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Review article

Role of neglected parasitic diseases in the era of COVID-19 pandemics

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ABSTRACT. There are some doubts about the exact relationship between neglected infectious diseases (NIDs) and COVID-19 disease, which remains to be clearly defined. The present review summarized the effect of parasitic infections as the risk factors or protective agents in the COVID-19 pandemic. Parasites could proficiently modulate immune responses. Thus, parasitic infections could have a different impact on the incidence and clinical severity of COVID-19 in different regions of the world. Also, restoring programs to prevent, treat, and control NIDs, in particular helminths, could help in reducing the incidence and mortality of COVID-19 in endemic areas and help to increase vaccination effectiveness. Changes in the gut microbiome associated with helminth infection may have systemic immunomodulatory effects toward suppressing host immune responses, reducing vaccine efficacy and increasing the severity of other infectious diseases. The cytokine storm observed in severe cases of COVID-19 is characterized by a predominance of proinflammatory cytokines, such as IL-6. However, it is possible that helminth infection could change the outcome of infection by modifying the Th2 response to limit the inflammatory component; this would be particularly apparent in areas endemic for helminthic infections, which suggests a possible protective effect against COVID-19. Because parasitic infections affect more than 2 billion people throughout the world, their impact on COVID-19-associated effects on public health could be considerable. Further studies with larger sample sizes would be needed to explore the possible role of neglected parasitic infections in the COVID-19 pandemic.

Keywords: neglected parasitic diseases, COVID-19

Introduction

Humankind has encountered various pandemics throughout history. After the very first records of the „black death" or Plague in the early 14th century (50–200 million deaths), to the „Spanish Flu" in the early 19th (50–100 million deaths), the world did not expect and was not ready for another infectious pandemic, due to the power of the health system in the new and modern world. But in the early days of 2020, this delusion of invulnerability has been proven wrong by the arrival of COVID-19 as a global threat that was pronounced to be a pandemic and has killed about 17 million people up to now [1,2].

Poverty and low socio-economic levels always have the strongest and closest relationship to infectious diseases. Disease prevalence and

hygienic conditions differ significantly in low and medium-income countries (LMICs) from high-income countries (HICs), so infectious diseases have a markedly higher prevalence in LMICs, including so-called neglected infectious diseases (NIDs) [3].

As the word points out, NIDs have been paid less attention to but cause some serious health complications. Among them, parasitic infections affect more than 2 billion people throughout the world, with disproportionately high prevalence rates in limited-resources settings. The global intestinal parasitic disease burden includes mostly parasites such as *Ascaris*, hookworm, *Schistosoma*, *Trichuris*, *Enterobius*, *Entamoeba*, *Giardia*, *Toxoplasma*, *Cyclospora*, and *Cryptosporidium* [3]. It is interesting to mention that in some areas, an inverse relationship has been reported between the number of cases of certain NIDs (e.g., malaria and *Wuchereria bancrofti*) and COVID-19. It means that cases with pre-existing infections are less susceptible to SARS-CoV-2, especially the severe form of it [4,5]. But there are some doubts about the exact relationship between them, and controversies remain to be clearly defined.

In the era of COVID-19 pandemics, it is noteworthy to dig deeper into the role played by the parasites. Are they risk factors or protective agents in the COVID-19 pandemic and *vice versa*?

The effect of parasitic infections on the immune responses

Shared pathogenesis

Pre-existence of chronic or persistent parasitic infections is shown to have a possible direct modulation effect on the host's immune responses due to shared pathogenesis, similar inflammation processes, and immune or allergic reactions leading to alteration of the clinical outcomes of other infections [6,7].

Misdiagnosis

Co-infections may lead to misdiagnosis and false estimates of the real prevalence of single infective agents because of similar symptoms observed in a number of parasites. Such co-existence may also cause misdiagnosis or false alarms that may lead to a more severe course of either infection [2,3]. The aforementioned process is estimated to occur largely in the SARS-CoV-2 pandemic. Co-infections may modify the host's immune response throughout, triggering the immune system towards TH2 responses and precluding TH1 hyper immune activation that leads to the severe COVID-19 outcome [8,9]. But it may act like a double-edged sword: parasitic infections alter the immune system, destroy tissue, cause anemia and malnutrition; they also have the potential to support viral infection and change the effectiveness of vaccines. But there is a bright side: parasitic immunomodulation may also protect against tissue damage by reducing inflammatory processes [2,3,9]. It is not clear yet which scale pan would be superior in an exceptional case. But it is known for sure that parasites can proficiently modulate immune responses. Their immunomodulatory potential has been used in the treatment of inflammatory and autoimmune diseases like multiple sclerosis and inflammatory bowel disease. Thus, it could be concluded that parasitic infections could have a different impact on the incidence and clinical severity of COVID-19 in different regions of the world [10].

What is known about the risk factors and pathophysiology of COVID-19

Older age and comorbidities such as high blood pressure, obesity, diabetes, and cardiovascular disease, as well as cerebrovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, or tuberculosis [11]; are among the most well-known risk factors for acute and severe COVID-19 disease, but parasites are not considered a risk factor or a protective factor against COVID-19.

What does happen in COVID-19?

Immune system responses in COVID-19: first line defense

When viral infection happens, the immune system starts to defend rapidly, mainly through the rapid formation and activation of T lymphocyte populations, especially CD8+. After a period of rising the number of lymphocytes, an opposing mechanism starts to react, mainly by producing apoptosis inducing molecules like programmed death-1 (PD-1) that will encounter massive activation of lymphocytes to keep T cells stable and tolerated. Continuing these counter reactions and inhibitory signals, the function and proliferation of T cells will be affected and T cell exhaustion will occur. This process will alter self-renewal and dysregulation in metabolic mechanisms and will

Table 1. Studies about co-infection of parasitic diseases and COVID-19

Parasites	Year	Country	Type of study	Population	Results	References
Toxoplasma gondii	2021	Egypt	Case-control	Covid-19 patients (N=100)	Toxoplasmosis increased the severity of COVID-19.	[24]
Toxoplasma gondii	2021	Czech Republic	Cross-sectional internet study	*Toxoplasma*-infected	The strongest effect on the risk of severe course of COVID infection.	[25]
Toxoplasma gondii	2022	Iran	Cross-sectional	Covid-19 patients (N=133)	The high rate of latent *T. gondii* infection was seen among COVID-19 with different severity. However, there is no significant relationship between latent *T. gondii* infection and COVID-19 severity and outcomes.	[26]
Malaria, *Schistosoma*, soil-transmitted helminths	2020	Uganda	Ecologic	Covid-19 patients (N=3,349,786)	Comparatively low COVID-19 cases/deaths in parasite-endemic areas.	[10]
Intestinal parasites	2021	Ethiopia	Observational	SARS-CoV-2 infected patients (N=751)	Parasite co-infection is associated with a reduced risk of severe COVID-19 in African patients.	[3]
Giardia spp.	2021	Italy	Case report	SARS-CoV-2 infection	The risk of reactivation of latent parasite infection should be considered during SARS-CoV-2 infection, especially during the acute or recovery phase.	[27]

increase the viral load that may be life-threatening in severe cases [12,13].

A storm is coming: cytokine and bradykinin

Overreaction of the immune system, so-called cytokine storm, is a critical and horrifying complication seen in COVID-19 [14] resulting in the production of a number of immune cells, attacking blindly the healthy tissue of the lungs and other organs. A serious concern raised in underdeveloped populations is the provocation of COVID-19 complications in people who have previously co-infected with parasitic diseases such as malaria. Chronic infection shifts the immune system toward type 2 immunity, characterized by the production of interleukin (IL-4), IL-5, IL-9, and IL-13 [15]. There is another storm proposed to play a role in the outcome prediction of COVID-19, the so-called bradykinin storm, which could explain other associated symptoms such as anosmia (loss of the sense of smell) and dysgeusia (loss of the sense of taste) and also abnormal coagulation. Disruptions of both the renin-angiotensin (RAS) and kinin–kallikrein pathways would send out bradykinin (a vasodilator peptide that causes vessel leakage). This process alters the oxygenation of the body tissues and causes hypoxemia and dyspnea, which are common findings in COVID-19 patients [16].

How could pandemics affect other infectious diseases?

True, frequent hand washing and disinfection have been proposed as highly effective in preventing pandemic transmission and reducing the number of parasites transmitted through dirty hands. But in the case of infectious diseases like malaria,

HIV, or TB, where close contact with the infected person is strongly inhibited, implementing lockdowns and restricting the movements of health care providers, closing schools, and depriving children of free meals in low-resource settings could result in more cases and deaths. It has been estimated that deaths related to HIV could increase by 10%, tuberculosis by up to 20% and malaria by 36% over the next five years. There has been a long fight against parasites during human history, but COVID-19 may push the fight back by at least a decade [17].

There is another opposing point of view that restoring programs to prevent, treat, and control NTDs, in particular helminths, could help in reducing the incidence and mortality of COVID-19 in endemic areas and help to increase vaccination effectiveness. In conclusion, it may be suggested to take a broad view of the cross-reactions between NID and COVID-19.

Effect of parasites on COVID-19

Systemic immunomodulatory effects

More severe cases of COVID-19 have been reported in some helminth-endemic regions. It has been proposed that helminth infection-related changes in the gut microbiome may have systemic immunomodulatory effects toward suppressing host immune responses, which may affect vaccine efficacy and increase the severity of other infectious diseases. Helminth infection would result in different forms of immunomodulation, leading to an increased susceptibility to some infections and a decreased susceptibility to others (Tab. 1) [18].

Morbidity and mortality

According to some reports, co-infection of helminth and COVID-19 would result in increased morbidity and mortality of COVID-19 due to inefficient immune system response and lower vaccine effectiveness in these patients [18].

Effect of COVID-19 on parasites

As many laboratories are now required to perform SARS-CoV-2 tests, they have had to suspend or reduce their typical parasitological testing duties, which has had a significant impact on the number of diagnosed cases of human parasites. However, we do not yet have accurate and reliable data on this matter [2].

Reasons for protective effect of parasites on COVID-19

Low incidence rate of COVID-19 in underdeveloped areas

The low incidence rates of COVID-19 in Africa are of high interest to scientists and WHO authorities, and it has been hypothesized that this could be a result of the increased exposure to parasites in under-developed countries (e.g. Africa and Latin America) than those in developing and developed countries [19–21].

In Africa, there are other contributory conditions like mass preventive chemotherapy of NTDs that may result in a lower number of COVID-19 cases there. Also, the younger age of the population and the high probability of prior exposure to cross-reactive viruses are among the possible reasons for fewer cases of COVID-19 in sub-Saharan Africa. If it proves to be true, it could be a possible treatment [21,22].

Modified immune response by helminths

The cytokine storm observed in severe cases of COVID-19 is characterized by a predominance of proinflammatory cytokines, such as IL-6. However, it is possible that helminth infection could change the outcome of infection by modifying the Th2 response to limit the inflammatory component; this would be particularly apparent in areas endemic to helminthic infections, which suggests a possible protective effect against COVID-19 [9,14].

Previous studies in animal models showed a protective role of helminth infection in other pulmonary diseases, not only COVID-19. For example, in a study by Schwartz et al. [9], a lower risk of respiratory viral infections such as influenza A and murine pneumonia virus has been reported in mice with schistosomosis, and *Trichinella spiralis* infection was found to limit the inflammatory pulmonary damage induced by influenza virus. In another study, Siles-Lucas [23] found that infection with *Heligmosomoides polygyrus* and *Trichinella spiralis* may limit immune response to viruses and enhance or reactivate viral infections in mice.

The antiviral Th1 responses in the early phases of infections could also have been altered by various infections. Some have discussed that helminth infections could enhance antiviral mechanisms, leading to a better control of viral load due to the increase of IL-4 and conditioning of the virtual memory CD8+ T cells (TVM cells) for more

rapid CD8 responses against the next coming antigen encounter [9]. Helminth infection may also induce highly responsive TVM cells that consequently force the human immune response to evolve a safety mechanism, so a counterbalance towards the anti-inflammatory effects related to type 2 immunity could result in more effective antiviral responses [9].

In conclusion, because parasitic infections affect more than 2 billion people throughout the world, their impact on COVID-19-associated effects on public health could be considerable. Therefore, it is too early to judge the role of parasitic infections in modulating or aggravating the COVID-19 infection. Because we are facing different mutations and new variants of this virus, and our information in this field is not sufficient and reliable; as a whole, further studies with larger sample sizes would be needed to explore the possible role of neglected parasitic infections in the era of COVID-19 pandemics.

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