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REVIEW ARTICLE

Current status and prospects of primary immunodeficiency diseases in Asia

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Abstract Primary Immunodeficiency Diseases (PIDs) are increasingly being reported across the World. Several advances have been made in the diagnostic and therapeutic research related to PIDs. With increasing awareness, the field of PIDs has rapidly evolved in Asia as well. In this review, we summarize the progress that has been made in the field of PIDs in Asian countries; major limitations and challenges faced by the clinicians working in this field in Asia; difference in spectrum of PIDs in Asia from rest of the World; current state of diagnostic and treatment facilities available in various countries in Asia and the future prospects of these diseases in the continent.

Introduction

Primary Immunodeficiency Diseases (PIDs) are a heterogeneous group of inherited disorders that lead to impairment in different components of the adaptive and innate immune system. PIDs are characterized by an increased susceptibility to infection, autoimmunity and malignancy. These disorders were initially considered to be rare and esoteric clinical entities. However, with increasing awareness and availability of better diagnostic facilities, more than 350 single gene defects have been recognized to cause PIDs.[1] Prevalence of PIDs has been reported to be as high as 1 in 1200.[2] Over the last 3 decades, there have been major advancements in our understanding of the pathogenesis, diagnosis, and management of these diseases. However, these disorders still remain under-recognized in several developing countries. This is predominantly because of the lack of awareness amongst physicians and also because of

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the non-availability of diagnostic facilities in resource-constrained countries.

Asia is the largest continent and is home to approximately two-thirds of the world's population. The population of Asia has increased by 4 times in the last century.[3] Several countries in Asia are still underdeveloped and there is wide disparity in the availability of health care. Mortality due to infectious diseases is much higher in Asia as compared to the Western world.[4] Approximately 7% of childhood mortality in South-East Asian countries has been attributed to vaccine-preventable diseases.[5] It is believed that immunodeficiency diseases are more relevant for the healthcare planners of a given country when deaths due to common infections have largely been controlled and children with PIDs are surviving long enough to be identified. Therefore, it has been observed that PIDs are more likely to be recognized when the under-5 mortality is below 15/1000 live births.[6]

Disparities in health care

Diagnostic and therapeutic facilities for PIDs in Asia are well developed in several Asian countries such as Japan, Iran and South Korea, and regions such as Hong Kong SAR and Taiwan region, even would match the standard of these facilities available in Europe and North America. India and China, the two largest countries in Asia, have shown a remarkable improvement in the care of patients with PIDs and several centers of excellence in PIDs have emerged. In this review, we highlight the current status of PID diagnosis and management in various countries across Asia, highlighting challenges faced by clinicians involved in PID care, differences in PID care in Asia as compared to rest of the World and future prospects of PID care in Asia.

Epidemiological data on PIDs from Asia and various PID registries (Fig. 1)

Japan and Korea

The first few reports of PIDs from Japan date back to the 1950s. The first survey and registration system for patients with PIDs in Japan was formulated in 1974 with the establishment of an All-Japan Immunodeficiency Registration Center at the Department of Pediatrics, University of Tokyo.[7] A survey of 497 patients admitted in Japan with PIDs from 1966 to 1975 was published in the year 1980. Commonly diagnosed PIDs in this survey were IgA deficiency, X-linked agammaglobulinemia (XLA) and ataxia telangiectasia. A research program under Japan's Ministry of Health, Labor and Welfare had established a clinical study group with the objective to perform epidemiological, pathological, diagnostic, and therapeutic studies on PIDs. The Primary Immunodeficiency Database Network in Japan (PIDJ) was established in 2008 with the objective of increasing research and outreach facilities. In 2011, a nationwide survey was published wherein 1240 PIDs patients were registered with an estimated prevalence of 2.3 per 100,000 inhabitants.[8] Although, this prevalence was higher than one previously reported prevalence of PIDs in Japan, it was much lower as compared to data from Western courtiers and Middle East. Several reasons have been postulated for this discrepancy. These include: low rate of consanguinity in this region, sample selection bias (asymptomatic selective IgA deficiency, transient hypogammaglobulinemia of infancy and few other PIDs were not included in this survey) and less recognition of PIds in adults.[8] Currently, facilities for diagnosis and management of PIDs are available in 66 hospitals across Japan.[9]

National registry on PIDs is also available from Korea. As per the registry data, 152 children were diagnosed with PIDs during the year 2001—05.[10] The prevalence of PIDs has been estimated to be 1.1 per 100,000 children less than 19 years of age. Antibody deficiency was the commonest PID followed by chronic granulomatous disease (CGD).[10]

China

The earliest reports of PIDs from China were published in the 1960s. Interest in PIDs in China became more evident in the 1980s.[11] A Pediatric Immunology section was formed under the Chinese Pediatric Society of the Chinese Medical Association in 1981. A collaborative network and patient registry for PIDs was framed in the 5th National Pediatric Immunology Conference in 1998. There has been a rapid increase in the number of patients with PIDs being reported in China. The largest cohort of patients with PIDs was reported from Children's Hospital of Chongqing Medical University, wherein 352 patients were diagnosed between 2005 and 2011. Genetic analysis results were available for 203 of these 352 patients.[12] Large cohorts of patients with PIDs have also been reported from other medical centers in China including Shanghai Jiaotong University Xinhua Hospital, Beijing Children's Hospital, and Guangzhou Children's Hospital.

In Taiwan region, the Primary Immunodeficiency Care and Research (PICAR) Institute at Chang Gung Memorial Hospital, Taoyuan City caters to a population of approximately 23 million and has established diagnostic and management facilities for various PIDs.[13] Another similar center is located in Taipei City.

The estimated incidence of PIDs in Taiwan region has been 2.17 per 100,000 live births, and Taiwan is the first region of South-East Asian area to incorporate the nationwide newborn screening for SCID in 2012.

The University of Hong Kong established a specialist service for children with PIDs in the year 1988 and facilities for molecular diagnosis of PIDs were first established in 1995. At present, the University of Hong Kong offers facilities for genetic diagnosis for several PIDs including whole exome sequencing.

Western Asia and the Middle East

In view of high rates of consanguinity in the Middle East, large number of PIDs have been reported from Turkey and Iran.[14,15] Turkey has two large centers for Pediatric Immunology in Ankara and Istanbul. The first Pediatric

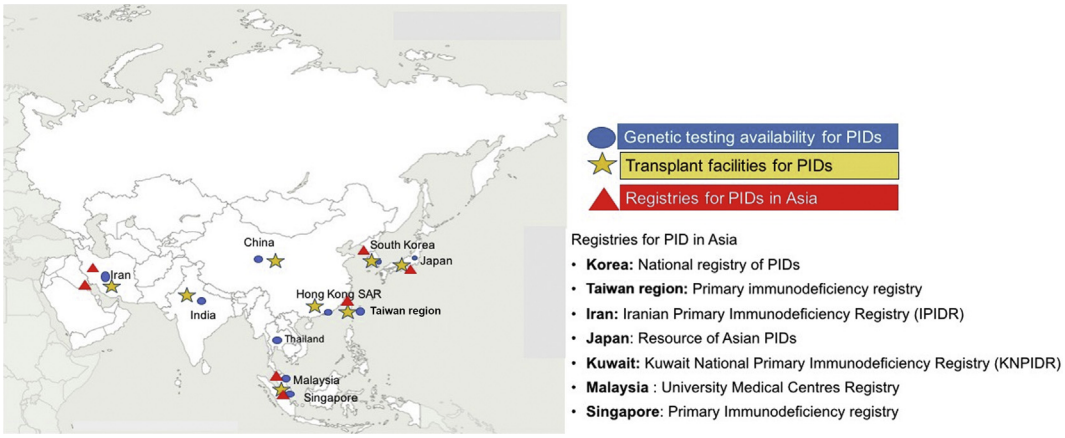

Figure 1 Geographical map of Asia depicting primary immunodeficiency diseases national registries, availability of genetic diagnosis and hematopoietic stem cell transplantation.

Immunology division was established at Hacettepe University Children's Hospitalin 1972. Autosomal recessive conditions are more commonly seen in these countries. The Turkish Society of Immunology was founded in 1974. Facilities for HSCT are also available and till date approximately 80 patients with SCID have been reported to undergo hematopoietic stem cell transplant (HSCT) in Turkey. Recently, two Jeffrey Modell Foundation (JMF) Centers for Immunodeficiencies have been established in Turkey: the Marmara University Department of Pediatric Allergy and Immunology in Istanbul, and the JMF Center at Hacettepe University.[15]

The first center for Clinical Immunology and Allergy in Iran was established at the Children's Medical Center, Tehran University of Medical Sciences, Tehran in 1977 by Professor Abolhasan Farhoudi.[16] A database for registration of Iranian patients with PIDs, the Iranian Primary Immunodeficiency Registry (IPIDR), was established in 1999. This is located at Children's Medical Center and covers major hospitals across Iran. As per the report of this registry, 3056 (with 1395 new cases) patients were registered in the IPIDR by the year 2018.[17] The Iranian Primary Immunodeficiency Association (IPIA) was founded in 1998 and aims at improving the diagnostic services, refining the management and treatment facilities and to promote research and education in the field of PIDs. Facilities for hematopoietic stem cell transplant for patients with PIDs are also available at several centers.

India

The earliest reported cases of PIDs from India date back to late 1960s. Case reports of patients with Wiskott Aldrich Syndrome (WAS), agammaglobulinemia and ataxia telangiectasia were reported first.[18–20] In the year 2012, Gupta et al published a study where in the clinical profile of patients PIDs at two large pediatric centers (Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh and the National Institute of Immuno-haematology (NIIH) and B.J. Wadia Children's Hospital, Mumbai) in India was compared.[21] It was found that the profile of patients with PIDs was different at the two centers. Antibody deficiencies were the commonest PIDs at Chandigarh, while familial hemophagocytic lymphohistiocytosis (HLH) was the commonest PID diagnosed at Mumbai. Other commoner PIDs diagnosed at Chandigarh were WAS, hyper IgE syndrome, ataxia telangiectasia and Hereditary angioedema. Mumbai, however, reported more cases of neutropenia, leukocyte adhesion deficiency (LAD), disorders of IFNγ-IL12 pathway and autoimmune lymphoproliferative syndrome.[21] With increase in the awareness, more cases of PIDs are now at Mumbai are now being diagnosed across the country.

The Indian council of medical research (ICMR) has funded 2 centers for advanced research in PIDs: The advanced Pediatrics center, PGIMER, Chandigarh and NIIH, Mumbai. Diagnostic and management facilities for patients with PIDs are available at limited centers across the country. These centers are now actively involved in the care of patients with PIDs since 2010. There has been an exponential increase in the number of published literature on PIDs from India since 2011.[22] There are several reasons behind this:

(i) Increased awareness among treating physicians;
(ii) Better facilities for diagnosis and treatment of these disorders. Several state governments have provided free of cost intravenous immunoglobulin (IVIg) replacement therapy for patients with PIDs. Hematopoietic Stem Cell Transplant (HSCT) facilities are also now available in many centers[23,24];
(iii) Indian Society for Primary Immunodeficiency (ISPID) and Foundation for Primary Immunodeficiencies (FPID) have played an important role in awareness about PIDs in India and establishment of diagnostic and treatment facilities at several centres.
(iv) Postdoctoral training courses in Pediatric Clinical Immunology was initiated in the year 2014 at PGIMER, Chandigarh, India. Several pediatricians who have trained at this centre are now working in different parts of the country to improve the care of patients with PIDs.

Other countries in Southeast Asia

Singapore is a growing hub for the diagnosis and management of patients with PIDs. In one of the first series that was published from Singapore in the year 2003, 39 patients were included. The data were collected from 3 large centers in Singapore that included the Children's Medical Institute, National University Hospital, Tan Tock Seng Hospital and KK Women's and Children's Hospital. The most common PID in this series was antibody deficiency followed by phagocytic defects.[25] Since then there has been a remarkable increase in the diagnosis of PID in Singapore. Facilities for HSCT are also available in many centers across Singapore.

Malaysia and Thailand are also catching up with the awareness and diagnostic facilities for PIDs. A National PID Initiative was started in 2007 to improve diagnostic facilities in various centers across Malaysia that led to improvements in PID care and the outcome of these patients.[26] The Malaysian Primary Immunodeficiency Network (MyPIN) was established in 2009 to improve diagnostic and treatment facilities for PIDs. More than 300 PID patients have been registered here.[27]

A study published in Thailand reported 72 patients with various PIDs from Ramathibodi Pediatric Allergy/Immunology/Rheumatology clinic from 1991-2011.[28] IVIg therapy is also available for most patients with PID at a subsidized rate in Malaysia and Thailand.[26,29]

Unique disease patterns of PIDs in Asia

The disease prevalence of PIDs varies across different nations in Asia. Because of high rates of consanguinity in Middle East countries, autosomal recessive diseases are relatively more common.[14] In several other Asian countries, X-linked forms of the disease are still more common. In studies from Japan and China, X-linked forms of SCID and CGD were found to be more common than AR forms.[30,31] While consanguinity may not be common, endogamous marriages are prevalent in many countries. As a result, autosomal recessive diseases are also very common in certain south-east Asian countries such as India, Pakistan and Bangladesh.[22] The genotype may determine the clinical profile of inherited diseases and may be modified by a host of environmental factors and may determine the final phenotype.[32] The environmental factors include the gut microbiota that the person is exposed to, the socioeconomic standards and the range of healthcare facilities available.

In addition to the difference in the spectrum of PID that is seen in Asia as compared to the rest of the world, patients with PID in Asia also have a unique and different pattern of infections. Some of these infections contribute to the major morbidity and mortality seen in these patients. Amongst these infections *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Burkholderia pseudomallei* and *Talaromyces marneffei* are the predominant ones.[6] Patients with CGD in Asia have been found to have a surprisingly high prevalence of tuberculosis infection as compared to patients with CGD from the rest of the world.[33] Because of higher endemicity of tuberculosis in many Asian countries, the Bacillus Calmette Guerin vaccine is given at birth. Therefore, in many Asian countries, disseminated BCG infection is the presenting clinical manifestation in many PIDs such as severe combined immunodeficiency (SCID), CGD, hyper IgM syndrome and defects in the IL12-IFN-γ axis pathway.[6] A high incidence of arthritis has also been reported in patients with XLA from Asian countries.[34] This is probably because of late diagnosis and subsequently a delay in the initiation of replacement immunoglobulin therapy in these patients. *Chromobacterium violaceum* has been reported as signature organism for phagocytic defects (i.e., CGD) in many Asian countries. It was initially reported in patients from Malaysia and was later reported in Vietnam, Thailand, Sri Lanka, India, as well as in Hong Kong SAR and Taiwan region of China.[35] Upto 50% mortality has been reported with the infection of this organism.[36] Similarly, melioidosis caused by *Burkholderia pseudomallei* is also endemic in many countries and is a major problem among patients with PID in Asia.[37] In the recent past, there is an identification of a number of PIDs associated with predisposition to endemic mycoses (e.g. *Talaromyces marneffei*, disseminated coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis) in this region. These fungal infections are especially related to defect in IL-12/IFN-γ axis, STAT1 gain of function and other T-helper 17 mediated diseases.[38,39]

Oral live polio vaccine is still being used in a few Asian countries and is a major problem for many patients with PID from these countries. Patients with hypogammaglobulinemia in these countries often receive oral polio vaccine even before their diagnosis of immunodeficiency is established. These patients may also get exposed to the vaccine strain of the virus through close contact in the family and community. Once these patients acquire live poliovirus, it is very difficult to eradicate it from their bodies. Immunodeficiency-associated vaccine-derived polioviruses (iVDPVs) thus remains a significant problem in these patients.[21,40] These patients also tend to act as a potential reservoir for transmission of poliovirus. In an international multicentric study, poliovirus excretion was studied in 653 patients with PID (570 had primary antibody deficiency and 65 had combined immunodeficiency). Thirteen patients (2%) excreted polioviruses and non-polio enteroviruses were detected in 30 patients. Five (0.8%) were classified as iVDPVs.[41]

Diagnostic facilities of PIDs in Asia (Fig. 1)

Most PIDs are inherited disorders and the easy availability of genetic confirmation by appropriate tests is necessary. The Ministry of Health, Labor, and Welfare in Japan took the lead in this regard and supported initiatives for research and treatment facilities for PID patients. The Japanese government established the RIKEN center (Rikagaku Kenkyûjo), Yokohama, for integrative medical sciences in 2001 which aims at collaborating with a network of 13 other institutions across Japan for genetic research on PIDs.[42] The Kazusa DNA Research Institute also provides genetic diagnostic facilities in Japan for PIDs. Riken IMS is supported by the Jeffrey Modell Foundation (JMF) and its collaborative centers. They have established the Primary Immunodeficiency Database (PIDJ) in Japan in 2008 which stores clinical data of more than 1500 PIDs patients. It provides a platform for diagnostic research and development of new therapeutic modalities. In Taiwan region, Chang Gung Memorial hospital is also recognized as a JMF diagnostic center for PIDs. It offers PID services through

Primary Immunodeficiency Care and Research (PICAR) Institute which provides facilities for diagnosis, prenatal screening and stem cell transplants in PID patients. China's mainland and Hong Kong SAR started collaborations between major centers across Asia specializing in PIDs in 2000. The network has been expanding continuously. The University of Hong Kong provides e-consultations and free genetic testing for patients with suspected PIDs from many countries across Asia. The Asian Primary Immunodeficiency (APID) Network was established in Hong Kong SAR in 2009 to serve as a better referral center for genetic testing in PIDs not only in China but among other Asian and African countries. Testing of 85 PID genes is provided via genomic PCRs, Gene Scan analysis, RT-PCR analysis and Next Generation Sequencing (NGS).

Resource of Asian Primary Immunodeficiency Diseases (RAPID) is a web-based portal where information related to genetic abnormalities associated with PID is stored to be used by clinicians and researchers across the world. It has been formed in collaboration with the Institute of Bioinformatics in Bangalore, India and the Immunogenomics research group at RIKEN Research Center for Allergy and Immunology in Yokohama, Japan. In India, diagnostic facilities are available at various centers across the country.

Next generation sequencing

PIDs are group of heterogeneous disorders with different clinical phenotypes, atypical presentation and overlapping clinical features. Definitive molecular diagnosis of most of these disorders is imperative for making treatment decisions, prognosis and for providing antenatal counseling. NGS has revolutionized the diagnostic armamentarium in the field of PID. The decrease in costs of these tests along with facilities for producing more stable DNA have made NGS a widely used tool for diagnosis of difficult PIDs. With the help of NGS several new disorders have been identified and unusual phenotypes have also been decoded. Largely there are three different categories of NGS technologies that are in use. These include: (i) Whole genome sequencing (WGS) i.e. sequencing of entire genome of a particular patient; (ii) Whole exome sequencing i.e. sequencing of entire protein coding region that is 2% of the whole genome and (iii) targeted gene panels i.e. sequencing of a fixed number of gene based on the clinical profile of patients. For patients with a predictable clinical profile, targeted gene panels are more cost effective. Several Asian countries are now offering the facilities for doing the NGS.[43,44] In India, genetic diagnosis for various PIDs is available at two centers including Chandigarh and Mumbai. Several commercial laboratories are now doing NGS at an affordable cost (approximately 450—500 USD for a whole exome sequencing).

Treatment facilities

The difference in care and management of patients with PIDs in Asia

There is wide variability in the culture, ethnicity and economic status amongst various nations of Asia, thereby leading to a spectrum of differences in the care of patients with PIDs in these countries. On one hand, Asian countries such as Japan, South Korea and Singapore, and some regions such as Hong Kong SAR and Taiwan region have shown strong commitment towards these rare diseases which is fully supported via legislation and regulations. These countries have channelized their resources in improving healthcare facilities for easy access to medical services for patients with PIDs. There are nationally funded research programs, patient support organizations, and public awareness promotions along with medical expense reimbursements for the welfare of patients with PIDs in these countries. However, these facilities are not freely available in all Asian countries. There is a need for trained immunologists in many parts of Asia, the need which remains largely unmet till date. Formal training for clinical immunology is being offered only in selected countries in Asia. However, the shortage of trained pediatric immunologists has been recognized and many countries have started adopting formal training programs to educate young doctors. In India, this training program was initiated in the year 2014, and to date, many trained immunologists have started providing care to patients with PIDs across different parts of the country.[22] Other nations in Asia who are not offering this training, need to adopt this policy soon.

Issues with intravenous immunoglobulin (IVIg)

IVIg is the standard of treatment for many PIDs especially XLA and CVID. However, the availability and cost of IVIg is a major limitation for its use in many developing countries. It is provided free for PID patients in government hospitals in many Asian countries like Malaysia. In other countries, the situation is not too optimistic. In the absence of government support and insurance cover, sustaining long term IVIg therapy can be extremely challenging for families.

Immunoglobulin replacement therapy via subcutaneous (SC) route has become a standard of care for patients with many PIDs in United States and European countries. Advantages of use of SCIG over IVIg include lesser systemic side effects, home based therapy, obviates need of venous access and improves overall quality of life.[45] Availability of SCIG in Asia Pacific region has improved gradually. However, the subcutaneous formulations are still unavailable across many Asian countries. In India, SCIG is not available and IVIg remains the mainstay of immunoglobulin replacement therapy.

In India, several state governments (e.g. Punjab, Haryana, Karnataka, Kerala etc.) have started reimbursing the cost of IVIg in patients with PIDs. There are many non-FDA/EMA approved preparations of IVIg that are available in the Indian market and are being used for more than 10 years now.[22] The use of these IVIg preparations has led to a drastic fall in the cost of monthly replacement therapy which is affordable to many families now. It is also a challenge to maintain a higher trough level of IgG in patients from developing countries. However, recent data from our own institute found that a lower trough level of approximately 400 mg/dl along with

the use of co-trimoxazole prophylaxis may be sufficient to prevent infections in majority of these patients.[46]

Hematopoietic stem cell transplant (HSCT) (Fig. 1)

HSCT is a definitive cure for many PIDs including severe combined immunodeficiency (SCID), WAS, CGD, HLH and many others. The main indications for transplant seen in the Asia Pacific are SCID, WAS, primary HLH. HSCT facilities are available in Japan since the year 1991.[47] In their annual nationwide survey, centers across Japan have registered 404 PID patients for HSCT from 1991 to 2011 and, 356 HSCT were performed in children and adolescents during this period. The major indications included SCID, WAS, and CGD. The follow-up studies have reported a comparable post-transplant cure and survival as in the Western World.[8,30,47] Korea has around 38 HSCT centers across the country. A series from Korea has described the results of PID HSCT performed in 26 patients from 2006 to 2016 at Samsung Medical center, Seoul.[48] The majority of them were CGD, WAS, and SCID. Hong Kong SAR has got 2 major HSCT centers for children. As per the available data, successful HSCT has been performed in 29 PIDs patients at Queen Mary Hospital for a wide spectrum of PIDs, including SCID, WAS, CGD, X-linked Hyper IgM syndrome, combined immunodeficiency, X-linked lymphoproliferative disease (XLP), LAD, severe congenital neutropenia (SCN), and immune polyendocrinopathy, enteropathy X-linked (IPEX), with an overall survival of more than 70%.[49] In China's mainland, 76 centers offer facilities for HSCT, but there is minimal data available on PID transplants from here. Singapore National University hospital reported its data on 7 patients with PIDs who were transplanted between 1996 and 2010 with a cure rate of more than 90%.[50] From India, a large series of 104 PID transplants was published by Uppuluri et al with good outcomes in more than 50% patients.[23] Over the last decade, several other centers have initiated programs for HSCT for PIDs. The number of successful transplants from other Asian countries is likely to show a rising trend in the near future.

Newborn screening

Taiwan is the first region in Asia to initiate a routine newborn screening programme for SCID in the year 2010 based on T-cell receptor excision circle (TRECs) copy numbers detected via dried blood spots (DBSs) from all newborn babies on day 3 of life. The Newborn Screening Center in Taiwan region screened 920,398 newborns in 78 months, 136 newborns were detected to have T cell lymphopenia, and 7 cases were diagnosed to have SCID. HSCT was carried out in 6 patients before they had any infection with a 100% survival rate. There are reports of newborn screening for SCID been conducted in Japan on a pilot basis.[51] In India, the TREC based assays are yet to be incorporated as the standard of care for newborn screening for SCID. However, pilot projects are necessary before the implementation of these strategies in a large country like India.[22] Since most of the SCID patients have lymphopenia at birth, evaluation of absolute lymphocyte counts has been proposed as a method of newborn screening in resource-limited settings.[52]

Professional bodies and their role in the progress of PID care in Asia

Asia Pacific society for Immunodeficiencies(APSID)

APSID was founded in April 2015 with the determined efforts from leading clinicians and scientists across Asia who were involved in the care of patients with PID. This society aims to provide better care and treatment facilities for patients with PIDs, provides better collaboration and education for PIDs across Asian countries. APSID was inaugurated in April 2016 in Hong Kong which was followed by the APSID Inaugural Scientific Congress. APSID has been organizing schools for young clinicians involved in the management of patients with PID. APSID will provide a platform for all PID related advancements across the Asian Countries through engaging governments, patient organizations & industry.[53]

Japanese society for immunodeficiency and autoinflammatory diseases (JSIAD)

JSIAD was established in 2017 with the merger of Japan Immunodeficiency Study Group, Autoinflammatory Disease Study Group, and Phagocyte Dysfunction Study Group. JSIAD aims to promote early diagnosis, treatment, and scientific research of primary immunodeficiency and autoinflammatory disorders. The society provides a common platform for the exchange of the latest information in the clinical and research field of PIDs. Their mission is to provide all the technological advancements in the field of PIDs to the patients, education of young doctors and promotes the social awareness of the disorders. JSIAD is committed to lead the field of PIDs, collaborate with those working in different clinical immunology fields and to promote a nation-wide discussion for better understanding and patient care for PIDs.[54]

Indian Society for primary immune deficiency (ISPID)

ISPID came into being in March 2011 and aims at providing better facilities for diagnosis, treatment and genetic counseling in patients with PIDs in India. It is also involved in creating awareness about PIDs via conferences, meetings, seminars, and collaboration with other medical societies. ISPID organizes one national and an international conference every other year. In addition to that, ISPID also conducts Continuing Medical Education (CME) programs for raising awareness about the diagnosis and treatment of PIDs in various parts of India.[55]

Foundation for Primary Immunodeficiency (FPID)

FPID was established in the US to support the education, early diagnosis, genetic counseling, therapy, and research of PIDs in both India and the USA. The Foundation supports

many activities in the US and India and has established many FPID Centers in India.[56]

Asia Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI), Asia Pacific Association of Pediatric Allergy, Respirology and Immunology (APAPARI)

APAAACI was formed at a regional allergy meeting held in Bali, Indonesia, in 1989, as the Asian Pacific Association of Allergology and Clinical Immunology (APAACI). The first Asian Pacific Congress of Allergology and Clinical Immunology (APCACI) was held in 1992 in Bangkok, and subsequent Congresses have been held every two to three years in major cities across Asia. APAAACI Congresses are a major educational program, used to encourage exchange between countries for training programs and research. Their major aim is to promote and support the development of the field of clinical immunology in the medical services across Asia. The Asia Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI) is an association of National/Regional societies of Allergy and Clinical Immunology in the Asia Pacific region. The objectives of APAAACI are to promote exchange and progress of knowledge on allergy, asthma, and clinical immunology in this region, exchange in training programs between member countries, development of programs for public information, dissemination of knowledge through organizing international congresses on allergy, asthma and clinical immunology.[57]

Patient advocacy organizations

Multiple organizations that provide international representation and support to PID patients group around the world have been established across Asia. The major organizations include (1) Indian Patients Society for Primary Immunodeficiency (IPSPI); Primary immunodeficiency Patients Welfare society (PiDPWs) from India (2) Thai Patient Organization of Primary Immunodeficiencies (ThaiPOPI); (3) PID Care China; (4) Perhimpunana Pasien Immunodefisiensi Primer Indonesia (PPIPI); (5) PID Korea; (6) PID Tsubasa-no-Kai in Japan; (7) Persatuan Pesakit Imunodefisiensi Primer Malaysia (Malaysian Patient Organisation For Primary Immunodeficiencies).

Limitations and future prospect

Despite recent advances and increasing availability of diagnostic and management facilities for PIDs in several Asian countries, there are several limitations and scope for future improvements. Awareness about these diseases amongst physicians, need of better and more easily available diagnostic facilities including NGS and availability of SCIg replacement therapy and HSCT are immediate need to improve the care of patients with PIDs in Asian counties. Newborn screening for SCID which is universal in USA and many European counties need to be implemented in Asia. Gene therapy is now an upcoming and established therapy for many PIDS in developed world. However, this therapy is largely unavailable in Asia. It is expected that in near future, several Asian countries would come up with better diagnostic and therapeutic facilities for patients with PIDs.

To conclude, PIDs in Asia are now being increasingly recognized. There have been major advances in the last decade in the form of increased awareness, availability of better diagnostic facilities including genetic diagnosis and management options. However, there are several lacunae and unmet needs for prompt diagnosis and treatment of these patients that are likely to be filled in near future.

Conflict of interest

The authors declare no conflict of interest.

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