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Evaluation of Immune Response to COVID-19 in Neonates

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ABSTRACT

Background: During the COVID-19 epidemic, many neonates were involved, but they had fewer complications and deaths than adults. Therefore, in this review study, we investigated the immune mechanisms of neonates in response to COVID-19.

Methods: We reviewed articles that evaluated the immune system, COVID-19, or SARS-COV2 in neonates. We searched the databases of Google Scholar, PubMed, Scopus, Web of Sciences, SciELO, and CNKI databases published up to December 2022.

Results: There are different immune mechanisms in response to COVID-19 in infants, which lead to a different response to COVID-19 compared to adults. The important mechanisms include lower expression of ACE2 receptor, abundant of naive T cells, absence of cytokine storm, abundant of immunosuppressive cells, less inflammatory reactions, breastmilk secretory IgA, transfer of IgG through the placenta, and absence of chronic comorbidities. Also, in comparison with pediatrics multisystem inflammatory syndrome in children (MIS-C) doesn't observe in neonates.

Conclusion: The exact immune mechanisms in response to COVID-19 in infants have not yet been discovered, but knowing the exact mechanisms can be effective in future treatments, the production of effective vaccines, and other viral treatments, so there is a need for more investigations in this field.

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-COV2) infection, the first pandemic of the time, causes the new coronavirus infection (COVID-19). SARS-COV2 appears to be less dangerous in children and associated symptoms are milder than in adults.[1,2] The

mechanism by which infants and children are less susceptible to severe SARS-COV2 remains to be elucidated. Angiotensin-converting enzyme 2 (ACE-2) is the receptor for COVID-19 entering the body, according to studies, ACE-2 is not as effective in children as it is in adults, and therefore, COVID-19 is less dangerous in children.[3] The most common manifestations in children are moderate cough, sore throat, fever, and rhinorrhea. The decrease in the incidence of SARS-COV2 in pediatrics, in addition to the greater number of mild and asymptomatic cases, continues to cause problems in determining the appropriate methods of treatment and prevention.[4] The similarity between the spike protein of the coronavirus (protein S) and the ACE-2 receptor, which is located in the heart, intestines, lung epithelial tissue, and kidneys may reveal some of the cardiac involvement of the SARS-COV2 infection.[5,6]

In adults, in response to acute infection with COVID-19, high levels of cytokines have caused damage to various organs. Research has shown that levels of pro-inflammatory cytokines increase in cases of severe COVID-19 infection, as described by a cytokine storm. Cytokine storm is characterized by increased levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) and a systemic inflammatory response as well as direct tissue damage.[7]

Child-specific risk factors for SARS-CoV-2 have not been defined, and to date, there is no clear reason to explain why neonates and pediatrics are at lower risk of developing SARS-CoV-2 after being infected with COVID-19. The neonates infected with COVID-19 may benefit from their biased immune tolerance phenotype.[8] In general, infants and young children are less likely to be affected by COVID-19 infection, and evidence shows that the disease is mainly asymptomatic or mild in infants and children. These observations show that the function of the immune system in pediatrics is different from that of adults. Our aim of this study was to investigate the immune responses of infants to COVID-19. Also, we investigated the possible immunological mechanisms of resistance to COVID-19 in infants compared to adults.

Immune response in COVID-19

Effects of SARS-CoV-2 on the human body: In short, SARS-CoV-2 is transmitted through respiratory droplets enters the nasal system by inhalation, and begins to multiply. The spike protein (protein S) on the surface of SARS-CoV-2 is compressed inside the host cell, where it binds to the ACE2 receptor. Here, the enzyme furin is present in the host cell and plays an important role in COVID-19 entry.[9] Then, the virus begins to spread with a limited innate immune response and is detectable by nasal swabs. The replicated and disseminated virus then reaches the respiratory tract, where it encounters a stronger innate immune response. At this stage, the disease becomes clinically apparent, and predictors of subsequent clinical course may be based on the severity of the innate cytokine response.[10]

Mechanism of the human immune system against COVID-19: Immune system responses are divided into three types: innate immunity (fast response), adaptive immunity (slow response), and passive immunity. There are also two types of passive immunity: natural immunity received from the mother and artificial immunity received from drugs. When the body is affected, inflammatory responses begin.[11] Sometimes, when the body first encounters pathogens, the immune system cannot function properly, and illness may occur. This failure of the immune system to function properly is what happened with SARS-COV2.[12] When cells of the immune system are trained, they complete their work by recirculating between peripheral and central lymph nodes and migrating to the site of injury via the blood. Blood carries naive and educated immune cells from place to place and flows throughout the body, acting as a pipeline for the immune system. After the

cells leave these nodes through the lymphatic vessels, they enter the bloodstream again to be transferred to the tissues of the whole body.[11] Since there is no vaccine or registered drug against SARS-COV2, the immune system is the best defense as it supports the body's natural ability to defend against pathogens and resist infections. As long as the immune system is working properly, infections like SARS-COV2 go unnoticed.

The main causes of death in patients with SARS-COV2 (Reasons for failure): So far, the potentially lethal mechanisms of COVID-19 have been reported. Several studies suggest that the main cause of death from COVID-19 is multiple organ failure due to multiple pathological mechanisms, including a genetic predisposition to an intense inflammatory response. Increased inflammatory response, affects the lungs locally as well as systemic thrombotic microangiopathy. In addition, the role of inflammation in the lungs and the changes that lead to hypoxia cannot be ignored. However, thrombotic changes in the microcirculation seem to be the most predominant.[13]

In particular, the main cause of death in patients with SARS-COV2 is respiratory failure due to acute respiratory distress syndrome (ARDS).[14] Secondary hemophagocytic lymphohistocytosis (sHLH) is characterized by fulminant, fatal hypercytokinemia with multiple organ failure and is underrecognized. Viral infection causes sHLH and also occurs in 3.7-4.3% of sepsis cases in adults.[15,16] Also, in sepsis, a systemic response to infection is observed, which is characterized by inflammation - vasodilatation, accumulation of leukocytes, and increased vascular permeability.[17] The sHLH, similar to the cytokine profile, is related to the severity of the disease of SARS-COV2, described by increased IL-2, IL-7, granulocyte colony-stimulating factor (GCS-F), monocyte chemoattractant protein 1 (MCP-1), TNF-α and macrophage inflammatory protein 1.[18] Another study found elevated IL-6 and ferritin, suggesting that mortality may be due to inflammation caused by the virus.[19]

Deregulated immune response and cytokine release syndrome (CRS) or cytokine storm

Inflammatory cytokines and chemokines including TNF-α, IL-6, IL-1b, and MCP-1 were significantly increased in acute COVID-19 cases.[20] High cytokine levels may also induce fatal complications of COVID-19. In acute subjects of COVID-19, with increased inflammatory cytokines, autopsy pathology has shown tissue necrosis and interstitial infiltration with monocytes and macrophages in the lung, gastrointestinal mucosa, and heart.[21] Immunomodulators may be a useful adjunct to antiviral therapy. Among the extreme cytokines, IL-6 is one of the key cytokines. Intense IL-6 signaling leads to various biological consequences such as increased cardiac arrhythmia, vascular permeability, and decreased myocardial contractility. It is this blockade that targets the host's immune system that may be useful for COVID-19. Also, Tocilizumab is a recombinant human monoclonal antibody against the IL-6 receptor.[4]

Neonate's Immune System and SARS-COV2

In a review article, Elahi evaluated immune-biased tolerance versus resistance strategy in the immune system of infants and children and SARS-COV 2. Recent advances in this field reveal fundamental differences in the immune system of neonates compared to adults, such that infants respond to pathogens through biased immune tolerance rather than resistance strategies. Thus, repeated and recent vaccinations in infants and children may result in learned immunity. Therefore, a highly regulated immune system, a physiological abundance of specific immunosuppressive cells, and exposure to attenuated vaccines may enhance trained immunity to limit the immune overreaction to SARS-COV2 in pediatrics.[22]

Infants and children are spared from SARS-COV2 (Why is SARS-COV2 less severe in children?)

1) lower expression of ACE2 receptor: Several studies have proposed hypotheses to explain age-related differences in disease severity. COVID-19 enters the human tissues mostly through the ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) in the nasopharyngeal cells. Disease severity as well as specific complications of SARS-CoV-2, such as loss of smell and taste, likely depend on the quantitative expression of TMPRSS2 and ACE2 in the respiratory, kidney, gastrointestinal, and cardiovascular systems.[23,24] This age-related expression is much less in pediatrics than in adults.[25]

2) Absence of Chronic Comorbidities in neonates: Comorbidities include hypertension, obesity, diabetes, hypercoagulopathy, chronic obstructive pulmonary disease (COPD), heart failure, malignancy, endothelial injury, chronic kidney disease (CKD) or drugs that increase the risk of disease severity, such as ACE inhibitors or angiotensin II receptor blockers (ARBs), are available in adults, and infants usually do not have these comorbidities.[26]

3) Abundant of naive T cells: Elderly people are described by reduced adaptive and innate immune responses, leading to reduced viral clearance. The higher proportion of memory cells in adults and the lack of naïve T cells, which are abundant in infants, may potentially contribute to the widespread release of T cell-derived cytokines seen predominantly in adults with ARDS. However, pediatrics are commonly exposed to coronaviruses but have lower T-cell responses and neutralizing activity compared to adults.[27] There are many mechanisms commonly observed in adults that influence host immune responses, including cytokine storm, macrophage hyperstimulation, and antibody-dependent enhancement (ADE).[28]

4) Absence of cytokine storm in neonates: In general, children appear to have milder symptoms and are often asymptomatic after contracting SARS-CoV-2 than adults. This suggests that a differential immune response to SARS-CoV-2 in adults versus neonates may induce a different clinical outcome. Found to preliminary data collected in SARS-CoV-2 cases, cytokine storm may play a role in the pathogenesis of the disease. For example, high levels of various cytokines, such as interferon (IFN) g, IP10, IL-7, TNF-α, MCP1, IL-1b, IL-1RA, GCSF, GMCSF, MIP1A, IL-8, IL-9, IL-10, PDGF, FGF, and VEGF, were diagnosed in plasma of patients compared to healthy adults.[18]

This initial evidence proposed that the cytokine storm may be related to disease severity. Despite high levels of cytokines that can promote Th1-mediated immune responses, IL-10 and IL-4 were also higher in SARS-CoV-2 cases. This is in contrast to the abundance of only proinflammatory cytokines IFN g, IP10, IL-1b, IL-6, IL-12, and MCP1 in SARS and Il-17, IL-15, and TNF- α in MERS coronavirus infections, which were related to excessive lung damage and pulmonary inflammation.[29]

5) abundant of immunosuppressive cells in neonates: Although neonates may benefit from a physiological abundance of immunosuppressive cells, these cells gradually disappear with age. So, other undiagnosed factors may be responsible for mild or asymptomatic infection in older pediatrics. Also, the existence of a regulatory mechanism mediated by different immunomodulatory cells may serve as a useful feature in the immune system of pediatrics. At the same time, there is an urgent need to assess how the immune system responds to SARS-CoV-2 in young populations compared to older populations. It was suggested that the highly regulated nature of the neonatal microenvironment could prevent the proinflammatory cytokine storm observed in adults.[30,31] Therefore, such differences can explain the underlying mechanism of such milder respiratory symptoms in neonates and pediatrics. However, further investigations are necessary to test such ideas. [22]

6) COVID-19 vaccination in pregnancy: Kalafat et al., in a review article, evaluated the vaccination of COVID-19 in pregnancy. They observed many investigations comparing perinatal outcomes between unvaccinated and vaccinated pregnant women have had encouraging findings and have shown no harmful effects on the pregnancy or the infant. Immunization with mRNA vaccines does not raise the risk of premature birth, miscarriage, low birth weight, maternal or NICU admission, fetal malformation, fetal death, or pulmonary embolism.[32]

7) Maternal immune response to COVID-19 and placental transfer of IgG: Santano et al. results showed that SARSCoV-2 infection during the third trimester of pregnancy leads to a strong cytokine and antibody response at delivery and causes an important decrease of the COVID-19-specific IgGs transplacental transfer, with a stronger negative effect when the infection is closer to delivery.[33]

8) Immune response of infants born to mothers infected with COVID-19: Conti et al. showed in their cohort study that infants who were breastfed during the first 2 months of life had considerably higher salivary IgA antibody levels compared to formula-fed neonates, and increased IgA immune complexes were observed in breastmilk. Also, it seems that mothers who are infected in the perinatal period not only protect the infant through the secretory IgA of the breast milk but also actively stimulate and train the infant's immune system through the immune complexes of the breast milk.[34]

9) Multisystem inflammatory syndrome in children (MIS-C): Several investigations have noted that people positive for COVID-19 show elevated blood markers such as C-reactive protein (CRP), which indicate inflammation.[35] MIS-c is a potentially fatal severe clinical manifestation of SARS-CoV-2 disease with different definitions. MIS-C was observed in children and not usually described in infants. Therefore, neonates do not experience the fatal effects of this syndrome.

Discussion

Several studies have shown that SARS-CoV-2 in pediatrics has a milder manifestation and a better prognosis than in adults. Previous research on the outbreak of pneumonia produced by COVID-19 was mostly based on knowledge of adult cohorts. Adequate information is not available for pediatrics with SARS-CoV-2, especially for infected neonates. In addition, evidence has shown that neonatal infection with COVID-19 is usually asymptomatic.[36] Pediatrics who died from COVID-19 appeared to be more likely to be older pediatrics, signifying a rising trend in risk with age. Infants infected with SARS-CoV-2 usually had a favorable outcome.[37] Different states of immunocompetence may account for differences in clinical manifestations and prevalence of SARS-CoV-2 infection in infants and adults. The underlying mechanisms of bypassing the severe form of the disease in neonates and pediatrics are unclear. Based on recent advances in neonatal immunology, the selection of the immune response to SARS-CoV-2 in pediatrics against adults may explain the different clinical outcomes observed.[31,38]

It is worth remarking that neonates, pediatrics, and younger adults (18 years old) have different immunity. Consequently, different potential mechanisms may describe the marked difference in their mortality after SARS-CoV-2 infection compared to adults. Given the increased levels of pro-inflammatory cytokines caused by COVID-19, SARS, and MERS infections, mild infection indications in neonates may be associated with immune tolerance mechanisms early in life. Therefore, the physiological abundance of MDSC and CEC may limit unreasonable inflammation in response to COVID-19 infection in neonates. Even though such preparatory data suggest a role for the cytokine storm in disease pathogenesis, more research is needed to verify these observations.[28]

Neonates may benefit from a physiological

abundance of immunoregulatory or immunosuppressive cells and have a well-regulated immune system. There is convincing proof for innate immune hyperactivity in the development of acute disease in adults infected with COVID-19. Certainly, this is only one potential mechanism as other mechanisms are probably complicated. However, distinct components of immunity in youth may prevent extravagant and potentially harmful immune responses to SARS-CoV-2 infection. Controlling the inflammatory response to the virus may be as critical as attacking the virus because an uncontrolled pro-inflammatory response in some adults can lead to infiltration of immune cells that trigger a cytokine storm that causes inflammation and lung damage.[22] Specifically, cases admitted to ICU had higher levels of IL-2, IL-10, IP10, IL-7, MCP1, GCSF, MIP1A, and TNF-α compared to cases who did not need ICU.[18]

Another potential mechanism may be the level of expression of SARS-CoV-2 receptors in the lungs and other organs of adults versus neonates and pediatrics. Therefore, the expression pattern of ACE2 and COVID-19 nuclear receptors (TMPRSS2) is different in adults and children, and the expression of these receptors is low in infants but high in adults, especially in their nasopharyngeal cells. It can be speculated that the differential expression of ACE2 and TMPRSS2 in pediatrics compared to adults could describe the different severity and outcomes of infection.[23–25] Also, nonspecific trained innate immunity can provide other descriptions for milder disease in children. Elderly individuals are described by reduced adaptive and innate immune responses, leading to reduced viral clearance. In adults, there is a greater proportion of memory cells and a deficiency of naïve T cells in releasing T cell-derived cytokines, leading to ARDS.[27,28] A complete picture of the critical host immune factors that lead to severe disease in some cases and milder disease in neonates and pediatrics is unknown. It is speculated that the unique immune component in pediatrics and underlying health conditions in adults may partly describe the mild or asymptomatic disease observed in this group of pediatrics.[22,39] A clearer characteristic seen in pediatrics with SARS-CoV-2 is referred to as MIS-C or "Pediatric inflammatory multisystem syndrome (PIMS)". This syndrome is not usually seen in infants, and this may explain why infants are more resistant to COVID-19 than children.[40] Severe post-infection clinical manifestations in pediatrics include MIS-C, which imitates Kawasaki disease (KD) or toxic shock syndrome (TSS) and develops weeks or months after the onset of SARS-CoV-2 indications.[28] Among the infants born to mothers with SARS-CoV-2, respiratory distress syndrome (RDS), and pneumonia are common events, Moreover, it appears that preterm neonates may have more severe symptoms compared to full-term neonates which can be attributed to the weaker immune system in preterm neonates.[41] Despite most cases of SARS-CoV-2 in children are asymptomatic or mild, neonates and pediatrics with underlying medical conditions often need hospitalization to prevent life-threatening complexities.[28]

Although COVID-19 infection in the pediatric population is rarely fatal, quantifying the mortality risk associated with SARS-CoV-2 can be difficult because they are commonly asymptomatic or show mild symptoms and signs. These values and differences in the immune system response to COVID-19 compared to adults are essential for making decisions about vaccination and prevention strategies for the pediatric population.[42] Consequently, more research on the host immune response to COVID-19 is justified, including a careful examination of the factors of healthy versus dysfunctional immune response to address our theory and better understand the immune associates of protection in neonates and pediatrics compared with adults.

Conclusion

In this review, we condense the last information on immune responses to COVID-19 in neonates. New evidence suggests that although neonates and pediatrics are susceptible to SARS-CoV-2, only a small number of them develop serious symptoms. Several immune mechanisms have been suggested to reduce involvement in infants compared to adults. The immune system of infants has differences from adults, which leads to different immune responses to COVID-19, such as fewer memory cells and more primary cells in infants. Also, in this review, we have mentioned the other possible mechanisms including less expression of receptors on the surface of newborn tissue cells, and less inflammatory reactions. Therefore, so far there is limited information about immune responses in neonates, and more research is needed.

Conflict of Interest

Authors have no conflict of interest.

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Ethical Considerations

None.

Author's Contribution

R.B. and F.A. conceived of the presented idea. F.A. developed the theory. M.G-T. encouraged R.B. and F.A. to investigate immune responses and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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