Primary Immunodeficiency Diseases in Iran: Past, Present and Future

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Abstract
Clinical immunology and its subset topics are rather newly emerging medical fields in Iran as well as other developing countries. Primary immunodeficiency diagnosis and treatment were revolutionized in the late 1970s; a period of time that coincided with the establishment of the Division of Clinical Immunology and Allergy at the Children's Medical Center, Tehran. Subsequently, the launch of fellowship training programs (in 1988), the development of a national Iranian Primary Immunodeficiency Diseases Registry (in 1999), the inauguration of Research Center for Immunodeficiencies (in 2009), and recently, the national primary immunodeficiency network (in 2016) significantly changed the picture of disease management during the last 40 years. In this review, we seek to elucidate the most important past events, current challenges and future directions regarding the field of primary immunodeficiency.

Keywords: Clinical immunology, Diagnosis, Immunodeficiency Diseases, Iran

Introduction
Primary immunodeficiency diseases (PID) constitute a group of approximately 400 inherited disorders caused by qualitative or quantitative defects of the immune system components.1 Depending on the defective component and etiologies, the affected patients can present with increased susceptibility to infections or other non-infectious manifestations including autoimmunity, immune dysregulation, allergic diseases, lymphoproliferation, and cancer.2 Of note, the history of clinical PID patients dates back to a report by Zakariya al-Razi (880-932 A.D) about the higher susceptibilities of some individuals to smallpox and measles compared to the public.3 However, the field of PID has been re-considered after the development of broad-spectrum antibiotics and preventive vaccines when physicians observed that despite these medical modalities, the severity of medical condition leads to morbidity and mortality in a selected group of patients.4

Recently, we have published several studies and reviews regarding the evidence demonstrating that Iran, as a leading country in the region of the Middle East, has made appropriate progress in both basic and clinical immunology, and described the influences of those achievements in the specific field of PIDs in Iran.5,6 This review aims to summarize those reports to highlight the strengths and weaknesses and, at the same time, address the expected challenges and opportunities in the future.

Progression of Primary Immunodeficiency Field
Improvements began when Professor Abolhasan Farhoudi (1924–2006), an academic member of Tehran University of Medical Sciences (TUMS), decided to launch the Division of Clinical Immunology and Allergy complemented by an Immunology Laboratory. The division and the laboratory were founded at Children's Medical Center.4 This step significantly changed the diagnosis and treatment of patients with PID by designing targeted medical archiving, family history taking and providing a sustainable treating unit for diagnosed patients.4 The next pioneering step was the evaluation of PID frequency at the national level which was performed by trained clinical immunologists of TUMS and their medical students in 1998.6 Their efforts toward their main goals lead to the establishment of a national registry which aimed not only to identify the national frequency of various PIDs entities, but also to improve the therapeutic modalities of patients with long-term follow-up, documentation of natural history and consequential complications experienced by patients in different organs, and subsequently to improve progressive molecular/clinical research in the field of PIDs in Iran.5,6

After five years of endeavors, the first data collected in the Iranian PID registry was published in 2002, including...
440 PID patients within the four main categories of the disease. Recently, we have published the 20-year survey of the PID registry from the recently structured national PID network organizing 31 collaborating hospitals affiliated to 26 medical science universities from the main provinces.\textsuperscript{7-10} Now, we have registered 3056 (39.3\% female) and with molecular diagnosis confirmed in 1014 patients (33.1\%). Although this report magnifies the magnificent improvement of expert training and increased awareness of targeted physicians (point prevalence of 1/26000),\textsuperscript{7,11,12} we estimate a prevalence of 1/600 for PIDs in Iran due to a higher rate of consanguinity in the country compared to Western countries. In other words, we expect more than 130000 undiagnosed patients based on the prevalence of PIDs in Iran; therefore, the current number of clinically registered PID patients (2.3\% of expected patients) indicates a long way to go and further required supports to accomplish the task. So far, definite diagnosis, assigned by molecular confirmation, has been made in 33.1\% of the total Iranian PID cases which represents an equal rate to the frequency of genetic diagnosis in Western countries with long-term established PID registries.\textsuperscript{7} Facing the therapeutic issues of registered patients and an increasing number of cases who need sustainable treatment, the Iranian Primary immunodeficiency Association (Iranian PiA) was established. This initiative led to an agreement between the country (http://isid.research.ac.ir). Of note, the national PID registry has had a great impact on novel PID gene discovery including finding mutations in the HAX1,\textsuperscript{16} G6PC3,\textsuperscript{17} ELA2,\textsuperscript{18} JAGN1,\textsuperscript{19} CARD9,\textsuperscript{20} STK4,\textsuperscript{21} LRB4,\textsuperscript{22} and CD70 genes.\textsuperscript{23}

During the last decade, several other research centers have also contributed to some aspects of PID in Iran. Of note, the immunology, asthma and allergy institute of TUMS was dedicated to setting up some advanced laboratory tests regarding specific phagocytosis and combined immunodeficiency diseases. Moreover, they have performed several studies toward the facilitation of hematopoietic stem cell transplantation and newborn screening of the patients. Other main centers active in the national network in term of patient identification and laboratory services include Non-communicable Diseases Research Center (Alborz University of Medical Sciences),

The majority of these advanced outcomes became possible due to the focused activity of a dedicated research center, Research Center for Immunodeficiencies (RCID, http://rcid.tums.ac.ir).\textsuperscript{7} Based on the commitment delivered by the Non-Communicable Diseases Center of the Ministry of Health, RCID was launched as a tertiary center for the molecular diagnosis of immunodeficiency diseases in Iran. Routine referrals of PID patients from peripheral centers to RCID are made for the performance of advanced immunologic tests and molecular diagnosis.\textsuperscript{13-15} The European Society for Immunodeficiencies (ESID) has currently accepted RCID as the only documenting center from Iran to update the epidemiological PID indexes from the country (https://esid.org/Working-Parties/Registry-Working-Party/Documenting-centers/AIR-Iranian-Primary-Immunodeficiency-Registry-IPIDR). The Jeffrey Modell Foundation, which documents the global rate of PID, denotes RCID as the only Iranian center reporting its annual PID registry update among 358 institutions from 86 countries spanning 6 continents (https://www.info4pi.org).\textsuperscript{5}

RCID, through a progressive foundation of different PID entity working parties, facilitates basic and advance research with the Iranian PID network for all collaborative parties and also provides unique materials and opportunities for international collaboration (http://ipin.tums.ac.ir).\textsuperscript{5} The structure of the network constitutes more than 60 main clinical immunologists and subspecialists from the 20 main treating PID centers of the country. Accordingly, since the beginning of the 21st century, more than 350 publications in the field of PIDs have been indexed in major medical journals in the field of immunology showing our significant advancement by standing among the top 15 countries in the field (Figure 1). Approximately 50\% of these publications are the outcome of international collaborations with advanced PID centers across the world (http://isid.research.ac.ir). Of note, the national PID registry has had a great impact on novel PID gene discovery including finding mutations in the HAX1,\textsuperscript{16} G6PC3,\textsuperscript{17} ELA2,\textsuperscript{18} JAGN1,\textsuperscript{19} CARD9,\textsuperscript{20} STK4,\textsuperscript{21} LRB4,\textsuperscript{22} and CD70 genes.\textsuperscript{23}

Figure 1. Scientific Output of Iran in the Field of Primary Immunodeficiency Diseases. A) Scientific output of the country during last 20 years (n = 347 documents). B) The ranking of 15 top countries with the highest scientific output in this field.
Pediatric Infections Research Center (Mofid Children’s Hospital, Shahid Beheshti University of Medical Sciences), Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (Shahid Beheshti University of Medical Sciences), Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease (Isfahan University of Medical Sciences), Hematology, Oncology and Stem Cell Transplantation Research Center (Tehran University of Medical Sciences), Acquired Immunodeficiency Research Center (Isfahan University of Medical Sciences), Allergy Research Center (Shiraz University of Medical Sciences), Allergy Research Center (Mashhad University of Medical Sciences), Non-communicable Pediatric Diseases Research Center (Babol University of Medical Sciences) and Pediatric Infectious Diseases Research Center (Mazandaran University of Medical Sciences).

RCID continuously follows the process of education and meetings on PID by organizing an annual international congress of PID (ICID) during World PID Week (WPIW) in Iran. This research center is also a sister of J-Project, entitled J-Persia, to take Iran as a pioneer country in Central Asia to expand and accelerate its essential impact in Persian-speaking countries (particularly Afghanistan and Tajikistan, [http://www.jprojectnetwork.com/]).

Continuing medical education programs for targeted physicians in different provinces, launching “Ph.D. by research” and “clinician-researchers” training programs in the field of primary immunodeficiency, publication of several international PID textbooks and guidelines, and having three PID researchers honored as the top 1% of the most-cited scientists in the category of immunology according to Thomson Scientific’s Essential Science Indicators (ESI, [https://clarivate.com]) are among other major achievements during the last decade. Publication of three specialized journals of “Immunology and Genetics Journal” ([https://igj.tums.ac.ir/index.php/igj]), “Iranian Journal of Immunology” ([http://iji.sums.ac.ir]) and Iranian Journal of Allergy, Asthma and Immunology ([http://ijai.tums.ac.ir/index.php/ijai]) has contributed to the visibility of PID research outcomes internationally. For details of these outcomes, please refer to the recent review published about the current status of PID in Iran.

Current Achievements and Obstacles in the Primary Immunodeficiency Field

The above-mentioned national activities and international collaborations have led to several current achievements about the practical aspects of diagnosis and management of patients with both well-known and newly described PID. Establishment and continued efforts for registration of clinical and immunologic profiles of patients improved genetic testing to guide both definitive diagnosis and decision making. With a current multidisciplinary approach to the diagnosis of PID, our national registry was involved in the identification of complicated immune dysregulation and unusual presentations of the diseases. These findings enabled us to participate in novel gene discovery and improved targeted therapies through an understanding of the mechanisms that underlie these events. By generation of comprehensive national networks and specific PID group working parties, we collected the best practices in the management of PID entities from an expert team as a consensus guideline. This guideline addresses basic and advanced immune function evaluation and practical advice for physicians regarding vaccination and treatment adjustment using available new products.

The improved survival rate of PID patients and late-onset presentation of the hypomorphic phenotypes urged us to not confine our practice to pediatric patients and address the increasing number of more adults with immune defects. The diagnostic workup of adult patients with suspected PID is more comprehensive by taking a detailed patient and family history, immunological and laboratory assays that would be followed by the next step, targeted or next-generation sequencing. These novel approaches for the identification of underlying PID-causing gene defects in both pediatric and adult patients have enabled rapid and cost-effective diagnosis and correct treatment.

With a combination of long-term follow-up and molecular advanced technology, we now have participated in the extension of the phenotypes of previously reported known PID genes presenting with distinct manifestations from the original description. However, we need further improvement regarding the scaling of the sequencing costs and pipeline time to provide faster and appropriate management for all patients nationwide. Allogeneic hematopoietic stem cell transplantation remains the main curative therapy for most severe PIDs and its application and patients who require this modality are increasing, related to better genetic diagnosis in the patients. Despite the presence of several studies reporting improved outcomes in PID patients who undergo transplantation, this treatment can be offered to only less than 5% of indicated patients in our registry due to costs, inappropriate infrastructure and difficulties in HLA-match donor selection. To tackle this limitation, we should punctually improve our experience in hematopoietic stem cell transplantation for PIDs to fulfill criteria that have been mentioned by the Primary Immune Deficiency Treatment Consortium.

Since immunoglobulin replacement is an essential component in the treatment of different types of PID affecting antibody production, sustainability and appropriate preparation of this modality were targeted by our national efforts. For all PIDs needing immunoglobulin replacement, standardized and practical guidelines have been defined for administration in hospital settings.
Regarding the remaining obstacles for replacement therapy, improved education (about the therapeutic modality) is an immediate need for patients and their families prior to the first course of therapy. By improving practices regarding pretreatment conditioning, immunoglobulin therapy should be improved by the availability of different commercial formulations including more concentrated solutions, more subcutaneous injection routes and more home-based care.\textsuperscript{7,15,37,57} The results of many different Western PID registry patients with complete modern modalities and biological agents for novel applications in patients with PIDs of treatment enforce the necessary activities toward development or importation of different modalities for our patients in the current routine including experience of thymus transplantation and other antagonist/agonist monoclonal antibodies.

Certain concerns still should be addressed for the current status in basic and clinical immunology education by revising study systems and residency programs, but efforts are ongoing with generating more postgraduate courses and fellowships to provide information and courses, especially on immunological diseases.\textsuperscript{7} Currently, almost 20 educational centers (in 17 cities including Ahvaz, Arak, Tehran, Isfahan, Babol, Birjand, Tabriz, Shaherkord, Shiraz, Semnan, Sanandaj, Kerman, Sari, Kermanshah, Hamedan, Mashhad and Yazd) train on the average 200 new basic immunologists in Master of science or PhD levels per year which sufficiently provide the need for human resources in this field. Although we have moved far from the poor conditions we had across the country to increase awareness about PID during the last decade,\textsuperscript{11,12} continuing education and training schedules are needed for pediatricians and general practitioners, as well as for specialists, to ensure that they have the same access to required information regarding diagnosis and the referring system.\textsuperscript{7,35} These efforts would improve early diagnosis and promote referrals to immunologists by the continuous support of the annual conference in the capital and peripheral symposia or summer schools for junior immunologists to help create networks of trained immunologists, and ensure updated information about PID.

**Future Direction and Strategy in Primary Immunodeficiency Field**

Personalized therapies and treatments of PID are the ultimate goals for clinical immunologists that should be provided for the patients in our national registry, as well.\textsuperscript{15,59} Characterization of the molecular defect and its affected signaling in undiagnosed patients with complicated diagnosis due to digenic or polygenic features should be addressed in near future to selectively add with adjuvant drugs or disease-modifying agents.\textsuperscript{7,15,37,57} Even the interaction of epigenetic factors and environmental parameters should be studied to depict the mysteries behind this group of PID patients.\textsuperscript{35}

Although we are still struggling with standardization and the expansion of the newborn severe combined immunodeficiency and antibody deficiency screenings,\textsuperscript{50} we should also move forward for pre-symptomatic diagnosis of patients with other types of PIDs, including phagocytosis and complement deficiency. The current promising results of the newborn screening program have been highly efficient in the detection of affected neonates and therefore, we observed an increase in the rate of referrals for transplantation and earlier medical interventions, which have improved life-expectancy in these patients. However, with the current capacity in transplantation, we should be also ready to deal with the increasing number of requests and prioritization of the process as well as turn-over of reporting and follow-up confirmation of the preliminary positive results.\textsuperscript{50}

As we published our current activities for strong consensus recommendations towards the use of our genetic findings in managing patients with PID for prenatal diagnosis and treatment,\textsuperscript{7,15,59} future guidance for the use of genetic testing in PIDs should be completed by preimplantation genetic diagnosis and justifying the economic aspects of the right access of all patients and their families to these facilities.

Although we have estimated the burden of frequently diagnosed PIDs and the direct and indirect costs representing a heavy burden of disease on the patient and society,\textsuperscript{38-60} the process should continue to provide feedback to health care providers and policymakers regarding the decision for the administration of new agents or modalities for these patients.

We hope that the future will bring spectacular advances compared to the past decades and by current promising strengths,\textsuperscript{3} one can only imagine that hundreds of clinicians and basic scientists provide human and laboratory facilities to discover the different dimensions of PID that will affect therapeutic interventions. Perhaps the distinctions between primary and secondary immune effects will become blurred as we will discover the correct interaction of internal risks and external insults that cause susceptibility of the host to specific pathogens. We will apply in silico modeling and experimental assays to identify both key methodologies for the improvement of our knowledge regarding the pathophysiology of the novel PID diseases and related targeted medical action, and in the design of immune pathway studies. Given the complexities of our future concept of PID, there will be an ever-increasing need for better treatment paradigms regarding other common diseases including cancer, allergy, and autoimmunity.

Ultimately, better insights on the underlying genetic and non-generic factors of PID may help to understand the pathogenesis and predict the clinical prognosis, resulting in both advanced management of the PID-
associated complications and moving toward integration of personalized therapies for the highest quality of life.61-63 Systematic approaches within the field of PID and an established national PID network consisting of clinicians and basic scientists in the field will help us to reinforce all scientific progress and human resources within the countries to discover a better solution for current general and regional PID challenges.

Authors’ Contribution
AA and NR. The conception and design of the study, interpretation of data, revising it critically for important intellectual content and final approval of the version to be submitted. HA: Acquisition and interpretation of data, drafting the article and final approval of the version to be submitted.

Conflict of Interest Disclosures
None.

Ethical Statement
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending or royalties.

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