



Down's syndrome and COVID-19: risk or protection factor against infection? A molecular and genetic approach

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Abstract

Down syndrome (DS) is the most common genetic cause of learning difficulties and intellectual disabilities. DS patients often present with several congenital defects and chronic diseases, including immunity disorders. Elevated levels of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor alpha (TNF- α) have been seen, which appear to vary with age. At birth, patients present with combined immunodeficiency, with frequent infections that decrease with age. Furthermore, high levels of IL-4 and IL-10 with anti-inflammatory properties and low levels of IL-6 and TNF- α are described in children. The immune system is believed to play an essential role in SARS-CoV-2 pathogenesis, and it has been associated with elevated levels of pro-inflammatory cytokines and an exaggerated cytokine release syndrome (CRS) that may eventually trigger a severe situation called cytokine storm. On the other hand, genetic features seem to be involved in the predisposition to illness and its severity. Overexpression of DSCR1 and ZAKI-4 inhibits the translocation of activated T lymphocyte nuclear factor (NF-AT) to the nucleus, a main step in the inflammatory responsiveness. We discuss here the possible role of immunology and genetic features of DS in the infection and prognosis in COVID-19.

Keywords SARS-CoV-2 · Immunology · Genetics · NF-AT · TNF- α · Cytokine storm

Introduction

Coronavirus (*Coronaviridae*), one of the most contagious viruses, is primarily targeting the human respiratory system and infecting the epithelial cells of the respiratory tract, but it also has neuroinvasive capabilities to spread from the respiratory tract to the central nervous system (CNS) [1]. More than one-third of COVID-19 patients present neuropsychiatric symptoms during the course of the disease. Even in some patients, neurologic symptoms may be the initial or only presentations of the COVID-19 [2]. An association between major depressive disorder (MDD), alexithymia, and negative complications such as suicidal behavior in COVID-19 patients has been described. There is an increasing evidence that alexithymia

may be considered a risk factor for suicide, even simply increasing the risk of development of depressive symptoms or per se [3]. The prevalence of alexithymia is quite high in subjects with psychiatric disorders [4]. Therefore, the studies on relationships between alexithymia and suicide risk on clinical samples of patients with psychiatric disorders are very interesting as alexithymia may predispose to their development or worsen an existing one [3].

Previous studies highlighted the involvement of sensory perception in emotional processes as well as its prognosis. Engel-Yeger et al. examined the unique sensory processing patterns of individuals with major affective disorders and their relationship with psychiatric symptomatology. They have shown that hyposensitivity or hypersensitivity may be “trait” markers of individuals with major affective disorders. Thus, interventions should refer to the individual unique sensory profiles and their behavioral and functional impact in the context of real life [5].

Down syndrome (DS), initially described by John Langdon Down in 1866 [6], is the most frequent aneuploidy characterized by a genetic disorder that results from the triplication of human chromosome 21 [7, 8], also related to chromosomal abnormalities such as translocation and mosaicism [8, 9].

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There are three main types of DS: trisomy 21 (most common form, all cells have a triple copy of the 21st chromosome), mosaicism (some cells have three copies of chromosome 21 and some cells have two copies of chromosome 21), and translocation (a third copy of chromosome 21 is translocated to another acrocentric chromosome). It is also the most common genetic cause of learning difficulties and intellectual disabilities [7]. The incidence in Europe is about 1.1 per 1000 live births [10] and in the USA about 1.42 in 1000 live births [11], calculating that in the world there are around 6 million people affected [12]. The survival of individuals with Down syndrome has increased in recent decades (owing mainly to improved management of congenital heart defects), resulting in large numbers of adults with DS.

DS is characterized by developmental delay, with typical dysmorphic characteristics and mild intellectual involvement [13], showing CI punctuations between 37 and 70 with an average of 50, while in the general population, it ranges from 85 to 115 with an average of 100 CI [14].

Many conditions can occur in DS, such as congenital heart problems present in 50% of cases [15], gastrointestinal problems [16], and hypothyroidism [17]. It should also be noted that in DS, the immune system is usually compromised, which makes this population more exposed to infections and autoimmune conditions such as celiac disease, thyroid disease, or type I diabetes mellitus, in addition to autoinflammatory conditions [18]. DS is also related to eating problems with overweight, obesity, hypercholesterolemia, and vitamin and mineral deficiencies [19].

Concerning neuronal aspects, there are generalized alterations in neurogenesis, an excessive number of astrocytes, dendritic atrophy, and problems in establishing new neuronal connections [20]. It has also been related to a smaller brain volume, maturation disorders, and reduced neurotransmitter release. The lower brain volume is related to psychomotor impairment, which affects cognition, gait quality, and voluntary movement [21]. Moreover, hypoplasia that mainly affects the cerebellum in addition produces speech balance and coordination problems [22].

Regarding neurodegenerative processes, DS is associated with the presence of early Alzheimer's, between the age of 40 and 50 years [23]. DS dementia is the most common form of dementia in individuals under 50 years of age [24]. However, the causes of this early deterioration are currently under discussion, being attributed to neuronal changes associated with insulin levels [25], which plays a neuroprotective role against ischemia, oxidative stress, apoptosis, and toxicity of amyloid- β (A β) [26]. Besides, the association between Alzheimer's disease (AD) and DS has been described, together with high levels of tumor necrosis factor alpha (TNF- α) and interleukin (IL)-6, which are pro-inflammatory cytokines [27, 28]. Parkinson's and Huntington diseases have also been correlated with DS [7]. Down syndrome (DS) is also characterized

by overexpression of the APP and DYRK1A genes, located on the triplicated chromosome 21. This chromosomal abnormality leads to a cognitive decline mediated by amyloid- β (A β) overproduction and tau hyperphosphorylation as early as the age of 40, and it has been speculated DS individuals may benefit from active immunotherapy against A β from a young age [29].

In addition, killer-specific secretory (Ksp37) gene is commonly expressed by NK, CD8(+) T, $\gamma\delta$ T, and CD4(+) T cells, suggesting that Ksp37 has cytotoxic properties. An increase of Ksp37 protein serum levels has been shown during the acute phase of Epstein-Barr virus (EBV), and chronic infection by EBV is frequently present in subjects with Down syndrome. Salemi et al. showed that in fibroblasts and leukocytes of Down syndrome subjects, the KSP37 gene expression was increased compared with control subjects. The results of this study suggest that the expression of Ksp37 gene might be associated with increased susceptibility of individuals with Down syndrome to EBV infections and autoimmune problems [30].

Nuclear factor- κ B1(NF- κ B1) regulates the transcription of many genes involved in immune response, cell adhesion, differentiation, proliferation, angiogenesis, and apoptosis, and increased NF- κ B1 activation is involved in inflammatory response [31]. Regarding immune activity in subjects with DS, another study has found down-expression of NF- κ B1 in cells from DS patients compared to normal subjects. The minor expression of NF- κ B1 may relate to the association of this gene to the same pathway of expression that in this case favors the activation of the pro-apoptotic mechanisms in DS. In fact, inhibition of NF- κ B1 has been linked directly to apoptosis, inappropriate immune cell development, and delayed cell growth [32].

In February 2020, the World Health Organization named COVID-19 disease, which means coronavirus disease 2019 [33]. The virus that causes COVID-19 is called SARS-CoV-2 (severe acute respiratory syndrome coronavirus); previously, it was called 2019-nCoV [34, 35]. The World Health Organization (WHO) announced the new disease's official name as "coronavirus disease 2019" (COVID-19), and the International Committee on Virus Taxonomy named it SARS-CoV-2. On March 11, 2020, the WHO declared the pandemic [33]. Since the start of the pandemic until July 14, 2020, more than thirteen million cases have been reported worldwide [36]. Currently, its genomic sequence has already been made public (Wuhan-Hu-1, GenBank Accession No. MN908947). However, the pathogenic mechanisms and the genetic role in them are not yet fully understood.

Immunology

SARS-CoV-2 infection activates the innate immune system, generating an excessive response that could be related to more significant lung injury. Pro-inflammatory cytokines (IL-2R,

IL-6, IL8, IL10, and TNF α) have been also found to be associated with a hypercoagulability state [37] leading to the development of vascular disorders such as heart [38] and cerebrovascular diseases [39], and worse clinical evolution. Clinical observations suggest that when the immune response is unable to effectively control the virus, as in older people with a weakened immune system, the virus would spread more efficiently, causing lung tissue damage, which would activate macrophages and granulocytes and could lead to the massive release of pro-inflammatory cytokines [40]. A Chinese research team has described the activation circuit of this immune pathway from the activation of aberrant CD4+ and CD8+ T helper (Th) lymphocytes (with higher expression of inflammatory markers, compared to healthy controls). In patients with SARS-CoV-2 pneumonia admitted to the intensive care unit (ICU) compared to those not admitted to the ICU, and with healthy controls, they observed a correlation with a higher proportion of CD4+ T cells that produce IL-6 and GM-CSF (granulocyte-macrophage colony-stimulating factor) with the severity of COVID-19 cases [41]. Other studies have observed the presence of elevated levels of IL-6 and other pro-inflammatory cytokines in patients with severe COVID-19 [42]. This activation could carry cytokine release syndrome (CRS), which can trigger a positive feedback loop that overwhelms counter-regulatory homeostatic mechanisms and results in a cytokine storm [43] (Fig. 1). It would be associated with acute respiratory failure syndrome or adult respiratory distress syndrome (ARDS), which has been described as the main cause of death from COVID-19 [44]. CRS occurs when large numbers of leukocytes (neutrophils, macrophages, and mast cells) are activated and release large amounts of pro-inflammatory cytokines [45]. The central

cytokines involved in CRS pathogenesis include IL-6, IL-10, interferon (IFN), monocyte chemotactic protein 1 (MCP-1), and GM-CSF. Other cytokines such as tumor necrosis factor (TNF), IL-1, IL-2, and IL-8 have also been described during the CRS. This syndrome has been observed in other viral infections such as SARS, MERS, or Ebola, although through the alteration of different pathways. Furthermore, an increased plasma concentration of various cytokines has been observed (IL-1 β , IL-6, IL2, IL-2R, IL7, IL10, GSCF, IP10, MCP1 MIP1A, TNF α , etc.) in patients with COVID-19 mainly in patients with more severe symptoms [46].

Over the past decades, the immune system in DS has been studied extensively. DS patients have been reported to have an increase in circulating cytokines other than TNF- α , including interleukin β and interleukin γ levels, and impaired cell-mediated immune function. These anomalies might cause an abnormal exacerbated inflammatory response and more severe disease in response to viral infection, as described in COVID-19 [47]. Enhanced expression of pro-inflammatory mediators (IFN γ , IL1 β , IL15, MIP3 α , G-CSF, and IL17A) has been observed in the hippocampi of animal models of DS significantly reduced by the chronic administration of an anti-IL17 mAb [48].

In the other hand, Cetiner et al. suggest that a poor anti-inflammatory state with low IL-6 and TNF- α would explain the cause of susceptibility to infections in DS children [47]. They found reduced levels of IL-6 and TNF- α , and higher levels of anti-inflammatory cytokines IL-10 and IL-4, which inhibit the synthesis of pro-inflammatory cytokines such as IL-6 and TNF- α . It has been known that subjects with DS have an increased susceptibility to bacterial and viral infections, and autoimmune disorders according to healthy population, due to the impairment of the immune system [49–51].

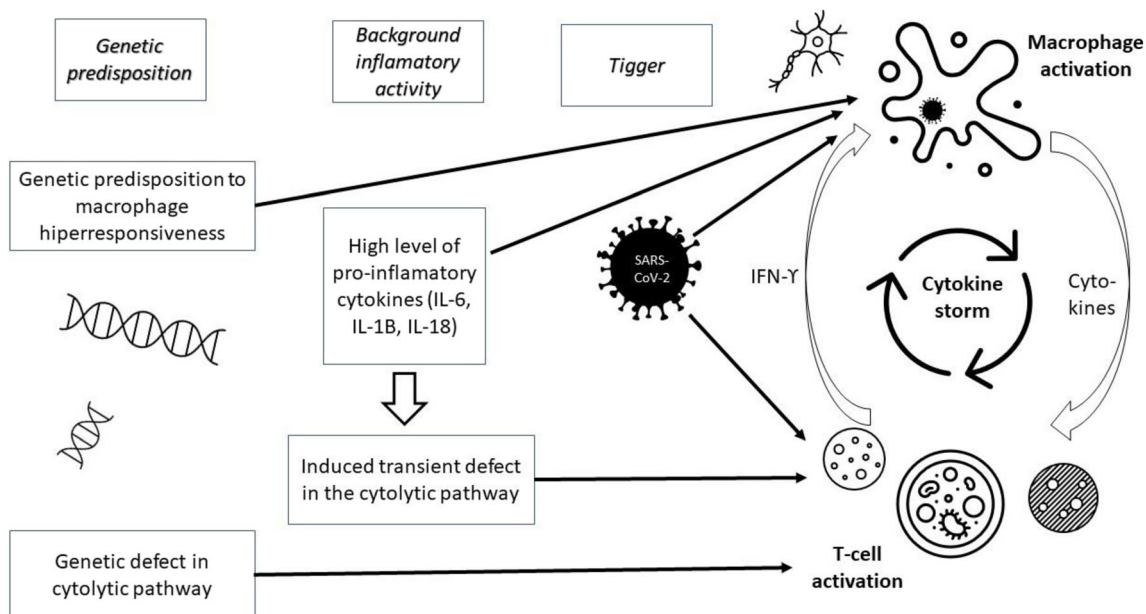


Fig. 1 Model of pathogenic events leading to the cytokine storm

In addition, individuals with trisomy 21 show more severe consequences during viral lung infections, such as increased rates of hospitalization during respiratory syncytial virus (RSV) and H1N1 influenza A infections [52, 53]. The results of the study from Cetiner et al. might suggest that continuing anti-inflammatory state in DS is the cause of recurrent infections in DS child. In a recent study with 3 cases of DS infected by SARS-CoV-2, Krishnan et al. have speculated that repeated viral infections in the first years of life may boost natural humoral and cellular immunity explaining decreasing infections with age [54]. Patients who had a history of repeated viral infections had milder clinical courses in response to SARS-CoV-2 infection. And those who did not have frequent viral infections as a child had a more severe and prolonged course of SARS-CoV-2 infection [54]. Then, the variable levels of circulating cytokines reported probably reflect the ages of the patients studied, their environment, and associated disorders as well as previous exposure to infections. Thus, DS could be a risk factor for infection and COVID-19 in the child, while in older adults, high levels of pro-inflammatory cytokines (IL-6 and TNF- α) could produce an exaggerated response to SARS-CoV-2 infection, leading to poor prognosis.

How trisomy 21 produces an alteration in the immune system is not yet completely known. However, there are several genes involved in the immune response whose overexpression could contribute to these abnormalities. Mainly the immune regulators encoded on chromosome 21 are four of the six interferon receptors: the two type I interferon (IFN) receptors IFNAR1 and IFNAR2, the type II IFN receptor IFNGR2, and IL10RB, which serve as receptor subunits not only for type III IFNs but also for cytokines IL-10, IL-22 and IL-2 [55–57]. These genes are overexpressed in all individuals with Down syndrome, regardless of sex, age, or ethnicity [58, 59]. Furthermore, a positive feedback mechanism likely exists between pro-inflammatory cytokine production, the A β burden, and the APP level, present in DS and AD [48].

Several lines of evidence demonstrate the hyperactivation of IFN signaling in DS [55]. Previous epidemics of coronavirus (SARS) and influenza (bird flu and Spanish flu) produced a high number of deaths. The cytokine storm is believed to be the cause. Preliminary studies conducted in Hong Kong [57] indicated that this was probably the leading cause of death during the 2003 SARS epidemic, as was the 2019–2020 coronavirus (SARS-CoV-2) [60].

Genetics

Solid malignancies (apart from testicular cancer) are less common, resulting in a lower overall risk for malignancies in Down syndrome [58, 61, 62]. Overexpression of DSCR1 and ZAKI-4 inhibits the transcription of calcineurin-dependent genes, by inhibiting the translocation of activated

T lymphocyte nuclear factor (NF-AT) to the nucleus [63]. Precisely the non-structural protein SARS-CoV 1 (Nsp1) induces the expression of IL-2 through the activation of NF-AT [64, 65] which could trigger the cytokine storm observed in patients. Therefore, over-activation of the DSCR1 protein, in addition to protecting against cancer, might be expected to do so in the effects of COVID-19. Prefferle et al. identified redundant interactions between SARS-CoV non-structural protein Nsp1 and a group of host proteins with peptidyl-prolylcis-trans-isomerase activity, including the cyclophilins/immunophilins PPIA, PPIG, PPIH, FKBP1A, and FKBP1B [65]. These modulate the calcineurin/NFAT pathway that plays an important role in immune cell activation [66, 67]. They showed that SARS-CoV non-structural protein Nsp1, as well as full replicating SARS-CoV, enhances the CnA/NFAT pathway and induces NFAT-responsive promoters. This point could be a target for ciclosporin A in treatment of the infection [65]. Like DSCR1, it inhibits this pathway in BS.

In addition, increased neuroinflammation in DS brains appears to be mainly mediated by the exacerbation of macrophage activation state 1 (M1) cells due to the triplication of some critical inflammatory-associated genes, including RCAN1, CXADR, ADAMTS1, ADAMTS5, TIAM1, and IFNGR2 [48].

The SARS-CoV-2 genome is made up of a single positively polarized single-stranded RNA chain (+ ssRNA) of approximately 30,000 base pairs. This RNA chain structurally resembles a messenger RNA (mRNA) of eukaryotic cells. However, unlike eukaryotic mRNAs, this viral genome contains at least six open reading frames (ORFs) [68–70]. Thus, the first two-thirds (closer to the 5' end) code for the viral replicating gene. This gene is made up of two ORFs (ORF 1a and ORF 1b) [68], which, at the beginning of the infection, will be directly translated into two large polyproteins called pp1a and pp1ab. These polyproteins will subsequently be proteolytically processed to generate 16 non-structural proteins (NSPs), which will be involved in the replication of the viral genome and the transcription of subgenomic mRNAs (sgRNAs) [71–74].

Conclusion

Even though the effects of DSCR1 overexpression are contradicted by the increase in IL-2 levels in DS and the probability of an exacerbated immune response, it could be explained by the differences between the infant and adult stages. That is, in children, there would be an immunodeficiency as already described in the last decades that would facilitate infections, with decreased levels of pro-inflammatory interleukins such as IL-2. However, in adults, there would be a pro-inflammatory state with elevated pro-inflammatory cytokine levels, such as IL-2, IL-6, and TNF- α , as described in DS (also related to AD).

According to this hypothesis, DS could be a risk factor for suffering COVID-19 in the child, while in adulthood, DS would protect against SARS-CoV-19 infection, but with a worse prognosis due to an exaggerated immune response (cytokine storm).

Although DS cases have already been described with COVID-19, finding that on average they are admitted up to 10 years younger than the general population, and with greater severity of symptoms [75], this does not allow us to conclude that it is a risk factor, but those who have been hospitalized showed more severe symptoms, without knowing their clinical history and comorbidities.

Therefore, with all the aforementioned, COVID-19 would not only affect depending on the person's state of health or age but could also be affected by genetic components such as the alteration of chromosome 21 present in Down syndrome.

On the other hand, it must be taken into account that despite the considerable increase in life expectancy in the case of DS [10], one of the characteristics of this group is accelerated and premature aging [76], so if we were to attend to the age of the organism, people over 40 would be in the highest risk group, as are those over sixty in the general population.

In brief, different pro-inflammatory and anti-inflammatory cytokine levels have been shown in DS from child to adulthood. Neuroinflammation would play a main role in the DS and other neurodegenerative disorders such as AD. It is postulated a hyperresponsiveness of the immune system involved in the neuropathogenesis of COVID-19 and related severity. Genetics and age could modify the infection response to SARS-CoV-2 in DS, with different features from COVID-19 patients without DS.

However, several limitations are present in this article. Here we describe only some characteristics of the immune system and genetics consequences from the triplication of human chromosome 21, but there are myriads of cross talking pathways that differ from healthy controls in addition to the mentioned. Besides, these molecular links determine a panoply of processes that change throughout the age of the controls, COVID-19 patients, and DS subjects.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This research is not involving human participants.

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