Chapter

SARS-CoV-2 Angiotensin Converting Enzyme 2 (ACE2) Receptor Expression and Its Effects on COVID-19 Epidemiology in Children

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Abstract

Children account for less than 2% of COVID-19 cases around the globe, and children experience relatively minor symptoms compared to the adult population. Various theories have been proposed to explain this phenomenon. One such theory is the involvement of angiotensin converting enzyme 2 (ACE2) in the pathogenesis of COVID-19. Previous studies have found a direct relationship between the abundance of pulmonary ACE2 receptors and the age of patients. Since Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) binds to the ACE2 receptor to infect a patient, it is hypothesized that the low abundance of pulmonary ACE2 receptors in children relative to adults accounts for both the mild symptoms experienced as well as the difference in the number of identified cases.

Keywords: COVID-19, ACE2, RAAS, SARS, children, epidemiology, cases

1. Introduction

The World Health Organization (WHO) declared a global pandemic in March 2020 as COVID-19, an illness caused by SARS-CoV-2, was spreading rapidly around the globe, causing severe illness and death. There are numerous theories regarding the pathogenesis of COVID-19; however, it's pathogenesis is not completely understood due to the novelty of SARS-CoV-2. Various studies have been performed to determine how SARS-CoV-2 infects human cells so we can better understand its pathogenesis and, therefore, potential targets for medications and effective immunizations. COVID-19 is less prevalent in children than adults, accounting for less than 2% of cases. A few studies have demonstrated the potential involvement of ACE2, a component of the renin-angiotensin-aldosterone system (RAAS), as an explanation for the drastic difference between the number of COVID-19 cases in children versus adults. Multiple studies confirm that SARS-CoV-2 binds to ACE2, and there is a higher abundance of pulmonary ACE2 receptors in adults compared to children.

These two conclusions together could provide insight into the lower number of COVID-19 cases and the lower severity of symptoms in children.

2. The coronavirus disease (COVID-19)

In December 2019, pneumonia of an unknown origin was linked to a seafood wholesale market in Wuhan, Hubei Province, China. Scientists isolated a novel coronavirus related to SARS-CoV. Therefore, it was named SARS-CoV-2, and the disease that it causes was named coronavirus disease 2019 (COVID-19). This novel disease began to spread globally due to its high rate of infectivity. Because of the high rate of mortality caused by COVID-19, the WHO declared a global pandemic in March 2020 [1, 2]. As of November 2022, the total number of cases in the United States was 98,481,551 including 305,082 new cases. The total number of deaths due to COVID-19 was 1,075,779 as of November of 2022, including 2,644 new deaths, and the number of hospitalizations was 25,224 with an average of 3,915 new admissions daily [3].

On December 14, 2020, the U.S. COVID Vaccination Program began where vaccines from Pfizer, Moderna, and Johnson & Johnson were administered around the globe [4]. Pfizer and Moderna each initially required 2 shots to be fully immunized, whereas Johnson & Johnson required 1 shot [5]. At that time, Pfizer vaccines were given to patients ages 12 and older, while Moderna and Johnson & Johnson vaccines were given to patients ages 18 and older [5]. As of December 2022, Pfizer and Moderna vaccines were being offered to children as young as 6 months of age [6].

3. COVID-19 illness symptoms and severity in children

Like adults, COVID-19 infection in children can cause severe illness, especially if they have an underlying health condition such as congenital heart disease, asthma, type 1 diabetes, obesity, cystic fibrosis, cancer, or immunosuppression [7–9]. In rare circumstances, children with severe COVID-19 infection may develop a condition known as multisystem inflammatory syndrome in children (MIS-C) [8].

MIS-C is a severe post-infectious inflammatory complication of COVID-19 in children where most patients (about 68%) required mechanical ventilation and ICU admission. The most common presentation of MIS-C was gastrointestinal symptoms such as diarrhea and abdominal pain. The majority MIS-C cases demonstrated neutrophilia and an elevated inflammatory marker called c-reactive protein (CRP) [10]. MIS-C commonly affects children ages 5–13 and has been associated with coronary artery aneurysms, left ventricular cardiac dysfunction, atrioventricular block, and multiorgan failure [11, 12]. New evidence suggests MIS-C infection in neonates, now termed multisystem inflammatory syndrome in neonates (MIS-N) [11, 13–17]. As of November 28, 2022, the CDC reports 9,139 confirmed cases of MIS-C and 74 deaths. Half of these cases were children ages 5–13 years old with a median age of 9 years old. 98% of children tested positive for COVID-19; the remaining 2% were exposed to COVID-19 [18]. **Figures 1** and **2** demonstrate the weekly cases of MIS-C throughout the pandemic and the number of cases per age range, respectively.

Recent research regarding COVID-19 infection in children versus adults is controversial. Children often experience a milder course of illness or are asymptomatic [19, 20], making it difficult to establish the number of pediatric cases. Research has shown that a component of the RAAS, ACE2, has been linked to lower COVID-19 infection

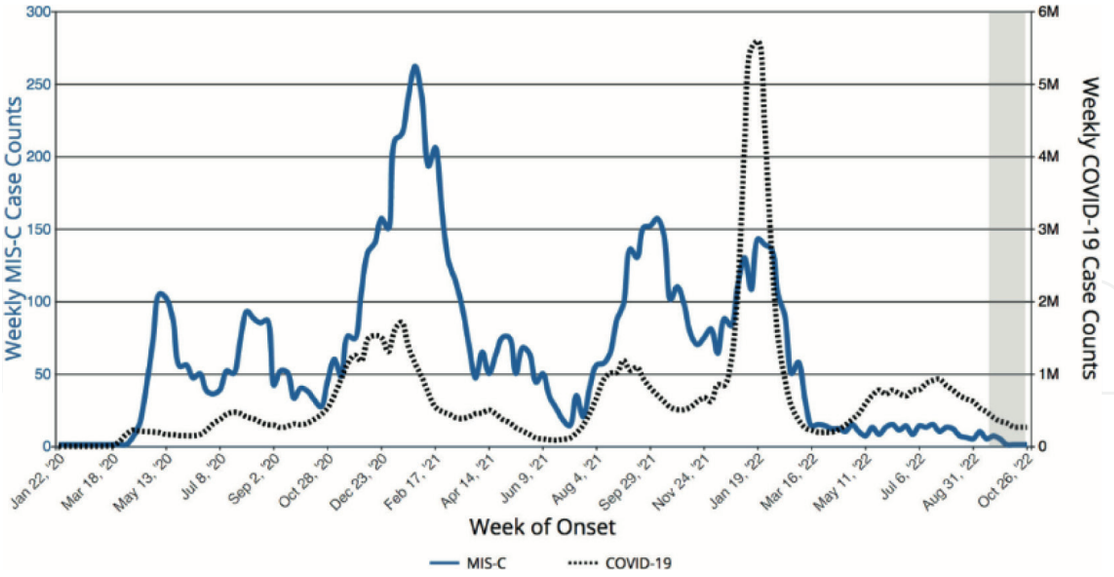

Figure 1.
Weekly MIS-C Cases and COVID-19 Cases Reported to CDC [18].

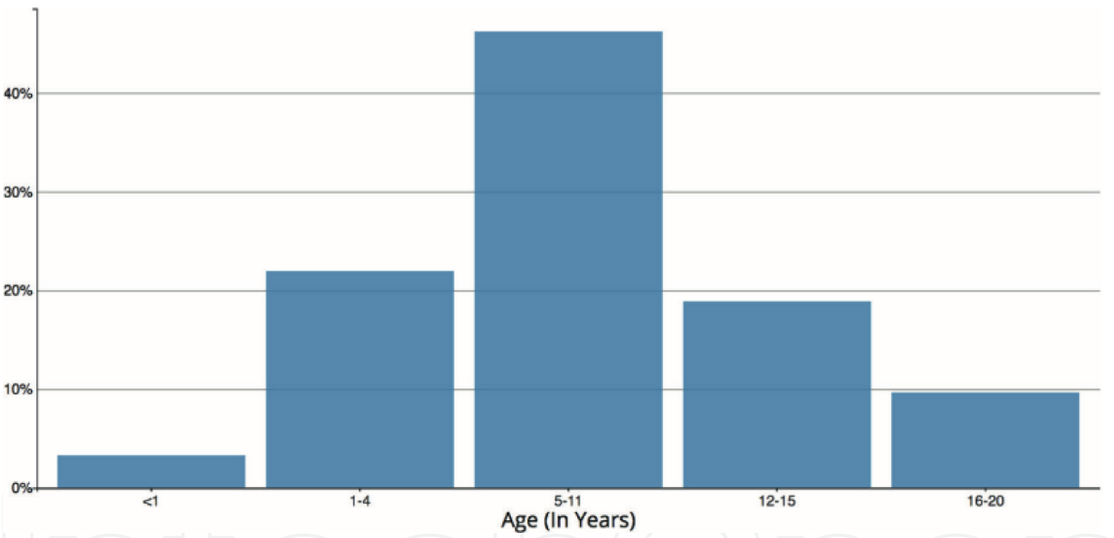

Figure 2.
MIS-C Patients by Age Group [18].

rates and milder symptoms of COVID-19 infection in the pediatric population compared to the adult population.

4. Renin-angiotensin-aldosterone system (RAAS)

Blood pressure is regulated by the kidneys via the RAAS. Juxtaglomerular (JG) cells in the kidney release renin, a protein that helps to increase blood pressure. A rise in blood pressure is accomplished when renin acts on angiotensinogen, which is released from the liver, to convert it into its active form, angiotensin I. Angiotensin I is then converted to angiotensin II via ACE in the lungs. Angiotensin II serves to increase blood pressure and blood volume by triggering the release of aldosterone and antidiuretic hormone (ADH). Aldosterone and ADH reabsorb sodium and water,

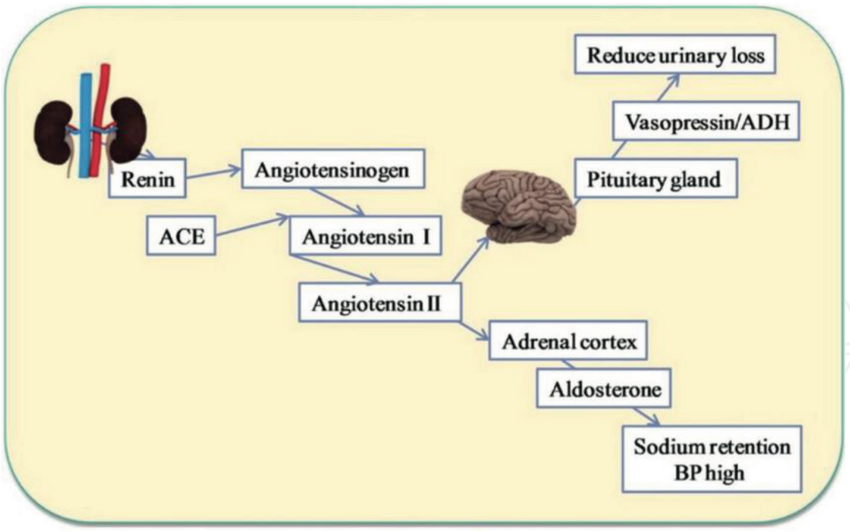

Figure 3.
Diagram of the RAAS [22].

respectively, from the kidney. As water follows sodium into the body, blood volume increases; therefore, blood pressure increases. Angiotensin II also causes vasoconstriction that leads to an increase in blood pressure. Because of these effects, classes of medications known as ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) can be used to manage the blood pressure of hypertensive patients (**Figure 3**) [21].

5. Biochemical comparison of ACE to ACE2

ACE2 was discovered in 2001 and was named ACE2 due to its structural similarity to ACE. Consequently, it was hypothesized that ACE2 could be another potential target for the treatment of hypertension. Despite its similarity to ACE, studies determined that ACE2 did not convert angiotensin I to angiotensin II, and ACEi were unable to inhibit ACE2 [23].

Studies determined that the major structural difference between ACE and ACE2 was that ACE is a carboxy-dipeptidase that removed C-terminal dipeptide, while ACE2 acted as a carboxy-peptidase that removed only a single amino acid. ACE2 hydrolyzes angiotensin I more poorly when compared to ACE; however, it was determined that ACE2 hydrolyzes angiotensin II with a catalytic efficacy of about 400-fold compared to ACE2 hydrolysis of angiotensin I [23, 25]. Originally, the main tissue sites that expressed ACE2 receptors were the testes, heart, and kidney [23, 24].

It is now known that ACE2 receptors are present in the respiratory tract, specifically the olfactory epithelium, the nasal septal epithelium, the nasal conchae, and the paranasal sinuses [26].

6. ACE2 and SARS-CoV-1

In 2003, a novel coronavirus known as SARS-CoV-1 [27] was identified as a distinct etiological agent for SARS [28–32]. SARS is known to be a lower respiratory tract disease, and numerous coronavirus particles were found in pneumocytes [32, 33], cells that are located in the alveoli of the lungs. Furthermore, a large number of

ACE2 receptors were found in type I and type II pneumocytes [32, 34], and few ACE2 receptors were discovered in the bronchial epithelium [32]. This evidence supports the hypothesis that SARS is likely linked to the ACE2 receptors as both were associated with each other in the alveoli.

The spike proteins of SARS-CoV-1 were found to target several ACE2 receptors located in various organs, including the immune system and respiratory tract, which can result in immunosuppression and respiratory distress, respectively. Therefore, it was concluded that SARS-CoV-1 was linked to the ACE2 receptor; consequently, ACE2 was hypothesized as a potential target for treatment of SARS.

7. ACE2 and SARS-CoV-2

As previously mentioned, recent research shows that ACE2 is linked to SARS-CoV-2. The binding affinity is vastly different due to amino acid differences at the biochemical level between ACE2 and ACE. There are stronger hydrophobic and salt bridge interactions between SARS-CoV-2 and ACE2 compared to those between SARS-CoV-2 and ACE. This was hypothesized as the explanation for the larger global influence COVID-19 has had compared to SARS-CoV-1 [35–37].

As stated above, the spike protein (S-protein) of SARS-CoV-2 and SARS-CoV-1 is what binds to the extracellular domains of ACE2 in the lungs. This leads to subsequent downregulation of ACE2 receptors which allows SARS-CoV-2 to be endocytosed into the cell it is infecting. ACE2 receptors have been found to protect the cells where they are expressed; therefore, their downregulation upon binding of SARS-CoV-2 is what allows endocytosis and subsequent COVID-19 infection [37–40]. **Figures 4** and **5** demonstrate the interactions between ACE2 and SARS-CoV-2 as well as the pathogenesis of COVID-19 and the human immune response.

The human immune system responds to the loss of ACE2 receptors via an imbalance of Th17 and Treg cell function leading to an overactivation of immune cells [37, 41–43]. The imbalance of the RAAS system along with ACE2 receptor loss in COVID-19 patients are additional factors that contribute to tissue and systemic inflammation [37, 44, 45].

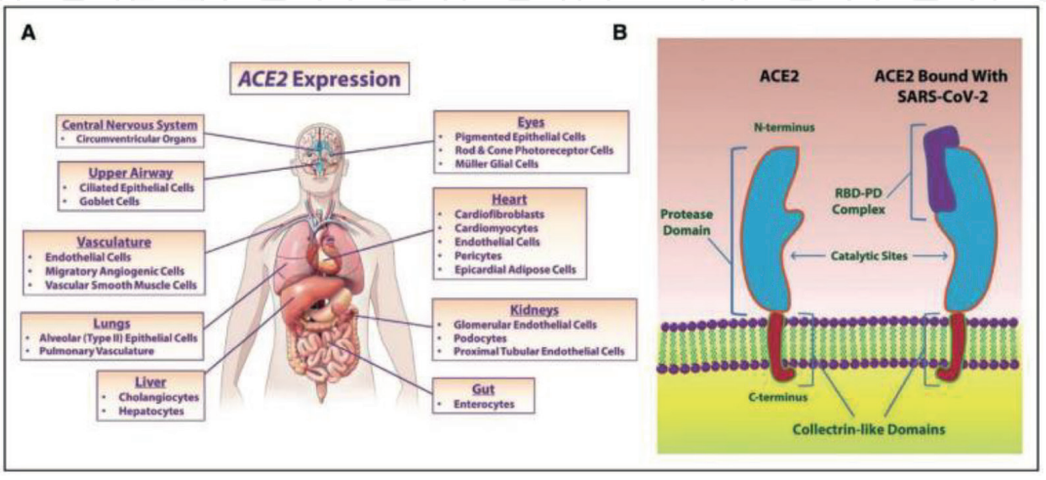

Figure 4.
Location of various organs that contain ACE2 receptors with their function (A) and ACE2 binding to SARS-CoV-2 (B) [37].

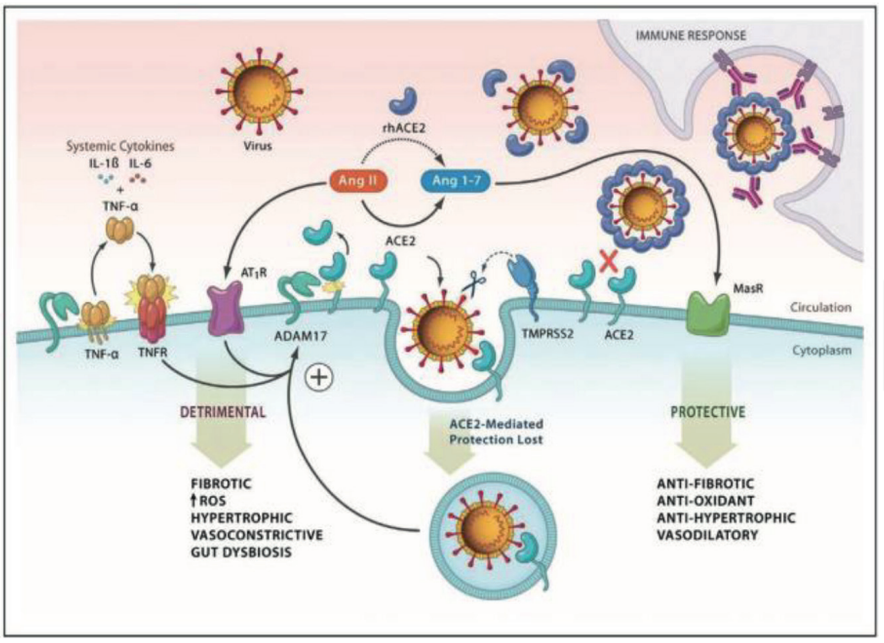

Figure 5.
Role of ACE2 in the pathogenesis of COVID-19 and the inflammatory response [37].

8. COVID-19 infection, children versus adults

As previously stated, the diagnosis of COVID-19 in children is more difficult than that of adults and can be controversial. This is because children who are infected with SARS-CoV-2 are often asymptomatic or mildly symptomatic; consequently, they are not typically tested for COVID-19. Anosmia and ageusia are not frequent in children, but when present, they are the strongest predictors of SARS-CoV-2 infection [46].

Data from the World Health Organization (WHO) from December 2019 to September 2021 showed that children under 5 represented 1.8% of global COVID-19 cases and 0.1% of global deaths. Children ages 5 to 14 years of age were 6.3% of global cases and 0.1% of global deaths [47, 48].

9. ACE2 receptor expression, children versus adults

It is known that the number of global COVID-19 cases in children is significantly less than that of adults. A proposed mechanism for this distribution is the hypothesis that the ACE2 receptor is expressed to a higher degree in the lungs of adults than it is in children. Data has shown that SARS-CoV-2 binds to ACE2 receptors before it is endocytosed into pneumocytes located deep in the lungs and into cells of the nasal epithelium; therefore, a lower expression of ACE2 receptors in children could explain the drastic difference in the number of cases between children and adults.

A 2020 retrospective study by Bunyavanich and colleagues involved 305 subjects between the ages of 4 to 60 years of age. They found that ACE2 receptor expression was age-dependent where the lowest number of ACE2 gene expression was found in children less than 10 years of age [49].

The number of ACE2 gene expression significantly increased as age increased [49]. Thus, the researchers proposed that this data could potentially explain why COVID-19 is less prevalent in children than in adults [49, 50]

Furthermore, it was previously mentioned that severe cases of COVID-19 in children, such as those seen in MIS-C and MIS-N, mainly exhibit gastrointestinal symptoms while severe cases in adults affect the pulmonary system more than the gastrointestinal system. A 2022 study by Schurink and colleagues found that as age increases, ACE2 receptor expression increases in the lungs and decreases in the intestines [51], which could explain why older individuals experience more severe pulmonary complications compared to children. Gastrointestinal issues in children can be caused by a variety of pathogens and can potentially be overlooked as a severe COVID-19 infection, which can also contribute to lower cases of COVID-19 cases in children.

10. Conclusion

The COVID-19 pandemic caused by SARS-CoV-2 has had a significant impact on the global population. Countless efforts have been made to decrease transmission of and eradicate the virus, including medications and vaccines. Several different studies have been performed to determine the pathogenesis of SARS-CoV-2 so we can better understand how it infects the population and to find targets for medications that can hopefully treat the infection and prevent severe illness.

Not only has COVID-19 significantly impacted the global population, but it has impacted children to a much lesser degree than adults with children representing less than 2% of global COVID-19 cases. A proposed mechanism for explaining why cases are much less prevalent in children is the lower expression of pulmonary ACE2 receptors, a component of the RAAS, in the nasal epithelium and alveolar pneumocytes of children compared to adults. Studies have shown that SARS-CoV-2 binds to ACE2 before being endocytosed into cells to cause infection. Studies also show the number of ACE2 receptors in the pulmonary system is directly related to age.

This proposed mechanism is controversial at this point in time, especially since COVID-19 cases in children may also be likely lower because they experience mildly symptomatic or asymptomatic illness. Future studies should involve compounds that specifically inhibit pulmonary ACE2 in adults to determine if the number of COVID-19 cases significantly decrease. Eventually, these developments can lead to medications to treat the virus at its early stages to decrease likelihood of transmission and, therefore, prevent severe illness.

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