

The Influence of Helminth Immune Regulation on COVID-19 Clinical Outcomes: Is it Beneficial or Detrimental?

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Abstract: Immunologically, chronic worm infections prevent themselves from strong immune responses by skewing the host response towards a T helper 2 (Th2) type. The regulatory response initiated by helminth infections is supposed to temper responses to non-helminth antigens including viral infections which will, in turn, alter the clinical outcomes of infections. In view of this, recent reports highlighted the possible negative associations of severe COVID-19 and helminth co-infections in helminth-endemic regions. As the pathology of COVID-19 is primarily mediated by an excessive immune response and subsequent cytokine storm, which contributes to the poor prognosis of COVID-19, helminth-driven immune modulation will hypothetically contribute to the less severe outcomes of COVID-19. Nevertheless, emerging reports also stated that COVID-19 and helminth co-infections may have more hidden outcomes than predictable ones. Herein, the current knowledge on the interaction of COVID-19 and helminth co-infections will be discussed.

Keywords: SARS-CoV-2, worm co-infections, cytokine storm, Th2 response

Introduction

COVID-19 becomes the most serious global public health crises in modern times.¹ However, the differences in the susceptibility to COVID-19 and the disease severity across nations continue to be a concern. Available reports showed that this new public health crisis has been most active in countries where helminth infections are rare.² Although the number of cases and deaths is on the rise, the morbidity and mortality of COVID-19 in low-income countries has been lower than predicted.^{3,4} Data coming from the COVID-19 pandemics show that pre-existing chronic diseases might influence the clinical outcomes of COVID-19 infection.⁵ In view of this, recent reports drew attention to the associations between chronic helminth infection and COVID-19 disease severity in helminth-endemic regions. Yet, reports vary considerably and there is no common understanding of the interaction between these two disease conditions. In different reports, the possible beneficial and detrimental effects of COVID-19 and helminth co-infections have been shown. The aim of this review is, therefore, to summarize the current understanding on the interaction of COVID-19 and helminth co-infections. The potential influence of helminth co-infections on the clinical outcome of COVID-19 patients will be discussed. For this purpose, peer-reviewed research articles, reviews and short communications by international organizations were reviewed. Search engines including PubMed Central, Scopus, and

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Google Scholar were used. In the search engines, we have used key words (phrases) including but not limited to COVID-19, Helminth infections, Immunomodulation, Immunopathology, Epidemiology, Interaction, and Clinical outcome. The search was restricted to English language.

COVID-19

Coronavirus disease 2019 (COVID-19) is caused by the novel betacoronavirus, now named severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2).^{6,7} According to the phylogenetic diversity studies, SARS-Cov-2 and SARS-Cov share about 80% nucleotide sequence. SARS-Cov had been a cause of an epidemic in 2002/3 which affected 26 countries with about 8000 cases.⁸ The first COVID-19 cases have been reported from the Chinese city of Wuhan by the end of 2019. Since then, cases have started to be reported in different countries, and the disease was declared a pandemic by WHO in March 2020. COVID-19 has currently affected more than 216 countries with over 200 million cases.^{9,10} Indeed, the overall burden of COVID-19 might be higher than the reported case counts because only a fraction of infections is diagnosed and reported. In Europe and the United States (US), for instance, seroprevalence surveys have shown that the rate of prior exposure to SARS-CoV-2 exceeds the incidence of reported cases by approximately 10-fold or more.^{11,12} The highest numbers of cases and deaths have been reported from the USA, Brazil, and India, however, Africa has a low number of COVID-19 cases and fatalities compared to other continents partly be due to limited testing capacity and delays in reporting confirmed cases.^{13,14} The sign and symptoms of COVID-19 vary from person to person.¹³ However, pneumonia and acute respiratory distress syndrome (ARDS) are among the serious clinical manifestations mainly in immune-compromised patients and elderly.^{6,15}

Helminth Infections

Helminths are a class of neglected tropical diseases, which comprise roundworms, flatworms, tapeworms, and flukes.¹⁶ Schistosomiasis and soil-transmitted helminths (STHs) are the most common helminth infections worldwide.^{17,18} Globally, the burden of STHs was accounted to be above 3 million disability-adjusted life-years (DALYs).¹⁹ Infections with worms, or *helminthiasis*, are the most common infectious diseases with disproportionately high prevalence rates in resource-poor settings.⁴ The human helminthiasis exhibit a tremendous diversity of pathology.

Usually, a small worm burden has limited or no pathology and may be commensal to the host.¹⁷ However, heavy infection with parasitic worms can lead to serious complications including death.^{20,21} Helminthiasis may cause life-threatening chronic health conditions such as blindness (onchocerciasis), adult-onset epilepsy (*Taenia solium* infections), bladder cancer (schistosomiasis), and liver and bile duct cancer (trematodiasis).^{22–24} In children, helminth infections may cause stunted growth and impaired cognitive development.²⁵ Furthermore, infection with parasitic worms can increase host susceptibility to other co-infections.²⁶

Immune Regulation by Helminths

Most helminth parasites are large, long-lived organisms, and mostly they are not able to replicate within their human host. Due to these features, antigenic variation and sequestration in specialized niches are not feasible for helminths to escape from the host defense.²⁷ In this regard, helminths use a different strategy, immune regulation, to survive within the host. Immune regulation, in this case, refers to the capacity of helminths to limit the excessive host immune response directed toward themselves. During long-standing chronic infection, helminths elicit limited inflammation in invaded tissues and install an immunoregulatory environment that ensures their survival.^{18,27} This kind of relationship between worms and the host evolves to a reciprocal beneficial outcome. On the one hand, it helps helminths to remain unrecognized in human tissues and protects them from being eradicated. On the other hand, the host is protected from excessive immune responses that may result in organ damage.^{27,28} Helminth infections may restrain host immune responses through different mechanisms, including but not limited to suppression of Th1/Th2 response, manipulation of pattern recognition receptors (PRRs), stimulation of regulatory cells, and induction of apoptosis in immune cells.^{29–31}

Immunoregulation during helminth infections is induced by helminth-derived products, which can be either parasite secretions, excretions, proteins, or extracellular vesicles that constantly interact with the host immune system.³² Immunoregulation by *Echinococcus granulosus*, for instance, was shown to be driven by the hydatid fluid and antigen B (AgB) which suppresses dendritic cells (DC) maturation and monocyte differentiation, resulting in reduced anti-parasite responses.³³ During *Trichuris suis* infection, prostaglandin (PGE2) appears to impair TLR4-associated myeloid differentiation primary response

protein 88 (MyD88) and the TIR-domain-containing adaptor-inducing interferon- β (TRIF) signaling.^{34–36} Similarly, the phosphorylcholine-containing glycoprotein (ES-62) released by the filarial worm *Acanthocheilonema viteae* was described to mediate the regulatory response.³⁷ Body fluid from adult *Ascaris suum* was also reported to induce hypo-responsiveness in human antigen-presenting cells (APCs) treated with Lipopolysaccharides (LPS) and modulate different human macrophage phenotypes.^{38,39}

Helminth and COVID-19 Co-Infections

It is well documented that the host–parasite interactions during worm infection cause the immune system to mount a type 2 response.⁴⁰ Type 2 responses will be followed by an increase in anti-inflammatory cytokines, eosinophils, regulatory T cells (Treg), and M2 macrophages.^{2,40,41} Being one of the powerful immune modulators, preexisting helminth infections may influence the clinical outcomes of COVID-19. Nevertheless, helminth-induced immune regulation may result in both beneficial and detrimental outcomes.

Beneficial Outcomes of Helminth and COVID-19 Co-Infections

COVID-19 pathology is mediated by an overreaction of the host immune system (cytokine storm).⁴² An exacerbated systemic inflammatory response and the massive release of IL-1, IL-2, IL-7, G-CSF, IP-10, MCP-1, MIP-1A, and TNF α was observed in severe COVID-19 cases.⁴³ Data coming from the COVID-19 pandemics showed that people with pre-existing conditions such as chronic pulmonary diseases,⁴⁴ cardiovascular diseases (CVD),⁴⁵ renal diseases,⁴⁶ and metabolic syndromes^{47,48} are at higher risk of severe disease and mortality when infected. These metabolic diseases are characterized by increased levels of proinflammatory cytokines.² Helminth infections, on the other hand, are known to induce an immunotolerogenic state and modulate responses associated with inflammation. In this case, helminth-induced immunoregulation will help to modulate COVID-19-induced inflammation and the interaction of helminth and COVID-19 coinfections may perhaps be beneficial for the patient. The beneficial interactions during helminth co-infections have been shown in previous reports. As reviewed in,⁴⁹ individuals with worm infections are less likely to have metabolic dysfunctions as compared to those without helminth infections. Rajamanickam and colleagues also reported that

type 2 diabetes patients with concomitant helminth infections had reduced levels of proinflammatory cytokines and, this effect was reversed following treatment of the helminth infection.⁵⁰ Furthermore, in a mice model by Rolot et al, prior exposure to *Schistosoma mansoni* eggs have shown a reduced disease severity of murid gamma-herpesvirus 4 infection.⁵¹

Besides, a previous study on mice coinfecting with *Heligmosomoides polygyrus bakeri* (*H. polygyrus*) and influenza virus showed a decreased lung consolidation possibly due to the immunosuppressive effect of *H. polygyrus*.⁵² In this regard, owing to helminths beneficial immunomodulatory effects shown on other infections, it may be feasible to propose a reduced risk of severe COVID-19 in patients with pre-existing helminth infections.^{3,53}

A recent data by Gebrecherkos et al⁵³ from Ethiopia reported that 33.8% of COVID-19 patients had helminth co-infections with either *Ascaris lumbricoides*, *Hymenolepis nana*, or *Schistosoma mansoni*, and COVID-19 was less severe in those patients with pre-existing helminth co-infections. Interestingly in the same study, COVID-19 patients with helminth co-infections were less likely to have non-communicable diseases (NCDs), including hypertension, cardiovascular diseases, and diabetes.⁵³ Along the same lines, an ecological study by Ssebambulidde and colleagues also stated that the comparatively low COVID-19 cases/deaths in parasite-endemic areas might be due to immunomodulation induced by parasites.³ Bradbury et al,⁵⁴ in a recent commentary, offer the view that both helminths and SARS-CoV-2 induce Th2 cytokines and the boosted type 2 cytokine responses could regulate the severe inflammatory responses during helminth and COVID-19 coinfection. Hays et al² also believe that chronic worm infections may protect COVID-19 patients from the severe pathological responses. However, contrary to Bradbury et al report, Hays and colleagues suggested that anti-inflammatory cytokines (IL-4 and IL-10) associated with COVID-19 may not be pathological responses by the virus. Instead, it is a normal regulatory and tissue-repair response to viral-induced inflammation.

Detrimental Outcomes of Helminth and COVID-19 Co-Infections

It does not often hold true that COVID-19 severity is lower in helminth-endemic regions. There are some

helminth endemic areas that have been heavily affected by the pandemic. The Amerindian peoples of the Brazilian Amazon have a high burden of soil-transmitted helminth infection (45–95%).⁵⁵ However, this area was hugely affected by COVID-19 and the mortality rate was 250% higher than the rest of Brazil.⁵⁶ The prevalence of soil-transmitted helminths in the rural communities of Venezuela is estimated to be 65%; however, the area has been heavily affected by the COVID-19 pandemic.^{57,58} These data show that COVID-19 and helminth co-infections may have more hidden outcomes than predictable ones. Indeed, previous pieces of evidence on viral infections reported that helminth co-infections may have detrimental clinical outcomes. On the one hand, the development of Treg and IL-10 production induced by helminths will impair the host immune responses, which in turn increases host susceptibility to microbial infections.⁵⁹ On the other hand, gastrointestinal parasites may modulate the gut microbiome composition which will, in turn, cause systemic immunomodulation.⁴¹ In agreement with this, Reese et al⁶⁰ and Osborne et al⁶¹ on their experimental studies on parasitic worm and virus co-infection in mice noted that the immunomodulatory role of helminths creates a favorable environment for the worms at the expense of antiviral immunity. In another study by Nayak and Kelley, increased mortality was observed in mice co-infected with *Ascaris suum* and influenza virus (90% vs 30%).⁶² Taking these reports into account, COVID-19 and helminth co-infections may possibly have detrimental interactions. A systematic review by Abdoli et al⁶³ projected that preexisting helminth infections may suppress the efficient immune response against SARS-CoV-2 in the early stage of the infection, and thereby may increase the morbidity and mortality of COVID-19. Aside from their role of immune interaction, Paniz-Mondolfi et al showed a different perspective in which the increased severity and mortality of COVID-19 in helminth endemic areas may be attributed to the nutritional and metabolic compromises caused by worm infections.⁵⁸

In parasite endemic regions, the management of helminth co-infections on COVID-19 patients remains controversial. Data on the outcome of treating helminth co-infections on COVID-19 patients is scarce. In fact, few reports showed the benefit of deworming in COVID-19 patients as it may decrease SARS-CoV-2 viral load and improve CD8+ T cell in the lung microenvironment.^{64,65} Nevertheless, owing to the limited clinical evidence, it will be very difficult to reach

such a conclusion that treating helminth co-infections is beneficial to COVID-19 patients.

Conclusion

COVID-19 and helminth co-infection may be a common phenomenon in low- and middle-income countries. However, their interaction is not yet well studied and understood enough. Data on pre-existing helminth and SARS-CoV-2 co-infection are just emerging. We are not certain whether treating helminth co-infections on COVID-19 patients will be beneficial or detrimental. There is therefore a need for prospective studies to examine the clinical and immunological perspectives of COVID-19 patients with helminth co-infections. The findings of such studies will be very important as they will determine the management of COVID-19 in areas where helminth infections are co-endemic. As the world is facing the third wave of the pandemic, understanding the interaction of helminth co-infections would clearly be of great interest.

Abbreviations

AAMs, alternatively activated macrophages; ARDS, acute respiratory distress syndrome; CD8, cluster of differentiation 8; COVID-19, coronavirus disease 2019; IL, interleukin; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; STH, soil transmitted helminths; Th1/Th2, T-helper cells; Treg, regulatory T cells.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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