Paediatric Neurology. 2006;10(4):207-9.

60. Aghamohammadi A, Kanegane H, Moein M, Farhoudi A, Pourpak Z, Movahedi M, et al. Identification of anSH2D1A mutation in a hypogammaglobulinemic male patient with a diagnosis of common variable immunodeficiency. International journal of hematology. 2003;78(1):45-7.

61. Farhadi E, Nemati S, Amirzargar A, Hirbod-Mobarakeh A, Nabavi M, Soltani S, et al. AICDA single nucleotide polymorphism in common variable immunodeficiency and selective IgA deficiency. Allergologia et immunopathologia. 2014;42(5):422-6.

62.Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schäffer AA, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia(Kostmann disease). Nature genetics. 2007;39(1):86-92.

63. Boztug K, Appaswamy G, Ashikov A, Schäffer AA, Salzer U, Diestelhorst J, et al. A syndrome with congenital neutropenia and mutations in G6PC3. New England Journal of Medicine. 2009;360(1):32-43.

64. Salipante SJ, Benson KF, Luty J, Hadavi V, Kariminejad R, Kariminejad MH, et al. Double de novo mutations of ELA2 in cyclic and severe congenital neutropenia. Human mutation. 2007;28(9):874-81.

65. Glocker E-O, Hennigs A, Nabavi M, Schäffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. New England Journal of Medicine. 2009;361(18):1727-35.

66. Vogt G, Chapgier A, Yang K, Chuzhanova N, Feinberg J, Fieschi C, et al. Gains of glycosylation comprise an unexpectedly large group of pathogenic mutations. Nature genetics. 2005;37(7):692-700.

67. Saghafi S, Pourpak Z, Nussbaumer F, Fazlollahi MR, Houshmand M, Hamidieh AA, et al. DOCK8 deficiency in six Iranian patients. Clinical Case Reports. 2016;4(6):593-600.

68. Abdollahpour H, Appaswamy G, Kotlarz D, Diestelhorst J, Beier R, Schäffer AA, et al. The phenotype of human STK4 deficiency. Blood. 2012;119(15):3450-7.

69. Alkhairy OK, Abolhassani H, Rezaei N, Fang M, Andersen KK, Chavoshzadeh Z, et al. Spectrum of phenotypes associated with mutations in LRBA. Journal of clinical immunology. 2016;36(1):33-45.

70. Rezaei N, Aghamohammadi A, Mahmoudi M, Shakiba Y, Kardar GA, Mahmoudi M, et al. Association of IL-4 and IL-10 gene promoter polymorphisms with common variable immunodeficiency.Immunobiology. 2010;215(1):81-7.

71. Javad M, Zahra P, Sara J, Shiva S, Kazem Z, Akbar PA, et al. Human leukocyte antigens (HLA) associated with selective IgA deficiency in Iran and Sweden. Iranian Journal of Allergy, Asthma and Immunology. 2008;7(4):209-14.

72. Kiani-amin M, Daneshi M, Ayazi P, Mohammadian S, Rezaei N. Serum immunoglobulin levels in splenectomized and non-splenectomized patients with major Beta-thalassemia. Iranian journal of pediatrics. 2011;21(1):95.

73. Rezaei N, Abolhassani H, Kasraian A, Mohammadinejad P, Sadeghi B, Aghamohammadi, A. Family study of pediatric patients with primary antibody deficiencies. Iranian Journal of Allergy, Asthma and Immunology. 2013;12(4):377.

74. Rezaei N, Mohammadinejad P, Aghamohammadi A. The demographics of primary immunodeficiency diseases across the unique ethnic groups in Iran, and approaches to diagnosis and treatment. Annals of the New York Academy of Sciences. 2011;1238(1):24-32.

75. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, et al. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. American Journal of Reproductive Immunology. 2006;56(2):145-51.

76. Farhoudi A, Aghamohammadi A, Moin M, Rezaei N, Pourpak Z, Movahedi M, et al.

Distribution of primary immunodeficiency disorders diagnosed in the Children's Medical Center in Iran. Journal of Investigational Allergology and Clinical Immunology. 2005;15(3):177.

77. Aghamohammadi A, Moin M, Rezaei N. History of primary immunodeficiency diseases in Iran. Iranian journal of pediatrics. 2010;20(1):16-34.

78. Mozaffari H, Pourpak Z, Pourseyed S, Moin M, Farhoodi A, Aghamohammadi A, et al. Health-related quality of life in primary immune deficient patients. Iranian Journal of Allergy, Asthma and Immunology. 2006;5(1):23-7.

79. 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. Journal of clinical immunology. 2002;22(6):375-80.

80. 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. Journal of clinical immunology. 2006;26(6):519-32.

81. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. Journal of clinical immunology. 2014;34(4):478-90.

82. Abolhassani H, Aghamohammadi A, Abolhassani F, Eftekhar H, Heidarnia M, Rezaei N. 3 Health Policy for Common Variable Immunodeficiency: Burden of the Disease. Journal of Investigational Allergology and Clinical Immunology. 2011;21(6):454.

83. Ghavamzadeh A, Alimoghaddam K, Ghaffari F, Derakhshandeh R, Jalali A, Jahani M. Twenty years of experience on stem cell transplantation in Iran. Iranian Red Crescent Medical Journal. 2013;15(2):93.

84. Hamidieh A, Behfar M, Babaki A, Jalali A, Hosseini A, Jahani M, et al. Hematopoietic SCT in Iranian children 1991–2012. Bone marrow transplantation. 2015;50(4):517-22.

85. Nourijelyani K, Aghamohammadi A, Sadaghiani MS, Behniafard N, Abolhassani H, Pourjabar S, et al. Physicians awareness on primary immunodeficiency disorders in Iran. Iranian Journal of Allergy,Asthma and Immunology.2012; 11(1):57-64.

86. Isaian A, Moin M, Pourpak Z, Rezaei N, Aghamohammadi A, Movahedi M, et al. DNA banking of primary immunodeficiency disorders in Iran. Iranian Journal of Allergy, Asthma and Immunology. 2006;5(4):201-2.