




Novel coronavirus infection in children outside of Wuhan, China

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Abstract

Background: Since December 8, 2019, an epidemic of coronavirus disease 2019 (COVID-19) has spread rapidly, but information about children with COVID-19 is limited.

Methods: This retrospective and the single-center study were done at the Public Health Clinic Center of Changsha, Hunan, China. We identified all hospitalized children diagnosed with COVID-19 between January 8, 2019 and February 19, 2020, in Changsha. Epidemiological and clinical data of these children were collected and analyzed. Outcomes were followed until February 26th, 2020.

Results: By February 19, 2020, nine pediatric patients were identified as having 2019-nCoV infection in Changsha. Six children had a family exposure and could provide the exact dates of close contact with someone who was confirmed to have 2019-nCoV infection, among whom the median incubation period was 7.5 days. The initial symptoms of the nine children were mild, including fever (3/9), diarrhea (2/9), cough (1/9), and sore throat (1/9), two had no symptoms. Two of the enrolled patients showed small ground-glass opacity of chest computed tomography scan. As of February 26, six patients had a negative RT-PCR for 2019-nCoV and were discharged. The median time from exposure to a negative RT-PCR was 14 days.

Conclusions: The clinical symptoms of the new coronavirus infection in children were not typical and showed a less aggressive clinical course than teenage and adult patients. Children who have a familial clustering or have a family member with a definite diagnosis should be reported to ensure a timely diagnosis.

KEYWORDS

children, clinical characteristics, coronavirus disease 2019

Qinxue Shen and Wei Guo contributed equally to this work.

1 | INTRODUCTION

Since December 8, 2019, a cluster of acute respiratory illness, now known as coronavirus disease 2019 (COVID-19), occurred in Wuhan, Hubei Province, China.¹ The disease has rapidly spread from Wuhan to other areas. The World Health Organization (WHO) subsequently named this novel coronavirus as 2019 Novel Coronavirus (2019-nCoV). The virus is similar to the coronavirus responsible for the severe acute respiratory syndrome (SARS-CoV), a member of the subgenus Sarbecovirus (Beta-CoV lineage B).² Common clinical manifestations in COVID-19 patients included fever, fatigue, dry cough, nasal congestion, runny nose, and other respiratory symptoms, as well as diarrhea, nausea, vomiting, abdominal pain, and other gastrointestinal symptoms. A few patients have developed severe pneumonia and they may present with acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulation dysfunction or even with death. Previous studies suggested that the infection of 2019-nCoV appeared in clusters was more likely to infect older men with comorbidities, and the earlier stage of the COVID-19 epidemic primarily involved adults older than 15 years.³⁻⁵ Compared with adults, the present 2019-nCoV infection in children is relatively rare, but there is an increasing trend, which requires great attention.

During the period from January 2020 to February 19, 2020, 246 patients were found infected with 2019-nCoV and hospitalized in the Public Health Clinic Center of Changsha, the capital city of Hunan province near from Wuhan, where the first COVID-19 patient was reported on January 21, 2020. Among all hospitalized patients, we identified nine patients under 14 years old. The purpose of this study was to describe the clinical characteristics and outcomes of children with COVID-19 in Changsha. As COVID-19 is still spreading in other areas and continents, we believe this information would be helpful to clinicians and researchers.

2 | METHODS

This retrospective and single-center study were done at the Public Health Clinic Center of Changsha, Hunan, China. We identified all hospitalized children diagnosed with COVID-19 between January 8, 2020 and February 19, 2020, in Changsha. Epidemiological, clinical, laboratory, and radiological characteristics and treatment and outcomes data were obtained with data collection forms from electronic medical records. The data were reviewed by two physicians. The information recorded included demographic information (age, sex, and geographic location), medical history, exposure history, clinical features (signs and symptoms at admission, dates of admission and diagnosis), important laboratory results, chest computed tomographic (CT) scans, treatment (intensive care unit, oxygen therapy, antiviral therapy, antibiotics, corticosteroid therapy), prognosis (any severe complications, including death), time from exposure to reverse transcription polymerase chain reaction (RT-PCR) negative, and discharge date. Efforts were made to reach families of patients to confirm the information.

All patients with COVID-19 were classified as follows⁶: (a) Asymptomatic infection: without any clinical symptoms and signs and the chest imaging is normal, while the RT-PCR is positive. (b) Mild: with symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows the congestion of the pharynx. Some cases may show no fever, or have only digestive symptoms such as nausea, vomiting, abdominal pain, and diarrhea. (c) Moderate: with pneumonia, frequent fever and cough, mostly dry cough, followed by productive cough, some may have wheezing, but no obvious hypoxemia such as dyspnea, and lungs can hear sputum or dry snoring and/or wet snoring. Some cases have no clinical signs or symptoms with lung lesions in CT images, which are subclinical. (d) Severe: Early respiratory symptoms such as fever and cough, may be accompanied by gastrointestinal symptoms such as diarrhea. The disease usually progresses within 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, with other hypoxia manifestations. (e) Critical: Children can quickly progress to ARDS or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life-threatening.

This study was approved by the Medical Ethical Committee of the Second Xiangya Hospital of Central South University (Approved Number KL-2020003), which waived the requirement for patients' informed consent referring to the CIOMS guideline.

3 | RESULTS

Nine infected children were identified between January 30, 2020 and February 26, 2020 (Table 1). Six patients were female. The median age was 8 years old, the youngest was 1-year-old and the oldest was 12 years old. Two children lived in Wuhan for several days before they came to Changsha and the others were infected locally. Six children could provide the exact dates of close contact with someone who was confirmed to have 2019-nCoV infection, among whom the median incubation period was 7.5 days, the shortest incubation period was 1 day and the longest incubation period was 16 days. The median time from onset of symptoms to hospital admission was 3 days (range 0-17 days).

The initial symptoms of illness of the nine children were fever (3/9; the highest temperature of the three febrile patients ranged from 37.5°C to 39.1°C, diarrhea (2/9), mild upper respiratory tract symptoms including cough (1/9) and sore throat (1/9). Two children had no symptoms but were tested positive for 2019-nCoV in a designated screening because of exposure to infected family members.

On admission the number of white blood cells and leukocytes of the children was in the normal range except for an elevation in the 1-year-old child, lactate dehydrogenase of all children was in the normal range, and the aspartate aminotransferase of two children was above the normal range. One child had an elevation of the level of erythrocyte sedimentation rate and two had an elevation of C-reactive protein (CRP) positive. Only two of the enrolled patients

TABLE 1 Characteristics of nine hospitalized children infected with 2019-nCoV outside of Wuhan, China

Characteristic	Patient								
	1	2	3	4	5	6	7	8	9
Demographics									
Age, y	1	2	8	8	8	9	9	11	12
Sex	Female	Female	Male	Female	Male	Female	Female	Female	Male
Exposure history in Wuhan	No	Yes	No	No	No	No	No	Yes	No
Family source of exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time between exposure to symptoms, d	None	None	10	1	9	14	3	6	None
Time between onset symptoms to hospital admission, d	10	2	5	15	0	1	17	3	2
Symptoms at onset	None	Fever	Fever	Fever and Diarrhea	Diarrhea	Sore throat	None	Cough	Fever
Highest temperature, °C	36.8	39.1	37.8	36.7	36.9	36.8	36.5	37.2	37.5
Laboratory results									
White blood cell count $\times 10^9$ (4-10)	16.1	7.88	5.43	4.98	5	5.45	7.06	6.06	8.34
Lymphocyte count $\times 10^9$ (0.8-4)	9.54	4.05	1.15	2.38	1.82	2.19	3.7	2.65	3.81
C-creative protein, mg/L (0-8)	3.58	13.17	2.24	0.2	5.9	1.78	0.2	1.45	0.3
Erythrocyte sedimentation rate, mm/h (0-15)	3.28	27	2	4	23	25	15	40	8
Lactate dehydrogenase, U/L (135-225)	218	230.7	153.2	159.4	152.9	177.1	175	140.9	132.1
Alanine aminotransferase, U/L(0-42)	15.66	18.69	19.69	17.1	15.81	14.48	14.2	13.55	10.5
Aspartate aminotransferase, U/L(0-37)	31.42	40.49	28.5	27.8	23.19	31.36	55.1	22.21	14.8
Chest x-ray and CT findings	Normal	Small ground-glass opacity	Normal	Normal	Normal	Small ground-glass opacity	Normal	Normal	Normal
Treatment									
Oxygen support	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intensive unit care	No	No	No	No	No	No	No	No	No
Mechanical ventilation	No	No	No	No	No	No	No	No	No

(Continues)

TABLE 1 (Continued)

Characteristic	Patient								
	1	2	3	4	5	6	7	8	9
Severe complications	No	No	No	No	No	No	No	No	No
Antiviral therapy	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir	lopinavir/ritonavir
Antibiotic therapy	Azithromycin	Azithromycin	Azithromycin	No	No	No	Azithromycin	No	Azithromycin
Meprednisone	No	Yes	No	No	No	No	No	No	No
Gamma globulin	No	Yes	No	No	No	No	No	No	No
Prognosis									
Time between exposure to RT-PCR negative, d	14	10	20	Positive	9	14	Positive	13	Positive
Time of hospitalization, d	16	12	22	In hospital	11	16	In hospital	15	In hospital

Abbreviation: CT, computed tomography; RT-PCR, reverse transcription polymerase chain reaction.

showed unilateral small unilateral ground-glass opacities of chest CT scans (Figure 1).

Nine patients received oxygen inhalation through a nasal cannula, but none of the nine children required intensive care or mechanical ventilation or had any severe complications. All of them received antiviral therapies (lopinavir/ritonavir tablets or oral liquid, 10/2.5 mg/kg twice daily, orally), four received antibiotics (azithromycin for suspension, 10 mg/kg once daily, orally) and one received meprednisone and immune globulin therapy for febrile convulsion. As of February 26, six patients tested negative for RT-PCR for 2019-nCoV and were discharged.

4 | DISCUSSION

In this retrospective study, we reported nine pediatric patients of 246 patients with laboratory-confirmed 2019-nCoV infection in Changsha. We described and analyzed the clinical characteristics of pediatric patients with COVID-19. Five of them were mild patients, two were moderate COVID-19 patients and two were asymptomatic carriers. More than half children were confirmed to have had a family source of exposure. Fever was the most frequent symptoms at the onset of illness. The pediatric patients showed few abnormalities in routine blood examinations. Most demonstrated normal CT images.

The proportion of infected children identified was very low. A case report (72 314) from the Chinese Center for Disease Control and Prevention found the frequency of positive COVID-19 patients under 19 years was 2% (965 cases).⁷ This may be due to a lower risk of exposure or incomplete identification due to a mild or asymptomatic presentation.^{8,9} Most cases demonstrated familial clustering and the study of COVID-19 in Chinese infants also showed that infants who were be infected by 2019-nCoV had come from families that had at least 1 other infected family member with the infant's infection occurring after the family member's infection.¹⁰ In the SARS studies, a majority of young children and teenage patients had a definite contact history with adult SARS patients (usually an immediate family member), which pattern was consistent with our study.¹¹⁻¹³ Six childhood patients were female, consistent with an infant COVID-19 case report (9),¹⁰ but previous studies in adults found higher percentages of infection in men than women.^{4,5} A retrospective study of 2143 pediatric patients with COVID-19 in China showed at all ages appeared susceptible to COVID-19, and there was no significant gender difference.¹⁴ Whether or not female children and infants may be more susceptible to 2019-nCoV infection than males requires further study.

The symptoms of childhood patients were mild and two of them were asymptomatic carriers. Most children had normal images. Two children showed pneumonia according to their CT scan, but the lesions were limited to small areas of mottling or ground-glass opacities. The most common symptoms at the onset of illness were fever, diarrhea, cough, and sore throat, which was different from the adult presentations. Studies across the country had shown that fever, cough, and fatigue were the most frequent symptoms and fever

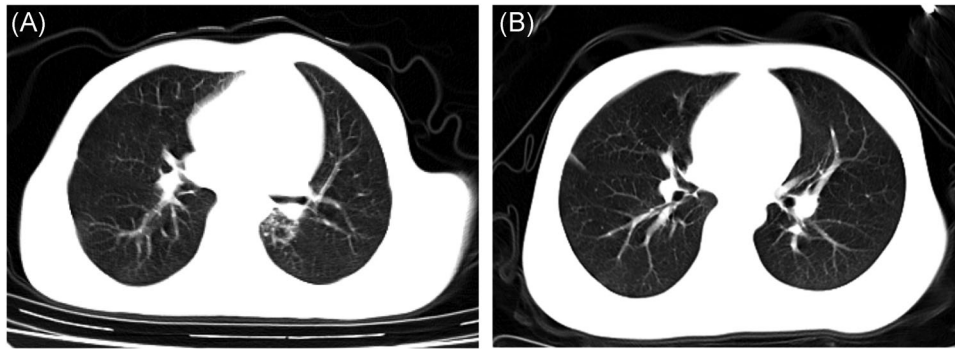


FIGURE 1 Chest computed tomographies (CTs) on a 9-year-old patient Case: (A) CT image showed ground-glass opacity in the left pulmonary lobe of a 9-year-old female with no sign and symptom on the first day of hospitalization, the followed (B) image showed absorption on day 7

affected nearly 90% and cough more than 50%.^{7,15-17} Studies of SARS in newborns and children reported that the clinical course and prognosis differed between pediatric and adult SARS patients. Young children (<12 years) experienced in general a less aggressive clinical course than teenage or adult patients.¹⁸

In 2019-nCoV infected children, most peripheral blood white blood cell counts and an absolute number of lymphocytes were normal, CRP was normal or slightly elevated, and liver enzymes were elevated in some children,¹⁹ which was consistent with our study. In our study, the child with an elevation level of white blood cells and lymphocytes was 1-year-old, however, considering other laboratory results of this patient, other possible infection of these patients was excluded. The immature immune system of the infant may as an interpretation of these abnormal results but still need more studies to prove that. No one required intensive care or mechanical ventilation or had any severe complications and most of them did not need to use meprednisone or immune globulin. But in existing studies of patients with COVID-19. About 20% to 30% of patients infected with 2019-nCoV need intensive care and more than 20% needed glucocorticoid therapy.^{4,5,20}

Most pediatric patients' cases were mild, with much fewer severe and critical cases (5.9%) than adult patients (18.5%).^{14,21} Why the children and infant patients demonstrated minimal symptoms and less severe compared with adults is not clear. This may be related to the fact that the 2019-nCoV has been reported to share the same receptor, angiotensin-converting enzyme 2 (ACE2) with SARS-CoV and that the ACE2 virus receptor expression is concentrate in a small population of type II alveolar cells (AT2). While the 2019-nCoV virus is able to use human ACE2 as a receptor, thus having some potential for replication in human cells,^{22,23} the inadequate expression of ACE2 cells or inadequate expression of ACE2 receptors or the immature function of ACE2 cells could possibly explain the milder symptoms in a child with COVID-19. Another explanation for this difference may be related to the immature immune system of children. Since the immune function of adults is well developed, the highly pathogenic coronavirus could induce a robust immune response, causing a substantial cytokine storm and producing

severe clinical symptoms.²⁴ As the immune function of children is not mature, serious immune damage would plausibly not be stimulated, and the clinical expression would be milder, just as the minimally pathogenic coronavirus infecting the upper respiratory tract and causing mild, cold-like respiratory illness. More research is needed to clarify the age-related changes in the inflammatory responses to these viral agents.

Limitations of this study include the small sample size and the restricted geographic origin of the subjects. A larger, more geographically diverse cohort study population will be needed to characterize more fully the clinical characteristics of childhood COVID-19 patients.

In conclusion, the clinical symptoms of the new coronavirus infection in children are not typical, which deserves a further and large-scale study. Children who have family clustering or have family members with a definite diagnosis should be reported to ensure a timely diagnosis.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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