



# Immune Response in Leishmania COVID-19 Coinfection

Bastidas G<sup>1\*</sup>, Bastidas D<sup>2</sup>, and Bastidas-Delgado G<sup>3</sup>

<sup>1</sup>Department of Public Health and Institute of Medical and Biotechnology Research, University of Carabobo, Venezuela

<sup>2</sup>Department of Public Health, University of Carabobo, Venezuela

<sup>3</sup>School of Medicine, University of Carabobo, Venezuela

## Abstract

This article analyzes information on the coinfection between leishmania and COVID-19, especially that observed in children, and on the host's immune response to this dual infection. In this document, the comparison of research efforts and challenges on the topic focuses on the bibliographic review of the existing global scientific knowledge on the matter. The writing is structured, after a concise introduction in three chapters: Leishmania-COVID-19 coinfection in children. immune response; leishmaniasis and its role in COVID-19 infection; and conclusions. The ideas expressed are intended to contribute to efforts to control both pathologies considered serious public health problems.

**Keywords:** Coinfection; Immune response; Leishmaniasis; COVID-19; Control

## Introduction

In early December 2019, an atypical lung disease that leads to respiratory distress syndrome called "Coronavirus Disease 2019 (COVID-19)" appeared in Wuhan (China) caused by the SARS-CoV-2 coronavirus that is transmitted through saliva droplets and with high affinity for ACE-2 receptors in the lower respiratory tract. COVID-19 spread rapidly around the world until it was declared a pandemic by the WHO in March 2020 [1].

In this pandemic panorama, coinfection with SARS-CoV-2 and neglected tropical diseases arises, especially with endemic leishmaniasis (in its two clinical forms, tegumentary and visceral) in Africa, Asia and South America with an average annual incidence of 400,000 cases. Hence the need to investigate the role of coinfection in the susceptibility and severity of coexisting infectious pathologies due to its great impact on public health, mainly in low-income countries [2-7].

The purpose of this paper is to show hypotheses and arguments about Leishmania-COVID-19 coinfection and the host's immune response that allow us to understand the infectious process and determine the natural history of the disease with the purpose of ensuring the most appropriate clinical intervention given that the Dual infection increases the risk of mortality, to which the overlapping clinical characteristics of both pathologies contribute, as they make timely differential diagnosis difficult.

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**\*Corresponding author:** Gilberto Bastidas, Department of Public Health and Institute of Medical and Biotechnology Research, University of Carabobo, Barbula Campus, Naguanagua, Carabobo State, Venezuela

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## Leishmania COVID-19 Coinfection in Children between 2 and 17 Years of Age - Immune Response

In children, COVID-19 usually presents in a mild form (it only requires supportive medical care) or without symptoms, but it can affect multiple organs, including the gastrointestinal, respiratory, skeletal muscle, and neurological systems [8-10], it can be confused with other febrile clinical conditions and coinfection with viruses, fungi, bacteria and parasites may occur, with the latter it has been described with leishmaniasis in children whose main clinical manifestation is long-lasting fever, then in cases of fever of unknown origin Visceral leishmaniasis should be ruled out in regions endemic for this protozoan where it most frequently affects children and where the COVID-19 pandemic has been reported [11-13].

Visceral leishmaniasis and COVID-19 are irremediably intertwined with unknown consequences for the health of the child, the first a neglected tropical disease, and the second an emerging one, both with the capacity to cause the death of the child (mainly visceral leishmaniasis) [14]. Likewise, erroneous diagnoses between both pathologies can be frequent due to the initial similarity between clinical symptoms (fever and asthenia) and laboratory parameters (leukopenia, thrombocytopenia and elevated transaminases), which makes it difficult to determine which etiological agent is causing the disease. The immunosuppressive state due to the persistence of visceral leishmaniasis parasites negatively affects the innate and adaptive immune responses [12,15].

In this sense, they are blood mononuclear cells stimulated with *Leishmania* spp. antigens. unable to produce antibodies [16], therefore, chronic infection can reactivate, even years after initial contact in immunocompromised or immunocompetent patients. In leishmaniasis-COVID-19 coinfection, repolarization occurs towards the Th1 immune response against SARS-CoV-2, but this allows the development of the symptoms of visceral leishmaniasis [17,18]. Caution should prevail because the infection between virus and parasite causes complex immune responses. It has been reported that visceral leishmaniasis can also polarize the response towards the host's susceptibility to SARS-CoV-2 infection. The correct scenario is still unknown [12,19].

## Leishmaniasis and its role in COVID-19 Infection

The COVID-19 pandemic caused by the SARS-CoV-2 coronavirus revealed serious individual and collective vulnerabilities in relation to the health systems of some countries, particularly those with low economic income, since this disease reduced the application of disease control programs. tropical diseases, especially neglected ones [20], for example, COVID-19 negatively influenced the fight against leishmaniasis



(tegumentary and visceral), a disease transmitted by blood-sucking insects of the order *Diptera* (*Lutzomyia* and *Phlebotomus*) and caused by the protozoan *Leishmania* spp. (intracellular parasites) of the order *Trypanosomatida* [7,21,22].

In the case of visceral leishmaniasis, the symptoms and signs are indistinguishable from those caused by COVID-19, since, in both pathologies, those affected may present fever, general malaise and arthralgia [23]. Visceral leishmaniasis is associated with the persistence of parasites (*Leishmania* spp.) with clear impairment of innate and adaptive immune responses as demonstrated by the inability to produce IFN- $\gamma$  by peripheral blood mononuclear cells stimulated by leishmania antigens. then leishmania-COVID-19 coinfection can generate reactivation of previously asymptomatic leishmaniasis [22,24-30].

Otherwise, it would be occurring with localized cutaneous leishmaniasis (one of the types that make up tegumentary leishmaniasis), since, in these patients, a significant reduction in morbidity and mortality from COVID-19 has been reported, possibly due to the cross protection that this would offer. pathology against COVID-19, as it would delay its development, a phenomenon that is fundamentally beneficial for low-income countries in the tropics and subtropics, where leishmaniasis is endemic [22,31,32].

The host immune mechanism of fighting leishmaniasis mainly involves CD8+ cytotoxic T cells, CD4+ T helper cells and the production of IFN- $\gamma$  [33,34], this last element of the immune defense controls parasite development within the host by its role in activating infected macrophages to produce nitric oxide (NO) which has the ability to destroy these intracellular parasites, as well as viruses. Hence, IFN- $\gamma$  is crucial in the control of COVID-19 infection; failures with these cytosines allow the replication of the virus in the lungs and its passage into the blood circulation to reach multiple tissues [22,29].

In favor of the premise of cross protection, the higher levels of T cells producing IFN- $\gamma$  in patients infected with SARS-CoV-2 are noted. In this sense, it is reported that COVID-19 is not serious in children, in whom have measured higher levels of this cytosine compared to adults [35,36], however, more and in-depth research must be conducted to explore the protective potential and duration of the immune mechanism initiated against localized cutaneous leishmaniasis that can significantly affect the development of the disease. SARS-CoV-2 infection, and therefore the genesis of severe or fatal COVID-19. The same proposal is made for coinfection between visceral leishmaniasis and COVID-19 [22,37,38].

## Conclusions

SARS-CoV-2 infection has caused a massive economic and social crisis in low- and middle-income countries with the interruption of control programs for neglected tropical diseases, among which leishmaniasis stands out. It is clear that leishmania-COVID-19 coinfection occurs in these countries; in children this represents a challenge due to the difficulty of differential diagnosis with other potentially fatal febrile conditions. Without a doubt, the immunosuppressive state imposed by *Leishmania* spp. influences innate and adaptive responses.

Thus, peripheral mononuclear cells stimulated with protozoan antigens seem incapable of producing antibodies; repolarization to Th1 against SARS-CoV-2 and the appearance of symptoms of visceral leishmaniasis are also evident. Durable cross-protection has been reported between localized cutaneous leishmaniasis and severe COVID-19 with a significant decrease in morbidity and mortality. It seems that cutaneous leishmaniasis is capable of generating so-called trained immunity, that is, the ability to train the innate and adaptive immune systems to generate active memory cells and associated components against COVID-19.

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