CURRENT PERSPECTIVES AND CHALLENGES OF PRIMARY IMMUNODEFICIENCY DISEASES IN MALAYSIA

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Abstract

Primary immunodeficiency disease (PID) or inborn error of immunity is a heterogenous group of inherited diseases affecting the immune system resulting in increased susceptibility to infections, immune dysregulation, autoimmune manifestations, lymphoproliferation and malignancy. Cases of PIDs have been reported in Malaysia since 1977 and the numbers of reported cases steadily increased for the past 30 years with more trained clinical immunologist available, better immunodiagnostic facilities, wider immunoglobulin replacement therapy availability and improved techniques in haematopoietic stem cell transplantation for PIDs. In this article, we highlight some of the limitations and challenges in the diagnosis and therapy of PID, and more recent efforts to establish PID service in Malaysia.

Keywords: Primary Immunodeficiency, Malaysia, Precision Medicine

Introduction

Primary immunodeficiency disease (PID) is a heterogenous group of inherited developmental defects and/or functions involving the immunological system in human. International Union of Immunological Societies (IUIS) produces biennial reports on PIDs classification and the latest publication in 2019 reported 430 monogenic defects causing PID [1]. Severe combined immunodeficiency (SCID) is one of many types of primary immunodeficiencies with a worldwide incidence of 1 in every 200,000 live births. However, with the introduction of newborn screening program in USA for SCID since 2010, the incidence of SCID detected increased to 1 in every 58,000 live births [2]. The actual incidence of each genotype causes of PID is rare, but collectively, PID is not as rare as previously described. Recent publication estimated that almost 6 million people may have primary immunodeficiencies globally, but only 27,000 – 60,000 have been diagnosed and included in patient registries [3].

Patients may present with broad clinical manifestations, ranging from increased susceptibility to infections to significant immune dysregulation, often leading to multiple autoimmune manifestations, lymphoproliferation and malignancy. It is important to diagnose PID early as the survival outcome correlates with early appropriate treatment delivery. Patients with SCID will not survive beyond their first year if detected late and did not receive allogeneic haematopoietic stem cell transplantation.

Primary immunodeficiency diseases (PID) are recognised in a 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 recognised when the under-5 mortality is below 15/1000 live births [4]).

Primary immunodeficiency disease is a perfect example of precision medicine. Precision
medicine are defined as tailoring therapy directed at the specific causative genetic defect of a particular disorder rather than applying a non-specific therapeutic approach [5]. The rapid identification of pathogenic mutation in patients suspected of having PID, enable the use of targeted curative treatment. For example, identification of genetic mutations for severe combined immunodeficiency enables the application of haematopoietic stem cell transplantation or gene therapy in correcting the defect. Identification of molecular diagnosis enables selection of biologics that targeted specific pathways such as Abatacept in CTLA-4 haploinsufficiency and Sirolimus for PIK3R1 defect [5]. Heterozygous germline mutations in CTLA-4 cause immune dysregulation manifestation and patients may present with autoimmunecytopenias, non-malignant lymphoproliferation, enteropathies, hypogammaglobulinemia and infection susceptibility. Abatacept is a CTLA-4 IgG fusion protein and have been shown to successfully treat the immune dysregulations observed in CTLA-4 haploinsufficiency [5]. PIK3R1 defect is one of the known mutations causing activated phosphoinositide 3-kinase δ syndrome (APDS). PI3K is a class IA lipid kinase that is responsible for generation of phosphatidylinositol 3,4,5-triphosphate by phosphorylation of phosphatidylinositol-4,5 biphosphate. Patients with APDS may present with recurrent infections, autoimmunity, non-malignant lymphoproliferation, severe or persistent herpes virus infections and B-cell dysfunctions. Sirolimus have been shown to effectively treat the lymphoproliferation and autoimmunity in APDS by inhibiting the mTOR pathway.

**PIDs in Malaysia**

Malaysia is a small country situated in South East Asia with a total population of 32.6 million, with the total live birth in 2018 of 501,900 and GDP per capita of USD 10,940. Estimated life expectancy in Malaysia is 74.5 years and 28% of the population of Malaysia are less than 18 years old, with the under-five mortality child rate at 7.8 deaths per 1,000 live births in 2018 [6].

The earliest reported PID case from Malaysia was in 1977, a case of selective IgA deficiency [7]). The only available cohort study describing clinical-epidemiological pattern of PIDs was published in 2013 [8]. The data presented was from 1986 until 2006 involving 4 hospitals in Malaysia which included Hospital Kuala Lumpur (1986 – 1993), Hospital Universiti Sains Malaysia (HUSM) and Hospital Kota Bharu (1994 – 2000) and Hospital Serdang (2003 – 2006). A total of 51 patients were diagnosed to have PIDs over the span of 20 years. Primary antibody deficiency made up the majority of PID diagnosed at 40.4% followed by phagocytic defects (17.3%), combined immunodeficiency (15.4%), other cellular immunodeficiency (11.5%), other defects such as chronic mucocutaneous candidiasis and hyper-IgE syndrome (9.6%), Chediak Higashi syndrome (3.8%) and myelodysplasia (1.9%). Five patients of severe combined immunodeficiency disease were detected. The documented diagnostic delays of 3.87 years in this study cohort were longer compared to other PID registries globally.

Most of the patients were diagnosed mainly based on clinical presentations coupled with basic immunodiagnostic assays that were available at the time. Genetic diagnosis was unavailable for most of the patients from this cohort. All these 4 centres are paediatric centres and there was no adult clinical immunologist available in the country. Thus, PIDs cases involving adult patients were not depicted and were significantly under-diagnosed in Malaysia.

The incidence and prevalence of PIDs were not able to be calculated from this cohort study as it was only representative of 4 centres in Malaysia. However, we expect that PIDs prevalence are not that rare and may be similar to other different parts of the world. Furthermore, with the ethnic heterogeneity and differences in microbial flora in our country, possibly many more novel PID gene mutations will be discovered. An association of *Burkholderia pseudomallei* and *Chromobacterium violaceum* infection have been shown to have special predilection in Chronic Granulomatous Disease patients from South East Asia [9].

**Challenges in Malaysia**

PID remains underdiagnosed and unrepresented in Malaysia. Only 51 PID cases were diagnosed within a span of 20 years in Malaysia according to available published cohort study [8]. The cases reported were very low compared to other reported cases in Asia. The reason for this discrepancy is complex and includes aspects related to not only medical education but also
economic, political and social priorities. These includes the unavailability of PID patient database registry, inadequate immunodiagnostic capacity, unavailability of national newborn screening program and reduced awareness among the healthcare workers on early detection of PID.

**Awareness among the health practitioners**
The delays in PIDs diagnosis reflected the low level of awareness on PID among the healthcare practitioners in Malaysia. There is an urgent need for continuous medical education on PID for practising medical doctors. A concerted effort by Malaysian Society of Allergy and Immunology (MSAI), Malaysian Patient Organisation for Primary Immunodeficiencies (MyPOPI) and PID research groups to provide continuous PID education are applauded.

**PID clinical services**
There are 5 clinical immunologists in Malaysia but 4 are based in Kuala Lumpur and one in Bertam, Pulau Pinang. The numbers are inadequate considering Malaysia is a country with 32.4 million populations, which gives ratio of 1 clinical immunologist to 6.48 million Malaysia’s populations. The expected ratio of clinical immunologist to a country population is suggested at 2 per 1 million populations [10]. Thus, more trained clinical immunologist is urgently needed to address the issues of inequality of access due to geographical locations.

At the moment, clinical immunology is still not recognised by the National Specialist Register, Malaysia as one of the sub-specialty field in Malaysia. This hinders the development of the field as only one trained clinical immunologist is available in the Ministry of Health (MOH), Malaysia. PIDs patients in MOH facilities were managed by various paediatrics subspecialties such as Paediatric Respiratory Specialist, Paediatric Infectious Diseases Specialist, Paediatric Dermatologist Specialist and General Paediatricians depending on the clinical presentations and availability of expertise in MOH facilities. This may be not apt and conducive as PIDs are becoming more complicated and diverse in the manifestations with more recent new PIDs discoveries are made with the advent in genomic sequencing.

**Immunodiagnostic capacities and the hurdles**
The enormous clinical and immunological heterogeneity in the PIDs makes diagnosis challenging, but there is no doubt that early and accurate diagnosis facilitates prompt intervention leading to decreased morbidity and mortality. Furthermore, although PIDs represent a high cost in health, it should be noted that the early diagnosis and early curative treatment leads to a decrease in the cost associated with more chronic morbidities.

We acknowledge that Flow Cytometry (FACS) could be as informative as a genetic test and that it can be used in the diagnosis of almost all known PIDs. Although FACS is a widely used technology in most developing countries, its pricing remains restrictive and, the access tends to be limited to the most common markers, such as CD3, CD4, CD8 and CD19. Even in PIDs specialized diagnostic laboratories, such as the PID diagnostic centre at Advanced Medical and Dental Institute (AMDI), the number of tests are limited, and in some cases, logistically restrictive. This happens as the centre receives clinical referrals from Northern and Eastern Malaysia (Kelantan and Terengganu).

Other tests that can be easily performed in our centres are the PMA-induced dihydrotriamine-1,2,3 (DHR) oxidation, switch memory B cells, detection of the CD40 ligand on the surface of in-vitro activated CD4+ T cells, CFSE cell proliferation assay and serum immunoglobulin levels. Other more specialized FACS-based tests, such as CD107 and Perforin expression, are quite difficult to perform in our centre, and although samples can sometimes be sent abroad, this can be logistically and financially difficult.

Several facilities for molecular diagnosis are available in Malaysia but were not specific to PIDs diagnosis. Access to genetic testing in Malaysia is often limited by cost, shipment of the samples and turn-around time depending on the method of gene sequencing requested.

Targeted panel next generation sequencing offers rapid assessment of a specific cohort of genes and maybe more cost efficient compared to Sanger sequencing. However, it is limited to listed genes in the panels and not available locally. Whole exome sequencing applies technique of sequencing the protein coding regions of a genome [11]. This protein coding regions contained approximately 85% disease-causing mutations. Major limitations of whole exome sequencing are the expensive cost and long turn-around time which might jeopardise patient’s clinical care. Another important issue is the interpretation of the genetic variants identified especially concerning on the variants of
unknown significant (VUS) and the ethical issues of handling cases with re-classification of previously classified as variants of unknown significance into pathogenic variants. The role of clinical immunologist as part of the teamwork needed for interpretation of VUS should not be undermined as errors in interpretation may cause a substantial damage to patients.

A recent effort by the PID Unit in Institute of Medical Research (IMR) in developing whole exome sequencing as a diagnostic PID tool have yield some interesting results. They identified and reported a novel de novo heterozygous NLRC4 mutation in a 12-year-old Malay girl [12]. PID research group from Advanced Medical and Dental Institute (AMDI), USM are also working on developing multi-locus sequencing panel for diagnostic of Severe Combined Immunodeficiency (personal communication with Dr Intan Juliana Abd Hamid). These appear promising as access to genetic testing are crucial in PIDs diagnosis and should be available to all patients irrespective of their socio-economic status and geolocations.

Development of PID in Malaysia

Malaysian Society of Allergy and Immunology (MSAI)
The Malaysian Society of Allergy and Immunology (MSAI) was officially registered in May 1997. The society actively promotes awareness and dissemination of knowledge on PID and allergies in Malaysia through their annual conference of Malaysian Congress and Exhibition on Allergy and Immunology which will become the 20th years in 2020. MSAI also hold a yearly National Clinical Immunology Symposium (NACLIS) as part of continuous training focusing on PID for medical practitioners. MSAI together with MyPOPI has come together and published a white paper on PID as a hidden health threat in Malaysia in 2017 [13]. Several recommendations were suggested via this position white paper to improve healthcare of PID patients in Malaysia, which includes:
1. Recognise clinical immunology (either combined with infectious diseases or stand-alone) as a sub-specialty.
2. Make a concerted effort to recognise SCID early (future plans to include Newborn Screening) and to provide haematopoietic stem cell transplantation facilities in regions where transport of babies bereft of immune functions is hazardous (particularly East Malaysia).
3. Prioritise immunoglobulin replacement therapy (IRT) for PID patients.
4. Provide access to a wide spectrum of immunoglobulin products, to provide optimal treatment for all PID patients.
5. Establish facilities for tertiary laboratory investigations to enable firm diagnosis of PID. When such facilities are centred in the Federal capital/Klang Valley, a push is needed for developing such facilities in major regional centres in Malaysia, especially East Malaysia.
6. Ministry of Health to work with the Malaysian Patient Organisation for Primary Immunodeficiencies (MyPOPI), Malaysian Primary Immunodeficiencies Network (MyPIN), and Malaysian Society of Allergy and Immunology (MSAI) to raise awareness about PID throughout Malaysia including Sabah and Sarawak.

Malaysian Society of Primary Immunodeficiency (MyPOPI)
The Malaysian Society of Primary Immunodeficiency (MyPOPI) was established in October 2013 and is an associate member of International Patient Organisation for Primary Immunodeficiencies (IPOI). It is a non-profit organisation and a registered society helping and supporting families affected by primary immunodeficiencies in Malaysia. They are actively reaching out and promoting awareness and advocacy of PID within the community through medical conferences, road shows and health policy makers.

International collaboration efforts
Few collaborative works between clinical immunologists in Malaysia and international partners have brought fruitful diagnosis for patients. Two siblings from a consanguineous family whom presented with bronchiectasis and high level IgE were diagnosed with DOCK8 immunodeficiency which was the first ever described from Malaysia [14]. Apart from that, several Severe Combined Immunodeficiencies were diagnosed upon collaboration work with PID centre in Hong Kong [15].

Subcutaneous immunoglobulin replacement therapy
Immunoglobulin replacement therapy remains the mainstay of treatment especially for those with primary antibody defects. Intravenous immunoglobulin replacement therapy is provided for free at the moment in MOH facilities and some of the university’s hospitals. Only one patient from Universiti Kebangsaan Malaysia has
been on subcutaneous immunoglobulin replacement [13]. Discussion and proposals are still underway to bring subcutaneous immunoglobulin into the Blue Book, MOH so that it can be prescribed to all PID patients in Malaysia.

**Haematopoietic stem cell transplantation services in Malaysia**

The haematopoietic stem cell transplantation for paediatric patients is offered in few centres which includes Hospital Tunku Azizah and University of Malaya Medical Centre (UMMC) and primarily are for haematological and malignant disorders. However, the local centres have started to venture into non-malignant disease transplant. A total of 20 PID patients had undergone bone marrow transplant in UMMC from 1983 until 2018 with 90% survival outcome which is comparable to international centres [16]. They also highlighted delay in diagnosis as one of the major factors influencing the success of bone marrow transplant. Haploidentical haematopoietic stem cell transplantation program using T-replete approach with in vivo depletion of alloreactive using intravenous cyclophosphamide were introduced in UMMC since 2016 and became an attractive option for those without matched donors and limited resources. A haploidentical bone marrow transplant using TCR/CD19+ depletor graft manipulation was performed successfully in a SCID baby by the Hospital Tunku Azizah team in 2019 (personal communication with Dr Mohd Najib Mohammed).

**Conclusion**

Primary immunodeficiency development in Malaysia is promising due to concerted effort from various parties. Collaborative efforts among major stakeholders are important to ensure optimal PID healthcare delivery. PIDs as precision medicine should be the next focus of expansion in Malaysia.

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**References**


