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Pediatric Hematology Oncology Journal 7 (2022) 90–91

Contents lists available at ScienceDirect

Pediatric Hematology Oncology Journal

journal homepage: https://www.elsevier.com/journals/pediatric-hematology-oncology-journal/

Milder COVID-19 in children with inborn errors of immunity

Keywords:
COVID-19
Primary immunodeficiency disorder
Pediatric

To the editor

Inborn errors of immunity (IEI) refers to a group of genetic disorders with either deficiency or dysregulation in humoral, cellular or innate immunity. It is postulated that Coronavirus disease 2019 (COVID-19) in children with IEI will have different outcomes than general population due to their altered/dysregulated immune system. The mortality associated with COVID-19 is mostly due to dysregulated inflammatory response rather than the direct viral injury, or viral replication itself [1]. COVID-19, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) has posed a significant threat to global public health and patients with comorbidities are at higher risk of complications [2]. We have total of 31 children with IEI (Wiskott-Aldrich-5, Hemophagocytic lympho-histiocytosis-6, DOCK-8 deficiency-1, Common variable immune deficiency-1, Chronic granulomatous disease-1, Severe combined immunedeficiency-3, Heme-Oxygenase-1 deficiency-3, Chediak-Higashi Syndrome-1, Autoimmune lymphoproliferative syndrome-4, Agammaglobulinemia-4, GATA2 deficiency-1, CARMIL2 deficiency-1) in follow up at our hospital. During the period of pandemic out of these 31 patients only two children developed COVID-19 infection. None of them developed post COVID-19 multi-system inflammatory syndrome -children (MIS-C). Here, we describe outcome of COVID-19 in these two children with IEI.

1. Case-1

A 10-year-old male, diagnosed case of X-linked agammaglobulinemia (XLA) had been on regular monthly intravenous immunoglobulin (IVIG) infusions from one year of age. His previous male sibling had died of similar illness. He had low immunoglobulin levels at diagnosis and had bilateral pneumonia needing stay in intensive care unit. Mutation analysis for BTK gene was negative. He was generally doing well and had no comorbidities. He was detected to have COVID-19 by SARS-CoV-2 RT-PCR test in May 2020 after contact with COVID-19 positive family members. He developed mild symptoms with low grade fever and dry cough and received supportive care at home only. He became asymptomatic on day 5 of illness and recovered completely without any complications. Patient is now one and half year post-COVID-19 and is doing fine on monthly IVIG infusions.

2. Case-2

A 15-year-old male, diagnosed case of ALPS had been on sirolimus for last 6 year for recurrent cytopenia and cervical lymphadenopathy. At diagnosis he had left sided cervical lymphadenopathy 4×4 cm, immune thrombocytopenia and neutropenia. His double negative T cells were >2.5% of total T-cells and >1.5% of total lymphocytes. However, mutation analysis for ALPS came negative. His investigations in March 2021 had showed Haemoglobin-10.7 g/dl, Total leucocyte count (TLC)- $2.7x10^9$/L with Neutrophil-19% Lymphocyte-65% Monocyte-15%, Platelets- 348 $x10^9$/L, Double negative T cell (DNT)-2.5% of total T cell lymphocytes, IgG-1350 mg/dl. He had no other comorbidities. His mother had got hospitalized with COVID-19 in April 2021. A week later, he was detected to have COVID-19 by SARS-CoV-2 RT-PCR test. He had developed mild symptoms with low grade fever associated with loss of smell. He recovered completely with supportive care at home within a week. At present, he is 6-months post COVID-19 infection and is doing fine. He continued oral sirolimus throughout this illness. He was on tab sirolimus 1 mg orally twice daily and levels were not checked. However, he had normal renal functions and serum triglyceride levels.

Although exact pathogenesis of COVID-19 is still elusive, most studies suggest that it is due to immune dysregulation & hyperinflammatory response to virus [1]. Thus, its course in IEI is very unpredictable. Previous studies suggested that T-cell immunity is more important in COVID-19 to clear the infection [3]. It was also postulated that B-cell immunity does not have major role in viral clearance but leads to hyperinflammatory response which further increase morbidity and mortality due to COVID-19. X-linked agammaglobulinemia is considered advantageous IEI as B-cell deficiency may prevent inflammation, thus limiting major devastating sequelae of the disease [5]. This hypothesis of antibody defects leading to mild COVID-19 course is supported by few other studies [4,5]. Agammaglobulinemia patients who lack B lymphocytes showed milder course of disease and did not require any ICU care as compared to patients with common variable immunodeficiency (CVID) who are characterized by dysfunctional B cells and had severe disease [6,7]. Meyts et al. studied 94 patients of IEI with COVID-19 and reported that >30% had mild disease and mortality rate was 10% and it was mainly among patients with other co-

Peer review under responsibility of Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics.

https://doi.org/10.1016/j.phoj.2022.05.002
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morbidities like heart and kidney diseases [8]. They showed presentation and risk factors for severe COVID-19 in patients with IEI are very similar to those in the general population [8]. Al Yazidi et al. studied 140 children with IEI for a year during pandemic and many of them developed COVID-19 infection. However, none of them required hospitalization due to COVID-19 [9]. Both patients had mild CVOID-19 disease and did not require hospitalization. It has been reported in literature clearly that children with IEIs are not significantly predisposed to COVID-19 infection in comparison to apparently immunocompetent children [4–9].

Though complete B cell deficiency reduces allograft inflammation, B cell deficiency are well known for inflammation also. XLA have symptoms that are consistent with a diagnosis of inflammatory parenchymal disease, arthritis, inflammatory bowel disease or other inflammatory condition [10]. Contrary to previous studies, others have reported poorer outcomes among patients with IEI compared to the general population especially among patients with combined immunodeficiency and immune dysregulation, although whether SARS-CoV-2 infection contributed directly or indirectly to any of those deaths was unclear [11,12]. Both our cases showed milder course and did not require any hospitalization. However, it is very difficult to draw a conclusion from just two cases and to state that IEI are actually protective against severe COVID-19 disease is not prudent. It is quite possible that various IEI can have different outcomes with COVID-19 infection due to involvement of different immune pathways. Various IEI may behave differently to different microbes because of various types of immunological status of patients with different IEI (humoral, cellular, innate). Likewise, ALPS and XLA are completely different spectrum of IEI. Further studies needed for better understanding of impact of COVID-19 on IEI.

Disclosure

All authors have nothing to declare.

Consent

Informed consent was obtained from parents of both children included in this report.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of competing interest

The authors have no conflict of interest to declare.

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26 November 2021
Available online 7 May 2022