COVID 19: The Lack of ACE2 Provides Protection for Children

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Research article

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Abstract

Background In early December 2019, in China the novel severe acute respiratory syndrome coronavirus 2 has been spreading. It was reported that the number of children was lower than adults and they have fewer symptoms.

Method Published articles were searched in PubMed, Science direct, in the end 60 articles were collected.

Findings Three major findings were found after researching. First, The minority of cases in children category. Secondly, ACE2 resulting penetration in cells after the interaction with virus. And third, a poor presence of ACE2 in lungs children.

Discussion Molecularly, the link between the virus and ACE2 was explained, through a segment of viral protein S, comprising four residues nested in RBD. The outbreak due to Sars-Cov-1 has shown that the highest attack rate in China was aged between 20 and 39 (53%).Also, there was a decrease in mortality and severity of diagnosis for patients on ACE inhibitors. It causes a decrease in ACE2 levels. In addition, patients with severe diagnostics are diabetic which lead to the excessive expression of ACE2 in human tissues.

Conclusion the ACE2 factor was the aim of our study, but researchers can find many factors linked to the physiology of children.

Background

In early December 2019, in China many pneumonia cases were reported. Some patients, in critical condition, died in hospital. Following diagnosis and after investigations, a new virus was identified, and it was the novel coronavirus: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)(1). The disease, termed coronavirus disease 2019 (COVID-19), has been spreading across the borders. In the neighboring countries then in all the world many cases were reported too (2). That is why, the World Health Organization (WHO) declared it as a pandemic and it is a public health emergency of international concern (3).

SARS-Cov-2 has Angiotensin-converting enzyme 2 (ACE2) receptors similarly to SARS-CoV-1. Interaction of virus with receptors is one of the causes of pathogenicity. The viral protein S was linked with ACE2 which facilitates penetration of virus inside cells (4).

In March 2020, number of cases in China was 80174, in the other countries the number was 8774 with an intense gravity which contributes to mortality (1) (2). It was reported, during the outbreak that the number of young cases was lower than age range and children had fewer symptoms. In the beginning, studies were established in adult's hospital that is why a few cases of children were declared (1). Until now and in many countries, there is a significative difference between the cases number of adults and children (2). For example, in Italy the total number of children with COVID-19 represent 1% from all patients (5).

The objective of this review of literature, is to show if the deficiency of ACE2 is a factor who provide this protection for children from Sars-Cov-2.

Methods

Published articles were searched in PubMed, Science direct. Method had 3 steps: The first step, an initial limited search, was effectuated on the search engine mentioned before using those combinations: “COVID 19” and “CHILD”, “COVID 19” and “ACE2” and “CHILD” and “ACE2”. After that text words contained in the title, abstract, and of the index terms used to describe articles were analyzed. Secondly, 20 articles were collected, and the first step was repeated by using key words extracted from the previous articles to find 20 more articles. Finally, references of all identified articles were used to get 20 additional studies. So, in the end 60 articles were collected. The search terms used in searching are presented as follows:

Covid 19, Sars-Cov-2, Coronavirus, ACE2, Children, Pediatric.

N.B : all articles are published in 2019 and 2020.

Results

The low number of children affected by Sars-Cov-2

Firsts studies about prevalent cases of COVID-19 have not shown an important number of cases or mortality of children. Not only that, but morbidity too in link with Sars-Cov-2 was not severe (6). According to the latest estimate, the lowest number in this category of age and the difference between adults and children in case numbers were underlined. This minority of cases was explained by the example in Italy: the total number of children affected by Sars-Cov-2 represent 1% of all patients (5), or the American example, which the number of children suffering from COVID 19 represent 1.7% when the total is 149 000 cases (7). The age of children was less than 18 years old, in all studies included. Other studies established in china have shown that the cases number of children was 728 (34,1%) when the total of patients was 2135. All studies included (60 articles) reported that the number of children suffering from Sars-Cov-2 was significantly lower compared to the number of adults.

In addition, previous studies have shown that not all children were symptomatic. A Chinese study has shown that fever, for example, can be present in 57% of children cases when for adults represent 72% and same for cough it was present in 32% of children cases when with adults represent 51.6%. Dyspnea too was not be present with children in this study, but it was present with 40% of adults. Besides, study has shown that 90% of children suffering from Sars-Cov-2 was asymptomatic in hospital (3) .All studies included (60 articles) reported that symptoms were not identified by the same level or the same frequency as adults and children (8).

To know the absence of gravity in sick children, many studies included reported the low number of children in hospital or with symptoms 2% in china and less than 5% in Korea. Even though China had several serious cases at the start of the outbreak, but they did not report many several cases of children. The good prognostic of children suffering from Sars-cov-2 explained by the heigh number of cases without several symptoms (94%), The proportions of critical cases were 10.6% in group of children aged 1 year and one mortality. This proportions were reported in Chinese study (3). According to our study, the difference between children and adults in the prevalence and severity level of disease is important that is why it is important to know the responsible factor (9).

Briefly, studies have shown that children were minority during the outbreak, they were not symptomatic and if they were suffering from COVID 19 they were not in dangerous situations. Children was protected from disease and it is important to understand the protective factor.

The link between ACE2 and Sars-Cov-2

ACE2 is an enzyme belongs the renin-angiotensin-aldosterone system (RAAS), it participates in a cascade of reactions. Angiotensinogen is synthesized in the liver and represent a precursor for angiotensin, able to make a sustainable production of angiotensin I. Angiotensin I will be transformed in angiotensin II with the conversion role of ACE. At this level, ACE2 participates to convert angiotensin I to angiotensin (1–9) and angiotensin II to angiotensin (1–7) (10). ACE2 contains functional groups of amino acid residues like LYS 341 and GLU56. It forms the cavity of the active site can then participate in the reaction (11).

To know where the high distribution of ACE2 in human body, many studies have shown that this enzyme is highly existed on lung alveolar epithelial cells and on smooth muscle cells (10). Bronchial biopsies showed the strangest expression of ACE2 in the lung cells by an experimental study. In contrast, skin biopsies, lymphoid tissues and hepatobiliary structures have not presented a high expression of ACE2 (12). The expression of enzyme was reported in other studies to be significantly higher in nasal compared with blood and saliva (13). The Massive expression of ACE2 in the human body is in the pulmonary alveolar epithelial cells and small intestinal epithelial cells which explains the pneumonia symptoms and the mortality engendered by respiratory arrest (4).

Previous studies have shown the existence of affinity between Sars-Cov-1 and ACE2, that is why the interaction between Sars-Cov-2 and ACE2 was predicted. In addition, an experimental animal study in Ace2-knockout reported the importance role of this receptor in the pathogenesis of SARS-CoV-1 (10). In other sides, studies underlined the important interaction between ACE2 and Sars-Cov-2, by explaining that infection of human correlated with ACE2 expression. Besides, ACE2 able to colonize the cell, after that a ‘priming’ process will be done by the serine protease transmembrane protease, serine 2 (TMPRSS2) (14). It has also been shown that amino acid residues like LYS 341 and GLU56 of ACE2 has affinity to the amino acid residue ARG453 of S1 protein (11).

Relation between children and ACE2

The level expression of ACE2 in peripheral blood mononuclear cell is the same between adults and children without any significative difference but in upper and lower airways the difference was significative (13). The researchers verified the expression of the gene of ACE2 in nasal epithelial samples taken from patients aged 4 to 60 years. The result was that the youngest children expressed the lowest amounts of ACE2 (15). So, the interpretation was that the lower level of expression of ACE2 due to children physiology.

Discussion

The objective of this review of literature, is to show if the deficiency of ACE2 is a factor who provide this protection for children from Sars-Cov-2. Three major findings were found after researching. First, The minority of cases in children category. Secondly, ACE2 resulting penetration in cells after the interaction with virus. And third, a poor presence of ACE2 in lungs children.

Apart from the limited number of pediatric cases during the outbreak, the assessment of disease and severity was also significantly less dangerous than in adults. After microbiological confirmation that the person was positive, many studies have shown that clinically, children (age < 18) are more tolerant than adults: clinical signs with mild evolution such as fever, cough, and rhinorrhea. In addition, although radiological examinations are not highly recommended in pediatrics, studies found that the pulmonary lesions shown by chest CT were weaker and milder than in adults (16).

Molecularly, the link between the virus and ACE2 was explained, through a segment of viral protein S, comprising four residues (ARG449, PRO450, ARG453 and ASP454) nested in RBD. Residue ARG453 was connected coherently with LYS341 and GLU56 residues of ACE2 (11). Many hypotheses assumed that infection with SARS-CoV-2 makes a decrease in ACE2, internalized to ensure penetration into the cell (17). An immunohistochemical study has shown the strong presence of ACE2 on the alveolar parenchyma and smooth muscles of the lungs (18). One of the dangerous consequences of disease was breathing disorder, hypoxia was the most marked consequences of this epidemic, which can lead to mortality with dyspnea. A Western blot analysis for the quantitative measurement of the expression of ACE2 in the lungs of rats has shown that the content of the immunoreactive band decreases significantly with decreasing age. There had not a significant difference between adults and the elderly. This study agree with the results of this review and suggests that age influences the expression of ACE2(19).

This review effectuated can show the low prevalence of the disease in children. Results proved the low level of ACE2 in children (age < 18) and the link between the virus and ACE2 for cell penetration. The hypothesis was that the lack of ACE2 was a protective factor for children. Other data can support results of this review by reporting the age of illness persons by Sars-Cov-1. The outbreak due to Sars-Cov-1 during 2003 has shown that the highest attack rate in China was aged between 20 and 39 and they represent 53%, and in Canada the average affected age is 45 years. These reports were useful because there is a 75% close resemblance in amino acid sequence with Sars-cov-2, and ACE2 represented an entry point to the cell (20).

To show the hypothesis that the low of ACE2 was a protective factor. Not many studies have shown that, but there was a decrease in mortality and severity of diagnosis for patients on ACE inhibitors. ACE inhibitors can be used for blood pressure disorder or for heart disease. It causes a decrease in ACE2 levels for patients because it blocks the cascade of reactions leading to the synthesis of ACE2 (21). In addition, suppose that chloroquine and hydroxychloroquine have clinical efficacy in combating Sars-Cov-2. We checked its mechanism of action in previous studies to find a link to this review (22). These two treatments leaded to eliminate the glycosylation of ACE2 which is necessary for binding with the viral protein S (23). Theoretically, chloroquine and hydroxychloroquine played a role in the improvement of some cases and it reinforces that the level of ACE2 was essential for the attack of the virus and the degree of pathogenicity (22). Many therapeutic trials were effectuated to find the treatment of the disease. Experimental studies have shown that many oils had an impact on human health. Eucalyptus oil was one of this oils that made a significative amelioration of the illness persons suffering from coronavirus as the Sars-Cov-1. Studies showed the effect of Eucalyptus on ACE2 receptors. Eucalyptus has decreased the expression level of ACE2 and played the same role of ACE inhibitor. In addition, Eucalyptus is a bronchodilator when it will be inhaled and leads to decrease lung secretions. Researchers have not shown that Eucalyptus was a treatment, but there have shown the positive effect leading to ameliorate prognostic of patients suffering from Sars-Cov-2. We can suppose that Eucalyptus can be an adjuvant treatment(24) .

The literature suggest that diabetes was a risk factor for COVID-19, a meta-analysis has shown that 14.5% of patients with severe diagnostics are diabetic. Also, there have not a significative difference between the type 1 and type 2 of diabetes. It is true that diabetes affects the immune system and the individual will be more susceptible to infectious diseases in general (25). For example, Carey et al. have Showed that the ratio of the incidence rates of persons in hospital with infectious disease was 3.71 (95% CI 3.27–4.21) for people with T1D and 1.88 (95% CI 1.83–1.92) for people with T2DM (26). Not only that, but also, diabetes resulting the excessive expression of ACE2 in human tissues as well as in the lungs. This explained the binding of Sars-Cov-2 and ACE2 in the body and that the excessive expression of ACE2 is the factor that lead a high number of severe cases of diabetes in COVID unities. so diabetes is considered as a risk factor of Sars-Cov-2 (25).

This review of literature illustrated ideas that support our hypothesis and showed that the level of ACE2 played an important role in guiding the prognosis of patients infected with Sars-Cov-2. The high level of ACE2 has been shown to be a risk factor for worsening the situation, in contrast with children, whose expression of ACE2 was low compared to adults for physiological reasons was a protective factor (15).

Conclusion

Finally, children had a protection from Covid 19, in our study the ACE2 factor was the aim but researchers can find many factors linked to the physiology of children. Immunity system can report many values delivery to understand the low number of cases of children (7). In this review they are many suppositions must be confirmed by experimental way.

Abbreviation

SARS-COV-1 severe acute respiratory syndrome coronavirus 1

SARS-COV-2 severe acute respiratory syndrome coronavirus 2

COVID 19 Corona Virus Disease 2019

ACE2 Angiotensin-converting enzyme 2

ACE Angiotensin-converting enzyme

RAAS: renin-angiotensin-aldosterone system

Declarations

Ethics approval and consent to participate:

Not applicable

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Not applicable

Availability of data and materials:

PUBMED

Competing interests:

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Figures

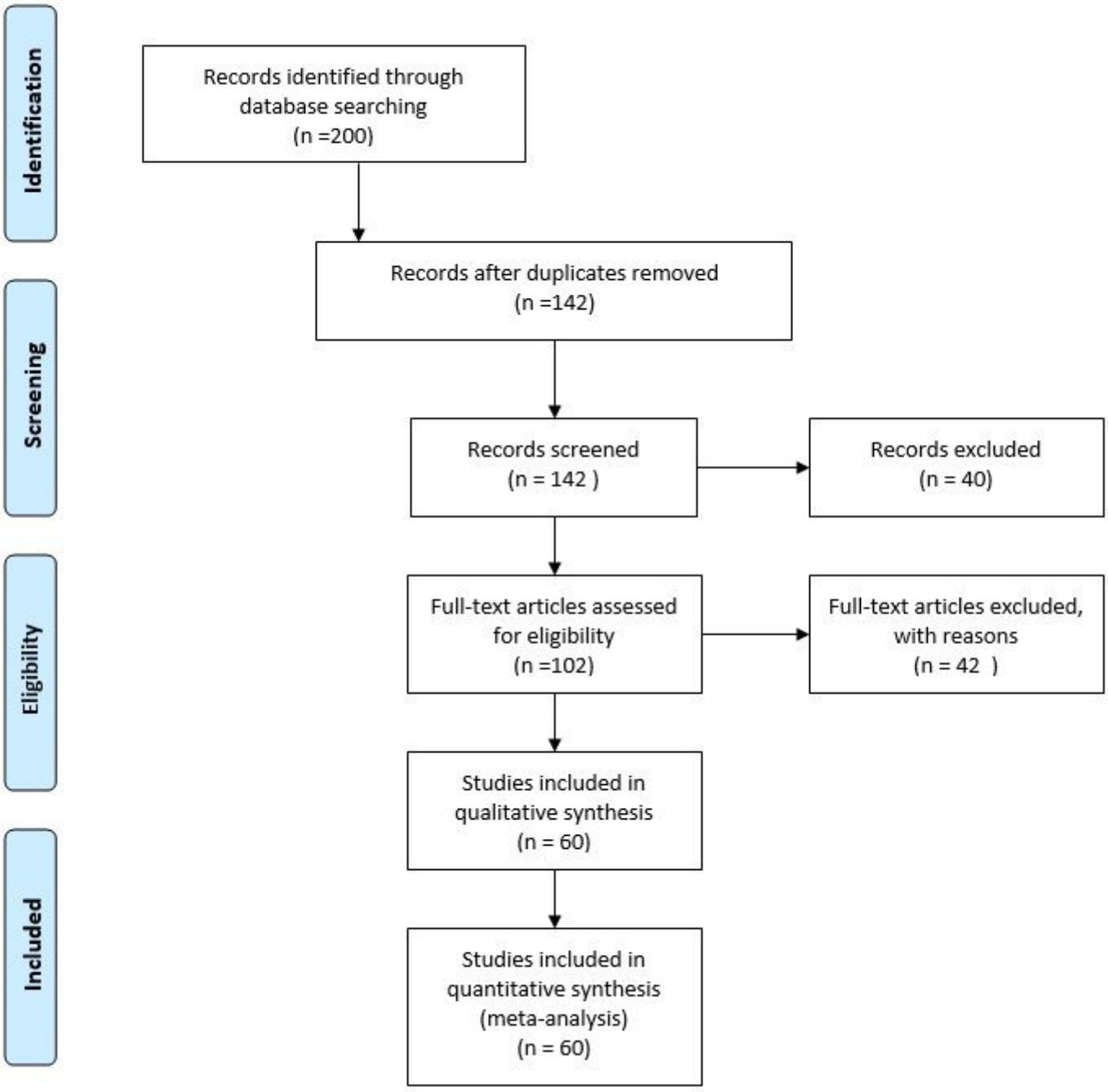

Figure 1

PRISMA 2009 Flow Diagram

Supplementary Files

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- PRISMA2009checklist.doc