EDITORIAL

COVID-19: Lessons from Paediatric Population and Primary Immunodeficiency

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Coronavirus timeline: In late December 2019, the Health Officials in Wuhan, China reported a cluster of pneumonia cases of unknown aetiology with a common link of being exposed to the Hunan Seafood Market in Wuhan [1]. This has raised an intense attention not only within China but also internationally as the world watched closely of what would be the cause and how bad it will be. Later, on 7 January, it was officially announced by the World Health Organisation (WHO) that the culprit of this outbreak was a new strain of virus that has not been previously identified or detected in humans, named novel coronavirus (2019-nCOV), and then renamed SARS-CoV-2 [1]. This new virus belongs to the same coronavirus family as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) that caused outbreaks in China and Saudi Arabia, respectively. The disease, named coronavirus disease 2019 (COVID-19), subsequently spread globally leading to the pandemic declaration by the WHO on March 11, 2020 [2]. The numbers continue to escalate daily; until this article was written, there were over 56 million confirmed cases resulting in more than 1.3 million deaths were reported worldwide. COVID-19 poses a global serious threat to human life and health welfare. When we first here about this outbreak, I believe majority of Malaysians would never in our wildest dream imagine that the virus could be tracked down in Malaysia. The first three COVID-19 cases in Malaysia was reported among tourists from China in Johor Bahru on 25 January, and the first two deaths was recorded on 17 March [3]. As of November 19th, a total of 51,680 positive COVID-19 cases and 326 deaths were reported in Malaysia.

Lessons from paediatric population: Most symptomatic cases have occurred in the adult population, characterised by fever, dry cough, malaise and difficulty in breathing. Elderly individuals and those with comorbidities are at particular risk for contracting the infection. Apart from the elderly, paediatric population is also perceived to be the most vulnerable. It is unusual that a viral infection would be less severe in children than it is in adults. However, emerging evidence has given us new insights, which may challenge our conventional way of thinking and understanding. Interestingly, at the beginning of the pandemic, there are only handful of paediatric cases infected with SARS-CoV-2. In the United States and globally, fewer cases of COVID-19 have been reported in children (age 0-17 years) compared with adults [4]. In June 2020, the Director General of Health announced that about 20% of COVID-19 cases in Malaysia were aged 18 years and below and no deaths or intensive care unit (ICU) cases involving this age group have been reported [5]. These infected children are usually asymptomatic or results in much more mild symptoms and less likely to lead to severe disease. Moreover, the case-fatality rates are also lower. This shows that COVID-19 cases in this age group have a better recovery rate. The SARS-CoV-2 enters the host cells by binding to the cellular receptor angiotensin-converting enzyme-2 (ACE-2) which can be found in the lungs. One of the probable reasons for children progressing better than adults is that they have less ACE-2 receptors in their lower airways, thereby limiting the chance of viral invasion [6]. In addition, children also have fewer chronic cardiovascular and respiratory conditions, which are the main predisposing factors for severe COVID-19.

Studies in China pointed out that gastrointestinal (GI) tract could also be a potential route of infection and children tend to have more GI symptoms than in adults [7]. Interestingly, GI symptoms can be the first manifestation of SARS-CoV-2 infection in the absence of respiratory symptoms [7]. Additionally, infected children with GI symptoms are prone to presenting with more clinical and laboratory abnormalities than those without GI symptoms [8]. The pathophysiology for SARS-CoV-2–associated GI symptoms remains unclear. Nevertheless, the ACE-2 receptors that are located in the lungs are also found in the intestine. This suggest that infection not only occurs through air droplets in the respiratory tract, but also through GI tract by faecal-oral transmission [9].

Beginning late April 2020, several reports emerged from the highly endemic countries, particularly in the United Kingdom and the United States, highlighting increased incidence of previously healthy children presenting with severe inflammatory syndrome similar to Kawasaki disease or toxic shock syndrome [10-12]. This later is known as multisystem inflammatory

syndrome in children (MIS-C), which comprises of fever, elevated inflammatory markers, and organ dysfunction not attributed to another infectious cause [13-14]. Strikingly, these children were asymptomatic during SARS-CoV-2 infection, but weeks later developed symptoms comparable to Kawasaki disease but they are much sicker in regard to hypotension, signs of shock and development of coronary artery aneurysms [15]. Fascinatingly, they did not have severe respiratory distress. MIS-C does seem to be a phenomenon unique to the paediatric population.

Lessons from primary immunodeficiency: Being a clinical immunologist, I cannot evade talking about primary immunodeficiency (PID) and the impact of COVID-19 on PID. PID refers to a heterogeneous group of disorders characterised by poor or absent function in at least one component of humoral or cellular immunity, leading to increased susceptibility to recurrent and persistent infections, infections by opportunistic organisms, and growth retardation. Conventionally, immunodeficient patients are considered to be at high-risk population for infectious diseases including viral infections, and therefore are also identified as a risk group for severe COVID-19. Little is known about the exact pathogenesis of this coronavirus. However, underlying immunological mechanisms such as hyper-inflammation and cytokine storms have been extensively studied. This mechanism is believed to aggravate the clinical profiles of COVID-19 patients [16-17]. Intriguingly, it was documented that some PID patients are not getting the SARS-CoV-2 infection as what have been projected. It was found that the risk factors for severe COVID-19 and mortality among PID patients were comparable to those in the general population [18]. Likewise, several case reports suggest a favourable outcome in PID patients who acquired the infection. Patients with X-linked agammaglobulinaemia (XLA) whom B-lymphocytes (B cells) are absent had milder course of disease as compared to those with common variable immunodeficiency (CVID) who are characterised by dysfunctional B cells [19]. One has postulated that PID could be protective against COVID-19 or render the disease severity. Maturation of B cells from pre-B cells requires an intact Bruton tyrosine kinase (BTK) protein. Interestingly, BTK protein, which is deficient in XLA patients, is shown to be involved in the activation of macrophages and IL-6 (a pro-inflammatory cytokine) production in COVID-19 [20]. The intrinsic lack of B cells is considered as an advantage by preventing the development of inflammation and cytokine storms in XLA patients. Future studies are required to provide more insights on immune modulation strategies to treat COVID-19 in patients with PID as well as the general population.

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