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Role of Host Immune and Inflammatory Responses in COVID-19 Cases with Underlying Primary Immunodeficiency: A Review

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Coronavirus disease 2019 (COVID-19) has spread rapidly and become a pandemic. Caused by a novel human coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), severe COVID-19 is characterized by cytokine storm syndromes due to innate immune activation. Primary immunodeficiency (PID) cases represent a special patient population whose impaired immune system might make them susceptible to severe infections, posing a higher risk to COVID-19, but this could also lead to suppressed inflammatory responses and cytokine storm. It remains an open question as to whether the impaired immune system constitutes a predisposing or protective factor for PID patients when facing SARS-CoV-2 infection. After literature review, it was found that, similar to other patient populations with different comorbidities, PID patients may be susceptible to SARS-CoV-2 infection. Their varied immune status, however, may lead to different disease severity and outcomes after SARS-CoV-2 infection. PID patients with deficiency in antiviral innate immune signaling [eg, Toll-like receptor (TLR)3, TLR7, or interferon regulatory factor 7 (IRF7)] or interferon signaling (IFNAR2) may be linked to severe COVID-19. Because of its anti-infection, anti-inflammatory, and immunomodulatory effects, routine intravenous immunoglobulin therapy may provide some protective effects to the PID patients.

Keywords: SARS-CoV-2, COVID-19, innate immunity, primary immunodeficiency, cytokine release syndrome, IVIG

Introduction

Coronavirus disease 2019 (COVID-19) was recognized in December 2019 in the city of Wuhan in Hubei province, China (Fauci and others 2020; World Health Organization 2020). Its causative agent is a novel human coronavirus (HCoV) called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, positive-sense, single-stranded RNA virus belonging to the beta-coronavirus subfamily (Peng and others 2020; Tang and others 2020). Compared with other acute respiratory illnesses, patients with COVID-19 show a significantly higher likelihood to be admitted to the hospital and have extended hospital stays (Shah and others 2020). The individuals contracting COVID-19 show variable clinical presentations and the course of COVID-19 can be divided into 3 basic phases: asymptomatic incubation period, disease onset with respiratory symptoms, and severe disease phase (Hall and others 2020). Severe COVID-19 is usually associated with acute respiratory distress syndrome (ARDS) and multi-organ failure, which necessitates intensive care unit (ICU) admission and often mechanical ventilation (Ragab and others 2020). A recent meta-analysis by Ou and others (2020) suggests that older age, low platelet counts, lymphopenia, elevated levels of lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, procalcitonin, creatinine, and D-dimer were associated with severe COVID-19 cases. These risk factors may be used for early identification or prediction of worsening illness. Interestingly, Dou and others (2020) recently proposed a geroscience approach to preventing pathologic consequences of COVID-19 and called for the need to develop interventions to prevent the complications of COVID-19, especially in older adults.

Severe COVID-19 disease is characterized by cytokine storm syndromes due to innate immune activation, which are also seen with SARS and Middle East respiratory syndrome coronaviruses, 2 other highly pathogenic HCoVs

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causing large-scale outbreaks in the past 2 decades (Fung and Babik 2020; Mehta and others 2020; Moore and June 2020; Peng and others 2020; Schett and others 2020). It has been demonstrated that recognition and treatment of cytokine storm may be important to decrease the mortality of severe COVID-19 cases (Titanji and others 2020). For example, Baricitinib, a Janus kinase (JAK) 1/2 inhibitor and potent anti-inflammatory agent, has shown promise in the treatment of moderate and severe COVID-19 cases (Titanji and others 2020). Tociizumab, an inhibitor of cytokine storm, is another attractive candidate agent being evaluated in different clinical trials and has also shown effective results for treatment of severe COVID-19 cases (Hu and others 2020).

There have been a series of excellent reviews summarizing the impacts of cytokine storm on the clinical course and outcomes in COVID-19 patients (Hu and others 2020; Mahmudpour and others 2020; Noroozi and others 2020; Ragab and others 2020). However, these barely covered primary immunodeficiency (PID) cases, a special patient population whose impaired immune system might make them more susceptible to severe infections, posing a higher risk to COVID-19, but might also lead to suppressed inflammatory responses and cytokine storm. Given that immune status plays an essential role in the immunopathogenesis of COVID-19 patients, it is an interesting question as to whether an impaired immune system constitutes a predisposing or protective factor for PID patients when facing SARS-CoV-2 infection (Babaha and Rezaei 2020). Also, it is still an open question concerning the role of the innate immune and inflammatory responses in the pathogenesis of COVID-19 in PID patients. Here, we review the current knowledge of host immune and inflammatory responses to SARS-CoV-2 infection, the clinical significance of cytokines, disease severity, and clinical outcomes in adult and pediatric patients with underlying PID, as well as the role of intravenous immunoglobulin (IVIG) therapy in the COVID-19 cases with underlying PID.

Host Immune and Inflammatory Responses to SARS-CoV-2 Infection and the Clinical Significance of Cytokines

The host immune responses to SARS-CoV-2 infection play a pivotal role in clinical manifestations, disease pathogenesis, and clinical outcomes (Hall and others 2020; Shi and others 2020; Yang and others 2020). Concurrent with the earlier mentioned 3 basic phases of COVID-19 infections, host immune response in COVID-19 cases may be categorized into an early local innate immune response (antiviral defense) phase in the lungs, a later local/systemic immune response phase, followed by uncontrolled inflammatory responses and cytokine storm syndromes (Hall and others 2020; Shi and others 2020). Of note, an upper airway gene expression analysis has recently suggested that SARS-CoV-2 infection may lead to diminished innate immune responses (Mick and others 2020), indicating that the virus may evolve with interferon (IFN) antagonists to counteract the host early innate immune responses.

In response to invasion of RNA viruses, the innate immune system represents a frontline of host defense armed with multi-layered mechanisms (Liu and others 2014; Esser-Nobis and others 2020). Of these, pattern recognition receptors, such as Toll-like receptors (TLRs) and retinoic-inducible gene-I-like receptors, sense viral nucleic acids, a major class of viral pathogen-associated molecular pattern, triggering intracellular signaling pathways that activate interferon regulatory factor 3 (IRF3) and NF-κB (Wang and others 2011; Shen and others 2012; Liu and others 2016; Birra and others 2020; Peng and others 2020; Ragab and others 2020). These 2 transcription factors play critical roles in the production of IFNs and pro-inflammatory cytokines/chemokines. Specifically, IRF3-mediated IFN production may play important roles in the early phase of the innate immune response to sense and curb viral replication, whereas NF-κB-mediated cytokine/chemokine production may be more associated with later inflammatory responses and cytokine storm (Li and others 2012; Wei and others 2016; Yang and others 2019; LeMessurier and others 2020; Ragab and others 2020). Among the pro-inflammatory cytokines, interleukin-1 (IL-1), tumor necrosis factor (TNF)-α, and IL-6 are considered the most important ones in terms of their association with pathogenesis with severe COVID-19 (McKechnie and Blish 2020; Ragab and others 2020). Cytokines can be produced by a wide variety of immune cells, including innate immune cells (eg, macrophages, dendritic cells, and natural killer cells) and adaptive immune cells (eg, T and B lymphocytes). A sudden, acute increase in circulating levels of different pro-inflammatory cytokines and IFNs results in the cytokine storm syndromes, which leads to the influx of various immune cells (eg, macrophages, neutrophils, and T cells) from the blood circulation into the site of infection (McKechnie and Blish 2020; Ragab and others 2020). This marked pro-inflammatory cytokine release may also lead to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte abnormalities (Yang and others 2020). A series of destructive effects on human tissue can be observed during the cytokine storm, including destabilization of endothelial cell-to-cell interactions, damage of vascular barrier, capillary damage, diffuse alveolar damage, multi-organ failure, and, ultimately, death (Ragab and others 2020). The detailed molecular mechanisms underlying the SARS-CoV-2-triggered cytokine storm is still illusive and needs further investigation.

It is accepted that there is an association between the cytokine storm and increased mortality in COVID-19 (Titanji and others 2020). The clinical significance of upregulated pro-inflammatory cytokines, for example, IL-6, in COVID-19 patients has attracted great attention by different research groups. For example, a multi-center, retrospective study of 150 severe COVID-19 cases showed that elevated ferritin and IL-6 levels are significantly associated with adverse clinical outcomes (Ruan and others 2020). Mandel and others (2020) found that there were significantly higher levels of IL-6 and TNF-α in patients who did not survive and that IL-6 can be used to predict 30-day mortality in hospitalized COVID-19 patients. The cut-off value of IL-6 to predict mortality was determined to be 163.4 pg/mL, with a high sensitivity of 91.7% (Mandel and others 2020). Chen and others (2020) demonstrated that there was a direct correlation between detectable serum SARS-CoV-2 viral load and drastically elevated IL-6 level in critically ill COVID-19 patients. This study also showed that IL-6 could be a potential therapeutic target for severe patients with an excessive inflammatory response.

COVID-19 in Adult Patients with Underlying PID

Given that antibodies play important roles in limiting infections, patients with underlying PID may receive long-

term IVIG therapy (Burton 2002; Law and Hangartner 2008). Though IVIG would help maintain normal immunoglobulin G levels, PID patients with their impaired immune system might still face a high risk to SARS-CoV-2 infection. Recently Gao and others (2020) performed a systematic review and meta-analysis to analyze the impacts of immunosuppression and immunodeficiency on 4,007 adult patients with COVID-19.The cases with immunosuppression and immunodeficiency were found to have a 3.3-fold and 1.6-fold higher risk of severe COVID-19 disease, respectively (Gao and others 2020).

Interestingly, multiple case reports suggest that patients with common variable immune deficiency (CVID) and agammaglobulinemia seem to have different disease severity and outcomes after SARS-CoV-2 infection due to different inflammatory responses and B cell status (Fill and others 2020; Mullur and others 2020; Quinti and others 2020; Soresina and others 2020). A recent case series by Quinti and others (2020) analyzed 7 patients (age range: 32–59) with primary antibody deficiencies (PADs) and COVID-19, among whom 2 had agammaglobulinemia and 5 had CVID. The 2 agammaglobulinemia cases without B lymphocytes showed mild COVID-19 symptoms with a short duration and favorable outcomes, whereas the 5 CVID patients with dysfunctional B lymphocytes developed a severe form of the disease requiring ICU admission, mechanical ventilation and IL-6-blocking drugs. Eventually, 1 CVID case died whereas the rest recovered. This case series hinted at a possible role of B lymphocytes in the host inflammatory response to COVID-19, as B cells are important immune cells producing IL-6, thereby enhancing the level of inflammatory responses (Arkatkar and others 2017; Quinti and others 2020). Lack of B cells in agammaglobulinemia patients might be considered as an advantage by avoiding the development of inflammatory responses and cytokine storm (Babaha and Rezaei 2020).

Similarly, 2 X-linked agammaglobulinemia (XLA) patients (age: 26 and 34, respectively) without circulating B cells due to Bruton's tyrosine kinase gene (*BTK*) mutations (S578Y) developed interstitial pneumonia and lymphopenia after SARS-CoV-2 infection, but they recovered without oxygen ventilation or intensive care (Soresina and others 2020). This observation suggests that B cells response might be unessential for overcoming severe COVID-19. Given that BTK is expressed in myeloid cells and involved in TLR-mediated production of pro-inflammatory cytokines, such as IL-6 and TNF-α, the lack of BTK in myeloid cells could also explain why these XLA patients did not develop fatal cytokine storm or inflammatory stage of the disease (Marron and others 2012; Soresina and others 2020). In contrast, Fill and others (2020) reported a CVID patient who developed ARDS after SARS-CoV-2 infection and required mechanical ventilation. Mullur and others (2020) published a case report describing a 42-year-old male CVID case who died of severe COVID-19.

In contrast to the seemingly ''protective'' effects in agammaglobulinemia patients due to lack of B cells (Babaha and Rezaei 2020), some PID patients with malfunctioning innate immune sensors or IFN immunity have been demonstrated to develop detrimental or even life-threatening outcomes (Bastard and others 2020; Pairo-Castineira and others 2020; van der Made and others 2020; Zhang and others 2020). van der Made and others (2020) reported that 4 young men from 2 unrelated families were identified with unique loss-of-function variants in X chromosomal TLR7 and developed severe COVID-19. These patients all required ICU admission and mechanical ventilation, and 1 patient died. Examination of PBMCs isolated from the patients showed impaired upregulation of IRF7, IFNB1, and ISG15, suggesting an impaired transcriptional host type I IFN response downstream of the TLR7 pathway. Collectively, this case series suggests that PID patients with rare loss-of-function TLR7 variants might develop severe COVID-19 (van der Made and others 2020). Similarly, a study by Zhang and others (2020) suggested that life-threatening COVID-19 may be more likely to occur among the patients with inborn errors of type I IFN immunity, for instance, potential loss-of-function variants associated with TLR3- or IRF7-dependent IFN immunity. Bastard and others (2020) found that there was a remarkable increase in the positive rate of auto-antibodies against type I IFNs in the cohort with life-threatening COVID-19 (10.2%, 101/987) than that with asymptomatic or mild symptoms (0%, 0/663). Interestingly, a genome-wide association study by Pairo-Castineira and others (2020) suggested that low-level expression of *IFNAR2* (IFN alpha and beta receptor subunit 2) as well as high expression of *TYK2* (tyrosine kinase 2 implicated in IL-6, IL-10, and IL-12 signaling) and monocyte/macrophage chemotactic receptor *CCR2* are associated with severe COVID-19. Taken together, PID patients with a deficiency in antiviral innate immune sensors or IFN signaling may be linked to severe COVID-19.

COVID-19 in Pediatric Patients with Underlying PID

Compared with case reports about adult patients with PID and COVID-19, the number of reported pediatric patients with underlying PID is scarce. Ahanchian and others (2020) reported that an 8-year-old Iranian boy with underlying primary specific antibody deficiency and COVID-19 presented with wet cough and rhinorrhea, which would be considered unusual symptoms in children with a normal immune system. After 7 days of hospitalization with treatment with meropenem, clindamycin, and hydroxychloroquine, the patient was discharged with ameliorated symptoms. This case highlights the importance of diagnosing and managing pediatric PID patients with an unusual manifestation of COVID-19 (Ahanchian and others 2020).

In addition, a systematic review by Minotti and others (2020) studied the impact of COVID-19 on children with immunosuppressive status and suggested that immunosuppressed patients with COVID-19 seem to have a low incidence in relation to the total number of infected cases. It was observed that a favorable outcome was often found among immunosuppressed pediatric patients as compared with other comorbidities. This could be explained by several unique features of the pediatric population. First, children do not smoke and have a lower expression of ACE2 receptor in their lungs (Abdulamir and Hafidh 2020; Brodin 2020; Minotti and others 2020). Second, different inflammatory responses are observed among children compared with adults. Children have higher numbers of B and T regulator cells, and they tend to be immune tolerant with a less inflammatory immune response (Abdulamir and Hafidh 2020; Brodin 2020; Minotti and others 2020). A weaker immune response might play a hypothetical protective role in leading to a milder disease presentation among

immunosuppressed children (Minotti and others 2020). But Minotti and others (2020) suggested that a mild disease presentation among pediatric patients with COVID-19 may cause underdiagnosis and that it is likely that immunosuppressed children may become a viral reservoir, leading to persistent viral spread and transmission.

Role of IVIG Therapy on COVID-19 Cases with Underlying PID

IVIG therapy has broad applications for treating severe infections, especially for PID patients (Babaha and Rezaei 2020; Hanson and others 2020). It has several advantages. First, IVIG is believed to provide a diversity of specific antibodies against pathogen components, virulence factors, and toxins (Pollack 1983; Schlievert 2001; Yanagisawa and others 2007). Pooled immunoglobulin may also contain antibodies to common cold HCoVs (eg, HKU1, NL63, OC43, or 229E), which may have the potential to cross-react with SARS-CoV-2 (Abbasi 2020; Infectious Diseases Society of America 2020). It is also likely that the pool of immunoglobulin collected after the outbreak of COVID-19 may contain specific antibodies to SARS-CoV-2 (Babaha and Rezaei 2020), though more data are needed to confirm this. Second, IVIG has anti-inflammatory effects as it may contain neutralizing antibodies against some cytokines, for example, granulocyte-macrophage colony stimulating factor, IL-1α, and IFN-α (Wadhwa and others 2000; Hanson and others 2020). Third, IVIG has immunomodulatory effects. Previous studies have demonstrated that pooled human immunoglobulin or IVIG has inhibitory effects on peripheral blood mononuclear cells to block its production of pro-inflammatory cytokines, for example, TNF-α and IL-6 (Andersson and Andersson 1990; Toungouz and others 1995; Wu and others 2006). Murakami and others (2012) also confirmed that IVIG has the ability to block release of pro-inflammatory cytokines in human monocytic cells stimulated with procalcitonin, which is reminiscent of severe COVID-19 cases with high procalcitonin levels (Ou and others 2020). Therefore, it might be suggested that routine IVIG therapy may provide some protective effects on PID patients (Babaha and Rezaei 2020). Of note, one of the authors (Dr. H.R.H.) of this review article is following up 300 PID patients (with CVID, XLA, Chronic Granulomatous Disease, or Job syndrome) at the University of Utah Hospital. Most of his patients are receiving IVIG therapy. Among them, only 5 CVID patients were confirmed to be infected with SARS-CoV-2, and all had mild respiratory illness and eventually recovered. IVIG therapy, wearing masks, and staying away from infected individuals may be important contributing factors to obtain such low COVID-19 incidence and good outcomes among these patients.

On the other hand, recent IVIG administration before sampling may affect clinical assays and complicate evaluation for infection (Babaha and Rezaei 2020; Hanson and others 2020). First, it is established that IVIG has impacts on serologic testing for infectious diseases. Recent IVIG administration may lead to equivocal or false positive results for different serologic tests due to the cross-reactivity with different pathogens in the IVIG (Ramsay and others 2016; Hanson and others 2020). Of note, the IVIG-containing antibodies from previous exposures to common cold HCoVs may lead to potential cross-reactivity with COVID-19 serology testing (Abbasi 2020; Infectious Diseases Society of America 2020). Second, due to its anti-inflammatory and immunomodulatory effects, recent IVIG therapy would likely exert inhibitory effects on pro-inflammatory cytokine release and detection among COVID-19 patients and cause false negative results.

Conclusions

From our review of the currently available literature to date, we can arrive at several conclusions about COVID-19 cases with underlying PID. First, similar to other patient populations with different comorbidities, PID patients are susceptible to SARS-CoV-2 infection. Second, PID patients with varied immune status may have different disease severity and outcomes after SARS-CoV-2 infection due to different inflammatory responses and B cell status. PID patients with deficiency in antiviral innate immune signaling (eg, TLR3, TLR7, or IRF7) or IFN signaling (IFNAR2) may be linked to severe COVID-19. Third, because of its anti-infection, anti-inflammatory, and immunomodulatory effects, routine IVIG therapy may provide some protective effects to PID patients.

It is important to acknowledge that this review has some limitations. First, most of the literature about the PID patient population is in the form of case reports and case series, which may not be able to represent the whole patient population. Second, the COVID-19 pandemic is a rapidly evolving situation and research on this topic will continue and accumulate swiftly. It is difficult to draw any final conclusions. Studies of large cohorts with comprehensive data analysis would be needed to draw more compelling clinical conclusions on the disease severity and clinical outcomes of COVID-19 cases with underlying PID.

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