Commentary

COVID-19, Ebola Virus Disease and Nipah Virus Infection Reclassification as Novel Acute Immune Dysrhythmia Syndrome (n-AIDS): Potential Curative Role for Immunomodulators.

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Highlights

COVID-19 and selected other fatal diseases are known to disrupt the immune system.

Monocytic dysrhythmia and altered Th1/Th2 balance trigger COVID-19 mortality.

n-AIDS is manifested by lymphopenia, causing ARDS and multi-inflammatory syndrome.

Para COVID-19 syndrome describes potential latent immune related complications.

Immunomodulators might be the cure of COVID-19 and other fatal diseases.

Abstract

In this manuscript, a suggested reclassification of COVID-19, Ebola virus disease, Nipah virus infection, SARS, and MERS to be considered as a novel acute onset immune dysrhythmia syndrome (n-AIDS) due to altered monocytic, Th1/Th2 as well as cytokines

and chemokines balances is provided. n-AIDs is postulated to be the cause of the acute respiratory distress syndrome and multi-inflammatory syndrome described with COVID-19 and potential curative immunomodulators are described for the mentioned diseases as well as for other disorders caused by Th1/Th2 imbalance. Meanwhile, para COVID-19 syndrome is a suggested to describe various immune-related disorders that are associated with SARS CoV-2 infection whether before or after recovery and to embrace a potential of a latent infection that might be discovered later as occurred with Ebola virus disease. Notably, our hypothesis has evolved out of our real-life practice that uses immunomodulatory drugs to manage COVID-19 safely and effectively.

Keywords: COVID-19, Ebola virus disease, Nipah virus infection, n-AIDS, Para CoVID-19 syndrome.

Almost three decades ago, a brilliant viewpoint has suggested that a dysregulated immunological switch in favor of Th2 type responses over the Th1 type response is associated with progression of HIV to AIDS and this switch was characterized by loss of the protective antiviral IL-2- and IFN-γ production; Furthermore, those expert researchers have suggested that thousands of seronegative, HIV-exposed (many on multiple occasions) individuals have generated strong Th1 dependent IL-2 responses to HIV antigens with [1]. Interestingly, a similar imbalance in Th1/Th2 types with a Th2 favorable switch or failure in the activation of Th1 and reduced IFN-γ production was observed in deceased SARS patients or critically ill MERS patients, whereas a Th1 strong response, which is pivotal in mediating virus-specific adaptive immunity, was observed in mild patients. Importantly, CD4 + and CD8 + T cell cytokines were significantly diminished in COVID-19 patients as compared to healthy controls and subverted T cell composition and/or homeostasis were also suggested to share in COVID-19 pathogenesis and IL-6 was implied to modulate this immunopathological process in patients suffering from severe or critical COVID-19[2,3]. Notably, SARS CoV-2 was suggested to dysregulate the antiviral immune response at an early stage leading to number depletion and functional exhaustion of NK and CD8+ T cells which were restored in those who survived and a recommendation to improve the immune response at the early stage of SARS CoV-2 infection was concluded[4]. However, Th2, Th17 cell, and Treg percentages were significantly lower in deceased COVID-19 cases than recovered and healthy control and a variable immunological response was suggested to predict mortality in COVID-19 patients[5], but COVID-19 high morbidity and mortality were suggested to be related to low Th1 immunity[6] and spike-specific Th1 cells capable

of IL7-dependent homeostatic proliferation was shown to predict survival from severe COVID-19[7].

Notably, ACE2 was suggested to regulate the immune response in SARS and SARS CoV-2 including activation of B cells, macrophages, Th1 cells and the inhibition of Treg cells and CD8 + T cells[8] to be correlated that it has been suggested that ACE2[9] and other discovered[10] and yet to be discovered genetic polymorphisms might be reflected through different T cell virus specific and other immunological responses. Thus, while some SARS CoV-2 exposed patients would remain asymptomatic, including asymptomatic seronegative COVID-19 patients[11], others suffer from mild-moderate or severe COVID-19. Similarly, some COVID-19 patients will recover smoothly while others complain of post COVID-19 autoimmune complications hypothesized to be due to transient immunosuppression of innate and acquired immunity[12].

Moreover, we have recently suggested a new terminology for SARS CoV-2 induced dysregulated immune response; monocytic dysrhythmia[13] and an imbalanced immune-inflammatory response was previously described to drive development of COVID-19[14]. Furthermore, we suggested to name para COVID-19 syndrome [15] to embrace a potential that SARS CoV-2 might persist latent, for yet unspecified period, in some cells and tissues[16] and/or a capability to induce immune-mediated disorders such as what is currently being described of several post COVID-19 diseases affecting the nervous system [17,18] or reactivation of various types of herpes viruses which are described in critically ill COVID-19 patients [19] and we recommend further investigations to assess potential SARS CoV-2 direct latency or indirect persistent functional dysrhythmia; respectively in some immune cells such as the migrating interstitial macrophages[20,21] as it is already

well known how SARS CoV-2 possesses several adaptive and immune evasive differences from other coronaviruses to be noted that our knowledge about RNA viruses and their capabilities to remain latent for long duration is still evolving and it might eventually resemble the newly described latent Ebola virus [https://www.sciencemag.org/news/2021/03/new-ebola-outbreak-likely-sparked-person-infected-5-years-ago].

Furthermore, a fourth RNA virus induced fatal disease; Ebola virus disease might also be considered to possess a similar potential as regards to its induced dysregulation of the immune system [22], its long lasting T and B cell immunological dysfunction which was further described in Ebola survivors[23] as well as the dysregulated inflammatory and immunological immune response in both Ebola virus disease survivor and deceased cases[24]. Additionally, a fifth RNA virus with a high fatality rate; Nipah virus might be similarly reclassified as it the has been shown to modulate the inflammatory and immunological response including the interferon homeostasis[25]. Moreover, Nipah virus was shown to modulate the pro-inflammatory and leucocyte attracting cytokines in a manner that determines the disease course[26] and to induce a dysregulated immune recruitment that led to acute vasculitis among other several induced immune-dysregulatory mechanisms[27].

Interestingly, we postulated that abnormal cytokine and chemokine, known and yet to be discovered, dependent lymphocyte distraction (clinically manifested by lymphopenia) into (causing ARDS) or away from the lungs (causing multiple inflammatory syndrome) might reason for COVID-19 pathogenesis and complications [28] and we would like to suggest that SARS, MERS and SARS CoV-2; the three virulent RNA corona viruses which

emerged in the past two decades, which are also anticipated to be joined by other potentially fatal similar viruses, and Ebola virus disease as well as Nipah virus infection should be considered for a novel immunopathological reclassification that acknowledges their main cause of complications and/or fatalities to be related to their peculiar immune monocytic, Th1/Th2, and potentially other immune cells dysrhythmia that though seems hyperactive, it is practically deficient/incompetent ultimately leading to an acute potentially fatal response; n-AIDS and probable latent effects as recently shown for Ebola and necessitates further investigations to be fully explored for SARS CoV-2; para COVID-19 syndrome. Furthermore, though the three potentially fatal coronaviruses share some similarities with HIV[29], and that other potential similarities between SARS CoV-2 and Nipah virus have been also described [30]; these viruses and Ebola virus also differ from HIV in several important aspects including their specific immunological targets and their main tendency for acute progressive onset and complications.

Taken together, we suggest that our suggested novel classification of acute immune-dysrhythmic syndrome might properly guide us in our quest for a cure as it is only when we know the cause, we can figure out the cure and we recommend to focus on immune-modulation as a potential effective COVID-19 therapy[6,13,31], Ebola virus disease[32] and Nipah virus infection[25] and we hypothesize that our evolved real-life immunomodulatory COVID-19 management protocol[31] that guided us to this hypothesis through its remarkable clinical efficacy against COVID-19 might be also beneficial when tested in clinical trials for early management of other RNA viruses that cause n-AIDS as well as other diseases caused by altered Th1/Th2 balance.

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Competing interests

The author declares no competing interests.

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