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From SARS to COVID-19: What we have learned about children infected with COVID-19



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ABSTRACT

Introduction: Coronaviruses, both SARS-CoV and SARS-CoV-2, first appeared in China. They have certain biological, epidemiological and pathological similarities. To date, research has shown that their genes exhibit 79% of identical sequences and the receptor-binding domain structure is also very similar. There has been extensive research performed on SARS; however, the understanding of the pathophysiological impact of coronavirus disease 2019 (COVID-19) is still limited.

Methods: This review drew upon the lessons learnt from SARS, in terms of epidemiology, clinical characteristics and pathogenesis, to further understand the features of COVID-19.

Results: By comparing these two diseases, it found that COVID-19 has quicker and wider transmission, obvious family agglomeration, and higher morbidity and mortality. Newborns, asymptomatic children and normal chest imaging cases emerged in COVID-19 literature. Children starting with gastrointestinal symptoms may progress to severe conditions and newborns whose mothers are infected with COVID-19 could have severe complications. The laboratory test data showed that the percentage of neutrophils and the level of LDH is higher, and the number of CD4+ and CD8+T-cells is decreased in children's COVID-19 cases.

Conclusion: Based on these early observations, as pediatricians, this review put forward some thoughts on children's COVID-19 and gave some recommendations to contain the disease.

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1. Introduction

A cluster of patients presented with pneumonia caused by an unknown pathogen that was linked to the seafood wholesale market in Wuhan, China, in December 2019. Subsequently, a new coronavirus was identified by sequencing the whole genome of patient samples (Zhu et al., 2020a). It was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the

Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (Gorbalenya et al., 2020), and the disease caused by the virus was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).

Of seven coronaviruses identified from humans, HCoV-229E and HCoV-NL63 belong to α -coronaviruses, and HCoV-OC43, MERS-CoV, SARS-CoV and SARS-CoV-2 belong to β -coronaviruses. Both SARS-CoV and SARS-CoV-2 first emerged in China. Although the genome-wide similarity is about 79%, the similarity of the seven conserved domains used for virus identification is as high as 94.6%. This indicates that SARS-CoV-2 belongs to the same genus as SARS-CoV. Additionally, studies have shown that SARS-CoV-2 could enter cells through angiotensin-converting enzyme 2 (ACE2) receptors on the surface of cell membranes, which is consistent with SARS-CoV (Lu et al., 2020a; Zhou et al., 2020).

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A total of 84,338 confirmed cases including 4,642 deaths had been reported in China by 25 April 2020 (China, 2020). The illness spread to other countries in a short time. By the same date, 213 countries had reported 2,724,809 confirmed cases including 187,847 confirmed deaths (WHO). The pandemic situation of COVID-19 remains a serious threat at this stage. As a new virus, the biological characteristics, epidemiology, pathogenicity, and immunity of SARS-CoV-2 have not been illustrated; efficient, fast and accurate detection methods are still lacking; and specific drugs and vaccines are still being investigated. Children as a special group show different clinical features when compared with adults. Therefore, it has been a significant challenge for the medical community to diagnose and treat children with COVID-19.

A group of pediatricians reviewed the available information and proposed the following questions: What are the similarities and differences between SARS and COVID-19 on epidemiological and clinical features? What are the determining risk factors that may result in developing mild or severe COVID-19 infection cases? Can the diagnosis and treatment experiences of children with SARS be extrapolated and give useful information and apply to children with COVID-19? Can anti-SARS-CoV antibodies have a cross-reaction with anti-SARS-CoV-2? How do we prevent and contain SARS-CoV-2 infection in children? To better explain these questions, this review compared the epidemiological and clinical features of SARS and COVID-19.

2. Research content and Results

2.1. Epidemiological comparison of SARS-CoV and SARS-CoV-2

SARS first emerged in Guangdong, China, in November 2002. It has caused global anxiety and resulted in 8,422 cases with 919 death in 32 countries (Yang et al., 2020). The most cases were concentrated in China, Taiwan, Hong Kong, Singapore, and Toronto, Canada (Wilder-Smith et al., 2020). In contrast, by 25 April 2020 > 80,000 confirmed cases and > 4,000 deaths had been reported within a matter of 4 months in China. Additionally, 213 countries with > 2,700,000 confirmed cases and at least 180,000 deaths had been reported. These notably increased numbers indicate that COVID-19 has stronger infectivity.

Children with SARS were sporadic and had a clear history of exposure. By contrast, children with COVID-19 showed a clear history of clustering in infected households and community spread. According to incomplete statistics, > 230 children were infected with COVID-19, of whom 69/257 (26.8%) had a history of exposure in Hubei province and 183/257 (71.2%) had a clear history of clustering in infected households (Chan et al., 2020).

Regarding disease spread, both SARS and COVID-19 can be transmitted through droplets and contact. Insufficient evidence has shown that newborns acquired SARS or COVID-19 infection through vertical transmission (Chen et al., 2020b; Zhu et al. 2020b; Pak et al., 2004). On the other hand, some studies have suggested that SARS may be transmitted through aerosols containing the virus (Yu et al., 2004) and the digestive tract (Chinese academy of pediatrics respiratory group, 2003). It is still unclear whether COVID-19 can also be transmitted through these ways. Fecal-oral tract transmission should not be ignored because studies have shown positive nucleic acid tests in feces (Guan et al., 2020; Holshue et al., 2020) even though no case has been reported as being transmitted through the digestive tract.

This review found that COVID-19 has a quicker and wider transmission, obvious family agglomeration, and higher morbidity and mortality. Digestive tract transmission cannot be ignored and maternal-infant vertical transmission is doubtful. It is suggested that the traditional public measures taken with SARS may not be enough to contain the COVID-19 pandemic. International

collaboration and information resource sharing can help to minimize the size of outbreak and reduce global deaths.

3. Comparison of clinical features between SARS and COVID-19 and analysis of special cases

3.1. Comparison of general cases between SARS and COVID-19

After comparing the clinical manifestations (Dong et al., 2020; Leong et al., 2006; Leung et al., 2004; Lu et al., 2020b; Fang and Luo, 2020; Nga et al., 2004; Zeng et al., 2003; Xu et al., 2020; Xie et al., 2006; Zou et al., 2005) this review found that children, including newborns, have been suspected as having COVID-19. The most common symptoms of these two diseases were fever and cough, and the majority of children had a good prognosis. Children with COVID-19 exhibited less fever and were more asymptomatic. Younger children, especially newborns, affected by COVID-19 had a poor outcome, which was different from children with SARS, which showed that increased age predicted a worse outcome. Moreover, digestive symptoms could be the first clinical manifestation and children who started with gastrointestinal symptoms may have a more severe clinical condition.

3.2. Death cases and critical illness cases

There was one death of a child with SARS in Guangzhou, China, in 2003. This case was a 10-year-old boy who had severe hepatitis 2 months previously. He was in close contact with a doctor who had consulted with a SARS patient. The child had fever and cough in the early days, with a progressively worse condition. He died 70 hours after transfer to ICU (Fu et al., 2004). Two children have died from COVID-19 to date. The first one was a 10-month-old child with intussusception who had multiple organ failure and died 4 weeks after admission (Lu et al., 2020b). The second was a 14-year-old boy from Hubei province (Dong et al., 2020).

The first child with a severe case of COVID-19 was reported in China. The child was a 1-year-and-1-month-old who came from an epidemic area and had no clear family contact history. The onset of clinical symptoms was diarrhea and vomiting, which rapidly progressed to acute respiratory distress syndrome, sepsis, shock, and acute renal failure. During hospitalization nucleic acid detection was performed three times but only the third had a positive result. Furthermore, it should be noticed that his family members did not have any clinical symptoms, so asymptomatic transmission should be considered (Chen et al., 2020a).

Therefore, although the majority of children have mild clinical symptoms and a good prognosis, it should not be overlooked that these children can develop a serious condition, especially those who have atypical manifestations, basic diseases, long-term use of immunosuppressants, and immunocompromised children.

3.3. Neonatal cases

There were no newborn SARS cases reported in China. Three newborns with COVID-19 have been reported. One had fever at the age of 5 days; another one was diagnosed after a home caregiver (first ill) and the mother were diagnosed; the third one was born to a pregnant woman with suspected COVID-19, and the nucleic acid test showed positive 30 hours after he was born (Lu and Shi 2020).

Great attention should be paid that although there is a low possibility of vertical transmission, an infant whose mother is infected with COVID-19 may have adverse reactions such as fetal distress, preterm delivery, respiratory distress, and even death (Chen et al., 2020b). The multidisciplinary team should make a collective effort in the labor room to improve the newborn survival rate.

3.4. Biochemical indicators between SARS and COVID-19

In general, both of these two diseases have the following characteristics: normal or decreased peripheral white blood cells, decreased lymphocytes, mild abnormal liver function, and myocardial enzymes. However, children infected with COVID have shown higher CRP, which is different from children with SARS (Bitnun et al., 2003; Xiong et al., 2003; Leung et al., 2004; Zeng, 2003).

A large number of studies have shown that decreased CD4+ and CD8+ T-cells, high LDH, and a higher percentage of neutrophils were positively correlated with the severity and mortality of SARS cases (Duan and Shen, 2006). The child infected with severe COVID-19 also showed a significant decrease in T-cell subsets and low levels of C3 and C4 in the acute stage of disease (Chen et al., 2020a). Therefore, clinicians should monitor and pay attention to these early warning biochemical indicators, which can help to identify severe cases.

4. Pulmonary image comparison between SARS and COVID-19

In general, the pulmonary images of children infected with SARS and COVID-19 were nonspecific in the early stages of disease. However, many children with COVID-19 cases have shown normal pulmonary images when compared with children with SARS (Guan et al., 2020; National children's medical center, 2020; Xu et al., 2020). In addition, a few children infected with SARS showed mild clinical symptoms but severe pulmonary radiographic changes (Xiong et al., 2003) and some children infected with COVID-19 had radiologic changes but did not have any symptoms (Lu et al., 2020b). Pulmonary imaging changes should therefore not be ignored, especially in those patients who are highly suspected as having the virus but their X-rays are normal. Chest CT detection is feasible to improve the positive rate of pulmonary lesions.

5. Treatment comparison of SARS and COVID-19

Long-term follow-up results showed that adults with SARS had different degrees of avascular necrosis of the femoral head, lung function impairment and pulmonary fibrosis. The reason for these outcomes may be related to the use of large doses of hormones (Xie et al., 2006). Many children infected with SARS were treated with hormones too, but recent a report has suggested that the available clinical evidence does not support the use of corticosteroids to treat patients infected with COVID-19 (Russell et al., 2020). Therefore, wide use of hormones in children infected with COVID-19 remains skeptical. Strictly controlled criteria for using hormones in clinical work, severe and critical patients can be used for a short time (Yi, 2020).

6. Pathogenesis comparison between SARS and COVID-19

6.1. Invader host cellular mechanisms

The envelope spiker protein of coronavirus associated with cellular receptors to mediate infection of their target cells and ACE2 is a functional protein of SARS (Li et al., 2003). SARS-CoV-2 and SARS-CoV have a similar receptor-binding domain, which suggests that SARS-CoV-2 might also use ACE2 as a cell receptor (Lu et al., 2020a; Zhu et al., 2020).

6.2. Immune response

Children with SARS and COVID-19 have shown a drastic decrease in the number of CD4+, CD8+ and CD3+T-cells in their blood (Chen et al., 2020a; Duan, 2006; Luo, 2020). These results

suggest that cellular immunity is severely damaged after coronavirus infection. However, the detailed mechanisms still need to be investigated.

The IFN α/β system is a powerful innate immune system with strong antiviral activity. A study has shown that SARS-CoV not only blocks the attack of the IFN system, but also actively inhibits the activation of IFN regulator 3 (IRF-3) to prevent activation of the IFN system and production of antiviral IFN by the body (Kuri & Weber, 2010). Whether these mechanisms are similar in COVID-19 requires additional research.

6.3. Nuclear factor

Membrane proteins of SARS-CoV can directly bind to I κ B kinase (IKK), inhibit the activity of nuclear factor kappaB (NF-kappaB) and reduce the expression of the cyclooxygenase2 (COX-2) gene and other transcription factors to regulate the body's immune and inflammatory responses (Fang et al., 2007). The mechanism for COVID-19 still need to be elucidated.

There is a significant deficit in knowledge and unanswered questions on SARS-CoV-2. For example, ACE2 is widely distributed in the lungs, kidneys, intestinal and other tissues; so why is the lung tissue more frequently damaged? Why do children with COVID-19 show mild clinical symptoms? Why do children with COVID-19 show less changes at the subtype T-cell level compared with adults (Duan, 2006)? Are there other pathways to enter into the cell?

7. Discussion

Although there are many similarities between SARS and COVID-19 from epidemiology to clinical characteristics, they also show differences (Table 1). The potential reasons for higher transmissibility are as follows: (1) the unique biological characteristics of SARS-CoV-2; (2) children could be the potential infectious source because of mild symptoms, which result in wider spread; (3) the asymptomatic children were overlooked; (4) children with normal pulmonary images were ignored; (5) there were false negative results in nucleic acid detection.

Why do children infected with COVID-19 have mild clinical symptoms? Why do they have none/mild abnormal biochemical indicators and pulmonary image changes? The potential reasons are as follows: (1) children have a variety of memory T-cells specific to the virus from frequent exposure to a variety of viruses in childhood, and it maybe that this has cross-reacted after SARS-CoV-2 virus infection; (2) vaccinations help the body to form protective immune responses; (3) children's immune systems are still developing, and an inadequate immune defense can prevent excessive host immune damage.

The current group of pediatricians has learnt from SARS and suggest that: (1) the possible transmission in children without/with mild illness should be emphasized; (2) multidisciplinary and strategic approaches should be used to diagnose children with COVID-19; (3) isolation measures be mandatory and taken in time for perinatal pregnant women infected with COVID-19, and the multidisciplinary team should be involved to improve the survival rate of newborns; (4) the following risk factors of severe cases should be identified early: younger age, higher percentage of neutrophils, higher LDH, decreased CD4+ and CD8+T-cells, and progressive pulmonary images; (5) in mild clinical symptoms, imaging examination should not be ignored in children with COVID-19, and chest CT can be used to improve the positive rate before the nucleic acid result, especially for those cases whose chest X-ray is normal; (6) the method of specimen collection with the nucleic acid test should be widely taught, and lower respiratory specimens are advocated to improve the positive rate; (7) the wide

Table 1
Comparison of the epidemiological and clinical characteristics of SARS and COVID-19.

| Characteristic | SARS | COVID-19 |
|---|---|---|
| Epidemiology | | |
| Transmissibility | Lower | Higher |
| Exposure characteristics | Sporadic, hospital cluster | Community spread, family cluster |
| Children spread | Not reported | Yes |
| Main transmission routes | Respiratory droplets, contact, fecal-oral tract | Respiratory droplets, contact |
| Possible transmission routes | Aerosol | Aerosol, fecal-oral tract, vertical transmission |
| Clinical spectrum | | |
| Incubation period | 2–14 days | 1–14 days |
| Age | 50 days to 17.9 years | 36 hours to 18 years |
| Clinical course | Most are mild | Most are mild and asymptomatic |
| Common features | Fever, cough, headache, malaise, myalgia, diarrhea | |
| Prognosis | Good, one death reported | Good, no deaths reported |
| Newborns born to mother with infection | | |
| First trimester | Spontaneous miscarriages, termination of pregnancies | Not reported |
| Late second/third trimester | Oligohydramnios, severe intrauterine growth retardation, severe gastrointestinal complications | May have adverse reactions such as fetal distress, preterm delivery, respiratory distress, and even death |
| Laboratory tests | Normal or decreased peripheral blood WBC, lymphopenia, mild elevated CRP, mild abnormal liver function and myocardial enzymes, decreased CD4+, CD8+ T-cells | |
| Pulmonary images | | |
| Similarity | Nonspecific in the early stage; as the disease progresses could manifest as patch shadow, ground glass shadow, lung consolidation | |
| Difference | Mild symptoms but severe pulmonary radiographic changes | Could be normal |
| Treatment | Severe cases treated with hormones | Wide usage of hormones is skeptical, severe and critical patients can be used for a short time |

use of hormones should be cautioned; (8) education about how to prevent SARS-CoV-2 infection should be advocated; (9) more clinical and basic research is necessary to understand COVID-19; and (10) a larger and polycentric clinical database should be built to analysis the children infected with COVID-19. A recent study found that anxiety, depression and stress are common in young people during the COVID-19 pandemic (Wang et al., 2020) and further research is required to study the mental health of young children infected with COVID-19.

8. Conclusion

There are limited data on children with COVID-19. There is an urgent need to define the clinical characteristics and severity of the disease, especially in those countries that lack pediatric patient data. At present, China has made initial progress in containing the spread of COVID-19, but many countries are still suffering from the disease. This paper summarized the differences and similarities between children's SARS and COVID-19 from epidemiological to clinical characteristics. It provided some suggestions on containing children's COVID-19. It is hoped that drawing upon the experience of containing SARS that this pandemic can be contained. It is hoped that these suggestions could help other countries to identify possible preventive and therapeutic strategies.

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