EDITORIAL

Severe Combined Immunodeficiency in Malaysia: It's Time to Shape a Future with No-One Left Behind

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PRIMARY IMMUNODEFICIENCY: DEFINITION AND CLASSIFICATION

Primary immunodeficiency disease (PID) is a heterogeneous group of genetic disorders that affect the development and/or function of innate and/or adaptive immunity. Classical PID has been recognised as a disorder with loss of function of the immune system with increased susceptibility to recurrent and persistent infections, infections by opportunistic organisms, and growth retardation. However, in recent years studies have shown that patients with certain types of PID are prone to develop immune dysregulation with autoimmunity, autoinflammation, lymphoproliferation, severe allergies or predisposition to malignancy. Therefore, the term inborn errors of immunity (IEI) is now used to refer to PID in the International Union of Immunological Societies (IUIS) classification. The IUIS expert committee on IEI met approximately every two years to revise the classification and consolidate advances of IEI and catalogue current genetic mutations linked to the disease. In the latest report published in June 2022, there are now 485 distinct disorders of IEI with different gene defects, and the diseases are classified into 10 different categories (1). This phenotypic classification is developed in order to help clinicians at the bedside to diagnose PIDs which focuses on clinical and laboratory phenotypes of specific PID, but also to promote collaboration with national and international research centres. Although more than six million people are affected by PIDs worldwide, only about 10-30% of them are diagnosed (2).

PID AND SEVERE COMBINED IMMUNODEFICIENCY IN MALAYSIA

In Malaysia, the first description of PID was reported in a child with IgA deficiency and bronchiectasis in 1977 (3). It was then followed by scattered case reports exclusively on clinical presentations with limited immunological data (4), including severe combined immunodeficiency which was described in 1997, 20 years after the first reported PID case (5).

In the mid-1980s, Dr Lokman Md Noh as the country's sole paediatric clinical immunologist had diagnosed PID in Malaysia at a modest rate of 2.5 cases per year until 2002, and three cases per year until 2006. Following the return of Dr Amir Hamzah Abdul Latiff from overseas, the number of PIDs diagnosed and recorded increased almost 10 times to an average of 24 cases per year from 2007 to 2011. The number of cases continued to increase from 2012 until now with another clinical immunologist in the country, Dr Intan Hakimah Ismail (6). The current rate of PID prevalence worldwide is 1 in 1,200, and hence the number of patients with PID in Malaysia is estimated at 25,000 (6). Until 2023, Malaysia only has eight active clinical immunologists based in the university, public and private hospitals to care for the PID cases in Malaysia.

Severe combined immunodeficiency (SCID) is the most severe forms of PID. It is characterised by severe defects of cellular and humoral immunity that render affected infants susceptible to opportunistic and recurrent infections. The overall SCID frequency is estimated to be 1 in 75,000-100,000 of live births, however, according to data from the newborn screening programme in the United States, it is now estimated at 1 in 58,000 live births (7).

SCID is characterised by absence of both T-lymphocyte and B-lymphocyte function which results in lymphopenia and hypogammaglobulinaemia. Affected infants often appear normal at birth but subsequently develop severe infections early in life, and if untreated, lead to fatal outcome within the first year of life. Therefore, identification of SCID is considered a paediatric emergency because survival depends on expeditious stem cell reconstitution as patients transplanted before age 3.5 months have more than 90% survival rate (8). Delay in recognising and detecting SCID can have fatal consequences and also reduces the chances of a successful bone marrow transplant.

SCID IN MALAYSIA IS A CAUSE FOR GREAT CONCERN

The SCID main manifestations are growth retardation and severe recurrent infections starting in the first year of life, caused by intra- and extracellular microorganisms.

It is crucial that babies be diagnosed before they are exposed to even the tamest bacteria or viruses – the common cold can be deadly to them. BCG vaccine which includes a weak but live microbe, given at birth can cause serious illness as well as disseminated BCG infections in newborns with SCID.

The number of SCID in Malaysia is increasing; since 2010 we are seeing at least 1-2 cases per year compared with six cases within 18 years period (1992-2010) (Proceeding of the International Primary Immunodeficiency Congress, 8-10 November 2017, Dubai, UAE). Since 2012, this number is showing an increasing trend whereby an average of 3-5 cases of SCID have been referred to the clinical immunologists in the country (Proceeding of the APAAACI 2023 International Conference, 23-26 October 2023, Singapore). However, it is frequently not suspected by primary physicians, even at the referral centres, hence delayed in diagnosis. This is due to several reasons which include, lack of recognised family history, absence of distinguishing physical or classical characteristic and their variability, lack of awareness among paediatricians on early suspicion and lack of available facilities to work up towards a diagnosis (distant from the primary hospital).

In credible centres overseas, there is more than 90% of survival. In Malaysia, the diagnosis is often late, and survival rate is low. Prior to 2016, almost all (100%) of SCID in Malaysia made a demise between 4 to 15 months of age. They died because of infection-induced end organ damage, particularly to the lungs and liver (6).

'BUBBLE BABY' DISEASE IN MALAYSIA – LIGHT AT THE END OF TUNNEL

SCID is known most widely by its nickname, the 'bubble baby' disease in reference to David Vetter, a boy from Texas who lived in a germ-free plastic bubble from birth until the day he died. Most children born with the disease die from opportunistic infection or otherwise self-limiting infections during their first year of life unless they are treated with bone marrow transplantation (BMT). Without transplant, SCID patients rarely live past their first birthday. Haematopoietic stem cell transplantation (HSCT), a type of BMT is curative with a very high chance of normal immunity, growth, and development, as long as the diagnosis is made early. BMT using stem cells obtained from a family-related, HLA-identical donor is currently the established mode for immune restitution and cure for children with SCID. However, the medical challenge is compounded by the absence of an HLA-matched sibling which occurs in 70-80% of individuals. In Malaysian setting, the probability of finding a matched-unrelated donor from the national donor registry is only 2–5%, due to a relatively small registry pool and ethnic heterogeneity (9). Stem cell transplant using an HLA-partially matched family donor, also referred to as haploidentical transplants, are increasingly being utilised. The first haploidentical parental BMT for SCID was performed in Malaysia in 2015 (6). Between April 2016 and December 2017, three patients with SCID underwent haploidentical transplants from a parental donor and one patient received an HLA-matched sibling HSCT, all with good outcomes (9). Subsequently, more SCID patients underwent HCST either using haploidentical donor or matched sibling donor. HSCT for PID is currently a feasible curative option in Malaysia and the latest report demonstrated a 90% overall survival for most types of PIDs (9).

Newborn screening (NBS) for SCID can identify infants before they get infections. NBS is a screening in babies performed shortly after birth for conditions that are treatable, but not clinically evident in the newborn period. Although NBS requires extra healthcare expenditure, it is important from a medical point of view, and can be cost-effective in the long run (7). When SCID babies are hospitalised for infections, their hospital bills can go up to thousands of ringgits (and maybe more) before they receive the transplant. NBS for SCID in Malaysia is now being lobbied to get it incorporated into the public healthcare system in Malaysia. If newborns are diagnosed within weeks of birth, they can get a bone marrow transplant that will let them grow a new immune system to replace the faulty one, essentially curing the disease. While waiting for the transplant, the best treatment for those SCID babies to stay alive is by giving them regular 2-3 weekly antibody or immunoglobulin infusions, which can be both costly and cumbersome to manage.

Family history of early infant death due to infection or known SCID is an important history which led to an earlier diagnosis. This is true for Malaysian SCID as we now have surviving SCID children saved by their deceased siblings. Once the babies are delivered, they will be monitored in the hospital until their immune results are available. Those confirmed to have SCID are referred to the bone marrow transplant team and transplant is carried out within the first 3 months of life. Here, we describe our youngest SCID patient who was successfully transplanted at the age of 1-and-a-half-month. MR who is now a 7-year-old boy was monitored and investigated soon after birth following the family history of his 3rd elder brother who died at the age of 8 months due to severe sepsis with coagulopathy secondary to SCID. The BCG vaccination was withheld, intravenous immunoglobulin was started, antibiotic and antifungal prophylaxis were commenced and he was kept in an isolation room. Instructions were given as not to transfuse unirradiated blood products. As soon as he was confirmed to have SCID, he was immediately transferred to the bone marrow transplant unit. At day 47 of life (about 1 month), he received an HLA-identical HSCT from his 2nd elder brother. Three months post-transplant, his immune parameters have markedly improved and lymphocyte numbers have normalised. As

the family members of surviving SCIDs in Malaysia once said "BMT offers hope, and we can now see some light at the end of the tunnel for SCID babies in Malaysia".

Advanced Medical Research in Allergology & Clinical Immunology (AMRAC) Universiti Putra Malaysia (UPM) is a centre dedicated primarily to improving the diagnosis and treatment of PID through clinical activities, research, education and advocacy. Starting as a Clinical Immunology Unit within the Department of Paediatrics, Faculty of Medicine and Health Sciences UPM, we have been the major referral centre for PID in Malaysia since 2007 and further established after 2012. We are the first in the country to provide both clinical and laboratory investigations for PID cases at one setting. We receive referrals from all over Malaysia (10). There are approximately more than 450 patients with PID currently being followed up at our centre.

CONCLUSION

It has become clearer now that PIDs in Malaysia are much more common that routinely appreciated. Unfortunately, most children are diagnosed only after the occurrence of severe and recurrent infection and its complications, with a significantly worse prognosis. Early and accurate detection of PIDs especially SCID in the affected children is therefore essential so that therapeutic measures can be taken quickly, hence help prevent sequelae and allow for quicker referral to therapy. Currently, Hospital Pengajar Universiti Putra Malaysia (HPUPM) or now known as Hospital Sultan Abdul Aziz Shah (HSAAS) UPM provides clinical consultation for patients with PID via the Allergy & Clinical Immunology Specialist (ACIS) Centre. We also offer basic immune tests and advanced tests to diagnose PID through our laboratory, Primary Immunodeficiency and Allergy Diagnostic & Research Laboratory (PEARL) (10). Our hope is to see SCID patients in Malaysia to be diagnosed early and managed promptly and appropriately, and emphasising the urgent needs for the implementation of newborn screening for SCID in Malaysia. **It's Time to Shape a Future with No-One Left Behind.**

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