A Review of Coronavirus Disease (COVID-19) in Children

Alireza Ghodsi[1],
Anoush Azarfar[2],
Sara Ghahremani[3*]

1 Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2 Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
3 Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

[*]**Corresponding Author**
Sara Ghahremani, MD
Email: ghahremanis@mums.ac.ir

Abstract
Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) with a high morbidity and mortality rate has spread globally and affected all age groups. Children can carry and transmit the novel coronavirus, but usually do not develop severe disease. The number of children who contracted coronavirus disease 2019 has increased significantly; however, compared to adults, there have been fewer reported cases of COVID-19 in the pediatric population. This review is mainly about the epidemiological features, clinical findings, laboratory tests, imaging, and treatment recommendations in children with COVID-19 disease.

Keywords: COVID-19; Coronavirus; Children; 2019 - nCoV

Introduction

In December 2019, a sudden outbreak of a new infectious disease first appeared in Wuhan, Hubei Province, China, but has now become a pandemic that is spreading rapidly around the world (1, 2). On January 7, 2020, a new type of coronavirus was successfully identified by the China Center for Disease Control and Prevention (1). And on January 12, 2020, the World Health Organization (WHO) temporarily named the virus 2019-nCoV. Later on February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) proposed naming the new virus SARS-CoV-2 because of its resemblance to SARS which emerged in 2003 (3). Accordingly, WHO named the disease caused by SARS-CoV-2 infection COVID-19. A few weeks after the initial reports of the infection, the prevalence of COVID-19 in South Korea, Iran, and Italy was reported, and several European, Asian, and North and South American countries also reported cases of the disease. Finally, on March 11, 2020, COVID-19 was declared a pandemic by WHO (4).

Many studies have examined the symptoms, characteristics, and treatment of COVID-19 in adults. Compared to adults, COVID-19 has been reported to be significantly less prevalent in children (5). This study aims to identify epidemiological features, clinical findings, laboratory tests, imaging, and treatment recommendations in children with COVID-19 disease.

Epidemiology

In the early days of the outbreak and before January 22, 2020, no cases of children under the age of 15 years were reported in Wuhan, among the 425 laboratory-confirmed COVID-19 patients (6). However, in another study conducted on January 29, 2020, among the 1,099 patients diagnosed, 0.9% of them were under 15 years of age, indicating that the disease could spread across the entire age range (7). Children of all ages can be infected with COVID-19, even young children and newborns (8).

Journal of Pediatric Nephrology | Volume 8| Number 3| 2020
This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

1

In a study on 44,677 confirmed COVID-19 cases in China, 2% of patients were between 0 and 19 years old, and 0.9% were under 10 years old (9). Italian data released on March 18, 2020 reported that 1.2% of 22,512 Italians with COVID-19 were under the age of 18 years, and no death was reported in this age group (10). In the United States, as of March 16, 2020, 5% of 4,226 patients were children under 19 years old (11); and in a systematic review study conducted between January 1 and March 18, 2020, children made up between 1 and 5% of COVID-19 patients (12). Conversely, an investigation on COVID-19 in Shenzhen, China, found that the rate of infection in children under 10 years of age (equal to 7.4%) was similar to the average population (7.9%) (13). Jiehao et al., in a work on children with COVID-19, reported that the age group of children with the disease was between 3 and 131 months with an average of 74 months, and the ratio of boys to girls was 1 to 1.5 (5). In contrast, in a research work by Dong et al., which was conducted on 2143 children with a mean age of 7 years, 56.6% were male patients (14). In a report on 171 children by LU et al., the average age of children was 6.7 years, and 60.8% were boys (15). According to the United States data, 2,572 children with COVID-19 had an average age of 11 years and 57% were boys (16). Out of 184 children in that study whose exposure information was available, 9% had a recent travel history and 91% had a history of contact with a COVID-19 patient in the family or community (16).

Clinical Findings

The incubation period in children is usually about 2 days (with a range of 2 to 10 days) (5). The SARS-CoV-2 virus uses its spike protein for binding to angiotensin-converting enzyme 2 (ACE2) receptors to replicate and spreads from infected cells to other cells (17). Also, the symptoms of the disease are milder in children than in adults (14). Few children need to be hospitalized. In a study in the United States, 147 children were hospitalized, and 15 children were admitted to the ICU, among 752 children with hospitalization information (16). In addition, among the 291 children whose symptoms information was available, 56% had fever, 54% had cough, and 13% had shortness of breath. Also, myalgia, sore throat, headache and diarrhea have been rarely reported in sick children (16). Another study at Wuhan Children's Hospital examined 171 children with confirmed disease, and the most common symptoms were cough (48.5%), pharyngeal arrhythmia (46.2%) and fever of at least 37.5 ℃ (41.5%) (15). Other symptoms included diarrhea (8.8%), fatigue (7.6%), rhinorrhea (7.6%), and vomiting (6.4%). Furthermore, 2.3% of children had a blood oxygen saturation of less than 92%, 28.7% had a tachypnea, and 42.1% had a tachycardia (15). In a research work by Xia et al., they reported fever (which is defined as the axillary temperature above 37.3 ℃) in 60% of cases, cough in 65%, diarrhea in 15%, rhinorrhea in 15%, sore throat in 5%, vomiting in 10%, tachypnea in 10%, and fatigue in 5% of cases (17). Physical examination of the moist rales was observed in 15% of cases, retraction in 5%, and cyanosis in 5% of patients (18). According to Dong et al., the severity of the disease in children was classified as 4.4% asymptomatic, 51.0% mild, and 38.7% moderate, accounting for a total of 94.1%, while severe and critical cases made up 6.7% and 0.7%, respectively (14).

In some cases, gastrointestinal symptoms can be the main and primary symptoms of the disease (19, 20).Some pediatric cardiologists have warned about the unusual manifestation of Kawasaki disease associated with COVID-19. The first published case of the classic Kawasaki disease associated with COVID-19 was announced late April at a hospital in Stanford, California, in which a 6-month-old infant was initially diagnosed with fever and rash (21). Since then, several other cases of this unusual COVID-19 manifestation have been reported in children, and a case-series from Iran is also being collected.

Infants usually have a milder illness (8, 22); on the other hand, it may be difficult to find symptoms in infants (23). Some symptoms such as irritability, decreased response, and poor nutrition can be a sign of infection (20). In a study on newborns of mothers with COVID-19, all infants were tested negative, so there is no evidence that COVID-19 is transplacentally transmitted (24). Farhat et al. in Mashhad, in a work on 25 pregnant women, fifteen mothers had prenatal symptoms suspected of the corona virus with 10 having postpartum symptoms. The coronavirus test was performed with a pharyngeal swab or tracheal tube sample (R.T PCR), and was positive in only 4 infants (25). Although a mild or moderate disease is most common in children, COVID-19 can be severe, especially in children with underlying diseases. Out

of the 345 children with COVID-19 studied in the United States, 23% had at least one underlying disease (16). The most common underlying diseases in those children were chronic lung disease (including asthma), heart disease, and immune system defects (16). In general, children have milder symptoms, faster recovery, and better prognosis than adults (26, 27).

Laboratory tests

In a work by Henry et al., who summarized the findings from 12 studies on 66 children, they found that 69.2% of children had a normal number of leukocytes and neutrophilia (4.6%) and neutropenia (6.0%). Only 2 children (3.0%) had lymphocytopenia. C-Reactive Protein (CRP) increased in 13.6% and procalcitonin in 10.6% of cases (28). In the study by Cai Jiehao et al., the average laboratory tests results were reported and shown in Table 1. It was also announced that 2019-nCoV RNA was detected 4-48 hours after the onset of symptoms in nasopharyngeal and throat swabs of all patients, and it became undetectable 6-22 days (average 12 days) after the onset of the disease. In six patients, a fecal sample was tested for 2019-nCoV RNA within 3-13 days after the onset of the disease, and 5 (83.3%) were positive. At the time of publication of their findings, those five patients still had 2019-nCoV RNA detected in feces within 18-30 days after the illness onset. Also, serum and urine samples of these five patients were tested for 2019-nCoV RNA, which were reported to be negative (5).

Table 1. Average laboratory tests in the study of Cai Jiehao et al (5).

Item	Value
White blood cell count	7.35×10^9 /L
C-reactive protein (CRP)	7.5 mg/L
Procalcitonin	0.07 ng/dL
Creatine kinase-MB	23 U/L
Alanine aminotransferase	18.5 U/L
Aspartate aminotransferase	27.7 U/L
Urea	3.1 mmol/L
Creatinine	35.5 µmol/L
Lactate dehydrogenase	25 U/L
D-dimer	0.45 µg/mL
Influenza virus A and B	Negative

Imaging

Lu et al. reported that the ground-glass opacities were observed in one-third (33%) of the 171 children diagnosed with COVID-19, and local and bilateral patchy shadowing were seen in 18.7% and 12.3% of cases, respectively (15). Another study looked at five children, and three showed moderate patchy ground-glass opacities in the CT Scan (29). Reported by other works, some patients with mild COVID-19 have had normal findings on the CT scan (30-33). Xia et al. examined 20 children's CT scan results and found that 16 (80%) were abnormal: 10 patients (50%) had halo sign consolidation, 12 patients (60%) had ground-glass opacities, 4 patients had fine mesh shadow, and small nodules were observed in 3 patients (15%) (18). Pleural effusion has also been reported in a number of children with COVID-19 (31, 34, 35).

Diagnosis

Children should be evaluated according to complaints, clinical findings, and a history of exposure to an infected person. Nucleic acid testing (NAT) or real-time polymerase chain reaction (PCR) with new fluorescent techniques has been proposed as the gold diagnostic standard for all patients suspected of contracting COVID-19 (36-38). Nevertheless, these tests have disadvantages such as being time-consuming and unavailable, also having false negative results that can be improved by repeated sampling (39). It is recommended that all findings from contact history, clinical features, number of blood cells, and CT scans of the chest, along with NAT/PCR tests, are considered as the standard diagnostic protocols in suspected children (22, 40). In a research work on 205 patients with COVID-19, the bronchoalveolar lavage fluid sample showed the highest positive result (93%), followed by sputum (72%), nasal swab (63%), fibrobronchoscopic biopsy (46%), pharyngeal swab (32%), feces (29%), and blood (1%). None of the 72 urine samples was positive (41).

Management and treatment

Asymptomatic COVID-19 children should be isolated at home for two weeks to prevent the spread of the virus. Symptomatic children should be screened for red flags, including hypoxia (less than 90% blood oxygen concentration), respiratory fatigue or acute hypercapnia, decreased level of consciousness, and hemodynamic instability (40).

Patients with mild symptoms and no red flag should be isolated at home, and supportive treatments (including fluid and electrolyte replacement, antipyretics, analgesics, oxygenation, and respiratory support) may be administered. Parents should be advised on prevention of the spread to other family members as well as the danger signs in children to return to hospital in case of any signs of danger. Children with a red flag, underlying disease, or with severe pneumonia should be hospitalized (40).

There is no need for routine antibiotic treatment. If there is any clinical or laboratory evidence of a secondary bacterial infection, appropriate antibiotics should be prescribed (23). There is insufficient evidence to suggest that hydroxychloroquine or chloroquine is effective in the treatment of COVID-19. There are however laboratory studies which showed that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 under laboratory conditions, and hydroxychloroquine appears to be stronger (42). The Chinese National Health Commission recommends the use of chloroquine and states that the progression of the disease and the duration of symptoms are reduced (43). Also, the Infectious Diseases Society of America (IDSA) recommends hydroxychloroquine/chloroquine for the treatment of COVID-19 in the field of clinical trials, but states that there is a knowledge gap (44). In a study, the recommended dose of hydroxychloroquine for children was 3-5 mg per kg per day (a maximum dose of 400 mg) to be prescribe twice daily for five days while carefully monitoring for cardiac arrhythmias, including QT prolongation and torsades de pointes (TdP) (40). Another research found that a treatment with hydroxychloroquine was significantly associated with a decrease or disappearance of viral load in COVID-19 patients, and that its effect was enhanced by azithromycin (45). While another study found no evidence of strong antiviral activity or clinical benefits of combining hydroxychloroquine and azithromycin to treat patients with a severe COVID-19 (46). High-dose surfactants, nitric oxide, corticosteroids, and interferon-α2b nebulization should be considered for children with critical illness (36, 47).

Conclusion
The COVID-19 pandemic has made the patient management and disease control more challenging.

Because the disease is so prevalent and there are no specific guidelines for diagnosis and treatment, especially in children, it has created many problems for the health care system. According to the data presented in this review article, this pandemic seems to be less serious for children than for adults. However, children infected with COVID-19 are more asymptomatic and can be the leading cause of disease spread in communities. Precautions should be taken to carefully control the infection and prevent it. This article also summarizes the treatment recommendations.

Conflict of Interest
The authors declare no conflicts of interest.

Financial Support
Not declared.

Authors Contributions
Azarfar A, Ghodsi A and Ghahremani S drafted, reviewed and finalized the manuscript.

References
1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet. 2020;395(10225):689-97.
3. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. bioRxiv. 2020.
4. Organization WH. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Internet] World Health Organization. 2020.
5. Cai J, Xu J, Lin D, Yang z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020.
6. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020;382(13):1199-207.
7. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl j med. 2020;382(18):1708-20.
8. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang Z-J. Novel coronavirus infection in hospitalized infants under 1 year of age in China. Jama. 2020;323(13):1313-4.

9. Surveillances V. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC Weekly. 2020;2(8):113-22.
10. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. Jama. 2020;323(14):1335-.
11. COVID C, Team R. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(12):343-6.
12. Feng Z, Li Q, Zhang Y. Novel Coronavirus Pneumonia Emergency Response Epidemiology, The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41:145-51.
13. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts. MedRxiv. 2020.
14. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatr. 2020.
15. Lu X, Zhang L, Du H, Zhang J, Li Y, Qu J. SARS-CoV-2 Infection in Children. N Engl J Med. 2020;382(17):1663-5.
16. Bialek S, Gierke R, Hughes M, McNamara LA, Pilishvili T, Skoff T. Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6.
17. Golsorkhi M, Ravanshad Y, Azarfar A, Ravanshad S. A Review on New Coronavirus Mechanism of Action. J Pediatr Nephrol. 2020;8(2).
18. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr pulm. 2020;55(5):1169-74.
19. Chen F, Liu Z, Zhang F, Xiong R, Chen Y, Cheng X, et al. Frist case of severe childhood novel coronavirus pneumonia in China. Chinese j pediatr. 2020;58:E005.
20. Zeng L, Tao X, Yuan W, Wang J, Liu X, Liu Z. First case of neonate infected with novel coronavirus pneumonia in China. Chinese j pediatr. 2020;58:E009.
21. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. 2020:hpeds. 2020-0123.
22. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet (London, England). 2020;395(10226):809-15.
23. Chen Z, Fu J, Shu Q, WANG W, CHEN Y, HUA C, et al. Diagnosis and treatment recommendation for pediatric coronavirus disease-19. J Zhejiang Univ Sci. 2020;49(1):0-.
24. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl pediatr. 2020;9(1):51.
25. Farhat AS, Sayedi SJ, Akhlaghi F, Hamedi A, Ghodsi A. Coronavirus (COVID-19) Infection in Newborns. Int J Pediatr. 2020;8(6):11513-7.
26. Society of Pediatrics CMA. Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition). Zhonghua er ke za zhii. 2020;58:E004.
27. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497-506.
28. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med. 2020;1(ahead-of-print).
29. Li W, Cui H, Li K, Fang Y, Li S. Chest computed tomography in children with COVID-19 respiratory infection. Pediatr radiol. 2020;50:796–9.
30. Ma H, Shao J, Wang Y, Zhai A, Zheng N, Li Q. High resolution CT features of novel coronavirus pneu monia in children [J]. Chin J Radiol. 2020;54:1005-201.
31. Ma Y-L, Xia S-Y, Wang M, Zhang S-M, DU W-H, Chen Q. Clinical features of children with SARS-CoV-2 infection: an analysis of 115 cases. Chinese j contemp pediatr. 2020;22(4):290.
32. Wang D, Ju X, Xie F, Lu Y, Li F, Huang H, et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. Zhonghua er ke za zhii. 2020;58(4):E011-E.
33. Feng K, Yun Y, Wang X, Yang G, Zheng Y, Lin C, et al. Analysis of CT features of 15 children with 2019 novel coronavirus infection. Zhonghua er ke za zhii. 2020;58:E007-E.
34. Zhou Y, Yang G-D, Feng K, Huang H, Yun Y-X, Mou X-Y, et al. Clinical features and chest CT findings of coronavirus disease 2019 in infants and young children. Zhongguo Dang dai er ke za zhi. 2020;22(3):215-20.
35. Sun D, Li H, Lu X-X, Xiao H, Ren J, Zhang F-R, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020:1-9.
36. Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. J med virol. 2020;92(6):564-7.
37. Wang L, Shi Y, Xiao T, Fu J, Feng X, Mu D, et al. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (First edition). Annals of translational medicine. 2020;8(3):47.
38. Ping K. Epidemiologic Characteristics of COVID-19 in Guizhou, China. medRxiv. 2020.
39. Yang P, Liu P, Li D, Zhao D. Corona Virus Disease 2019, a growing threat to children? J Infect. 2020;80(6):671-93.

5

40. Karimi A, Tabatabaei SR, Rajabnejad M, Pourmoghaddas Z, Rahimi H, Armin S, et al. An algorithmic approach to diagnosis and treatment of coronavirus disease 2019 (COVID-19) in children: Iranian expert's consensus statement. Arch Pediatr Infect Dis. 2020;8(2):e102400.

41. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. Jama. 2020.

42. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020.

43. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioSci Trends. 2020;advpub.

44. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, et al. Infectious diseases Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis. 2020.

45. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents. 2020:105949.

46. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020;10.

47. Hong H, Wang Y, Chung HT, Chen CJ. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. Pediatrics and neonatology. 2020;61(2):131-2.