

Down Syndrome and Covid-19: Mini Review

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Abstract

Down syndrome (DS), also known as trisomy 21 is a genetic disorder caused by irregular cell division occurring on chromosome number 21 [5]. People with DS are known to have a higher occurrence of autoimmune disorders, chronic immune dysregulation, impaired cell immunity, hospitalization for viral respiratory infections and higher mortality rate due to diseases related to the respiratory tract and pneumonia [26]. People with DS have immune responses that depict a strong interferon response which might only help fight off the initial COVID-19 infection, however since they have impaired cellular immunity, the infection might gain an advantage and cascade into a cytokine storm, producing excess cytokines [22]. The prevalence of Pneumonia amongst DS patients is high and amongst COVID-19 patients as well. The impact of COVID-19 on the immune system of people with DS remains unknown. However, since COVID-19 directly attacks the respiratory system, suggests why people with DS must be considered a 'high risk' population for the COVID-19 infection. Specifically, the impact of the immune dysregulation caused by DS which might result in an intense cytokine release syndrome relative to the symptoms of COVID-19 [1,11].

Keywords: Down Syndrome; Trisomy 21; COVID-19; Pneumonia; Immune Dysregulation; Cytokines; Interferon

Abbreviations

COVID-19: Coronavirus Disease 2019; DS: Down Syndrome; IFN: Interferon; rDC: Lung-Resident Respiratory Dendritic Cells; mRNA: Messenger Ribose Nucleic Acid; RSV: Respiratory Syncytial Virus; IL: Interleukin

Introduction

Trisomy 21

DS is the most prevalent genetic disease in humans, occurring in almost 1 in 400 children. It is caused due to the trisomy of the Human chromosome number 21 or the Hsa21 gene [4]. This additional chromosome is a result of non-disjunction division, where the chromosomes fail to separate correctly resulting in an additional chromosome, also known as an aneuploidy chromosome. It occurs when one out of the two parental gametes had 2 pairs of chromosomes 21 due to non-disjunction, and the other parental gamete was normal, when the two gametes fused together during fertilization the zygote formed, had 3 copies of chromosome 21 [24].

Due to the additional copy of Hsa21, it results in a larger expression of the genes encoded on that particular chromosome, Because of the imbalance between the expression of Hsa21 and non Hsa21 genes, it is portrayed that there are several phenotypic and genotypic differ-

ences between the two populations [12,24]. Individuals with DS may have physical and developmental disabilities, however at a cellular level they show a general prevalence of immune dysregulation [10]. They also have a much wider range of autoimmune disorders such as celiac disease and type 1 diabetes. Individuals with DS, even without the presence of any infections show features of inflammation such as high levels of inflammatory cytokines and chemokines [7]. In addition to these factors, people with DS face much severe consequences of lung infections such as respiratory syncytial virus (RSV) H1N1 Influenza A infection and a high mortality rate due to pneumonia [29].

Coronavirus and down syndrome

The novel, coronavirus, initially detected in December 2019 In Wuhan, spread rapidly all around the globe, leading to a global pandemic. The COVID-19 infection is known to have several symptoms; however, it attacks the lungs, causing permanent damage to them [9]. DS patients are prone to have a lower immunity in comparison to the euploid population, further risking them to succumb to the COVID-19 virus [3], thus the lack of data and the limitations posed by that suggest how individuals with DS must be considered as high risk of developing severe symptoms, require intensive care, acquire secondary bacterial infections and mortality due to the infection [14]. Hence establishing specialized care for those with COVID-19 and DS.

Several genes encoded on chromosome number 21 possess roles in regard to the immune control, and as a result of them being over-expressed they affect multiple aspects of the general phenotypic immune system of the individuals with DS [4,13]. Amongst the immune regulators encoded on chromosome 21, the most prominent ones are the interferon receptors; two type I IFN receptors (IFNAR1 and IFNAR2) type II IFN receptors (IFNGR2 and IL10RB). These are receptors for both type III IFN ligands and cytokines IL-10, IL-22 and IL-26 [7]. Interferons are types of molecules produced by cells as a response to any viral/bacterial infection [7,23]. They act on the infection, by affecting cells near them to prevent the infection from spreading even further, moreover they stop protein synthesis and activate the immune system. Since 4 out of the 6 interferon receptors are located on chromosome 21, cells that have trisomy 21 react extremely strongly to even small amounts of interferon in the environment [7,16,20]. It has been suggested that, if IFNs are constantly activated or being reacted to at high levels, it portrays that the body is constantly fighting viral infections, even when there is no infection present, which further causes damaging side effects. The overexpression of this gene is not only observed at an mRNA level, but also at the cell surface level, because based on recent observations; nonimmune and second immune cell types of individuals with DS are hypersensitive to IFN stimulation. Based on evidence, it has been concluded that IFN responses, which are vital to antiviral responses and initiating a cytokines storm, is much more active in individuals with DS, however it is being questioned as to how the immune response to COVID-19 in individuals with DS occurs and whether they are more or less likely to develop a cytokine storm [19,21].

At first, a hypersensitive reaction to IFN's might be considered beneficial, as it may allow the cells affected by trisomy 21 to initiate a stronger antiviral response, during the initial contact with the COVID-19 virus. When the viral particles enter the epithelial cells of the lung in an individual with DS, the resultant production of type I and type III IFN ligands might induce a stronger response in the neighboring cells as well [15,18]. This is advantageous as it can immediately stop the viral spread in the neighboring cells [31], however, the COVID-19 virus has been able to develop methods to escape the antiviral effects of the IFN responses, because the genome of this virus has several proteins encoded on them that can neutralize the effect of the IFN cascade which further enables the rapid spread of the virus, thus the IFN hyperactivity noticed in individuals with DS might not be adequate to provide additional protection to the COVID-19 virus [23,20]. In a situation where the COVID-19 virus escapes the initial immune response of an individual with DS by diminishing the IFN signaling and lifelong IFN hyperactivity that is experienced by these individuals, it is most likely that the immune system will then induce a cytokine storm. A cytokine storm occurs when the body releases too many cytokines in the blood at a very rapid rate, even though cytokines play an important role to the immune system as they fight off foreign pathogens, an abundance of them can cause harmful effects as they spread into cells that haven't been infected and start attacking healthy tissues [21,17].

The overexpression of the IFN receptor leads to hypersensitivity towards type I and III IFNs, when the lung epithelial cells, get exposed to the COVID-19 virus, the lung-resident respiratory dendritic cells (rDCs) obtain the antigens from the epithelial cells, hence activating

and moving to the cervical lymph nodes where viral antigens are processed and then presented to the T cells that are circulating [8]. When the Major Histocompatibility complex engages with the T cell on the interior of the rDCs, the T cells get activated and move to the infected tissue in the lung. When the virus specific T cells are in the lungs [8], they contribute to initiating a cytokine storm by producing multiple pro inflammatory cytokines and chemokines [21]. The T cell lining, in individuals with DS already show signs of hyperactivation even when viral infections are not present due to chronic IFN hyperactivity. Thus, as a result of this heightened immune activity, the immune system of individuals with DS becomes vulnerable to the cytokine over production [14].

Secondary bacterial infections and other potential risk factors

The impact of secondary bacterial infections in the COVID-19 pandemic, has been reduced due to the use of antibiotics, however these secondary bacterial infections yet pose as a danger for individuals with DS. Interleukin 10 (IL-10) [10], a cytokine with anti-inflammatory properties that help prevent host immune responses to pathogens. This cytokine is already elevated at a base level in individuals with DS and the T-cells affected by trisomy 21 over produce the IL-10 and several other pro inflammatory cytokines, further a subunit of the IL-10 receptor, IL10RB is encoded on one out of the four genes on the IFNR clump on chromosome 21 [10]. Thus, the elevated levels of the IL-10 receptors does not help balance the hyperactive immune response in individuals with DS, but the repressive effects of the IL-10 on the antibacterial branch of the immune system can increase the risk of secondary infections. Due to the decreased and suppressive signaling of the IL-10 could be the cause of bacterial pneumonia in individuals with DS. Bacterial pneumonia is the leading case of mortality amongst individuals with DS due to the impaired neutrophil function, thus it can be foreseen that individuals with DS would have a much higher risk of secondary bacterial infections related to the lung during the current pandemic [31].

Almost 50% of the individuals with DS are born with some form of congenital heart disease, due to which the severity of the COVID-19 infection might be high. Moreover, due to the abnormalities of the upper airways in individuals with DS, could expose the individuals to a higher chance of lung infection. To conclude, there are several other risks associated with DS that could contribute to a more severe form of COVID-19 [31].

Discussion and Conclusion

Generally, the threat of immune dysregulation several other risk factors suggests that individuals with DS, who have been affected by COVID-19, must go through a more detailed monitoring based on their physiological responses to such a lung disease. Moreover, Individuals with DS, must be considered as prime candidates for trials based on immunosuppressants and other methods that help decrease the cytokine storm. Evidently, due to the lack of access to clinical trials and data to state the exact impact of COVID-19 on individuals with DS, the hypothesis stated in this paper, mustn't entirely approached without any doubts or further investigations. Nonetheless, this review might help individuals with DS and provide them with special observations to counteract the harsh effects of the cytokine storm.

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