Clinical Analysis of 25 Novel Coronavirus Infections in Children

Ke Bai, MD, Wenjun Liu, MD,* Chengjun Liu, MD,* Yueqiang Fu, PhD,* Jun Hu, MD,* Yanran Qin, MD,* Qiaoying Zhang, MD,* Hongyan Chen, MD,† Feng Xu, PhD,* and Changda Li, MD‡*

Background: To describe the characteristics of clinical manifestations of children with 2019 novel coronavirus (2019-nCoV) infection in Chongqing.

Methods: All 25 children with laboratory-confirmed 2019-nCoV infection by real-time reverse transcription-PCR (RNA-PCR) were admitted from the 4 designated treatment hospitals of 2019-nCoV in Chongqing from January 19 to March 12, 2020. Clinical data and epidemiological history of these patients were retrospectively collected and analyzed.

Results: The diagnosis was confirmed through RNA-PCR testing. Among the 25 cases, 14 were males and 11 were females. The median age was 11.0 (6.3–14.5) years (range 0.6–17.0 years). All children were related to a family cluster outbreak, and 7 children (28%) with a travel or residence history in Hubei Province. These patients could be categorized into different clinical types, including 8 (32%) asymptomatic, 4 (16%) very mild cases and 13 (52%) common cases. No severe or critical cases were identified. The most common symptoms were cough (13 cases, 52%) and fever (6 cases, 24%). The duration time of clinical symptoms was 13.0 (8.0–25.0) days. In the 25 cases, on admission, 21 cases (84%) had normal white blood cell counts, while only 2 cases (8%) more than 10×10^9/L and 2 cases (8%) less than 4×10^9/L, respectively; 22 cases(88%) had normal CD4+ T lymphocyte counts, while in the remaining 3 cases(8%) this increased mildly; 23 cases had normal CD8+ T lymphocyte counts, while in the remaining 2 cases (8%) CD8+ T lymphocyte counts were mildly increased as well. All Lymphocyte counts were normal. There were no statistical differences of lab results between the groups of asymptomatic cases, mild cases and common cases. There were only 13 cases with abnormal CT imaging, most of which were located in the subpleural area of the bottom of the lung. All patients were treated with interferon, 6 cases combined with Ribavirin, and 12 cases combined with lopinavir or ritonavir. The days from onset to RNA turning negative was 15.20±6.54 days. There was no significant difference of RNA turning negative between the groups of interferon, interferon plus ribavirin and interferon plus lopinavir or ritonavir treatment. All the cases recovered and were discharged from hospital.

Conclusions: The morbidity of 2019-nCoV infection in children is lower than in adults and the clinical manifestations and inflammatory biomarkers in children are nonspecific and milder than that in adults. RNA-PCR test is still the most reliable diagnostic method, especially for asymptomatic patients.

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An outbreak of the 2019 novel coronavirus (2019-nCoV) that began in Wuhan, China, which the World Health Organization declared as a pandemic on March 11, 2020, has swept into at least 114 countries and killed more than 4000 people.[1–4] As of March 12, 2020, a total of 80,793 cases in China and 37,371 cases outside China have been confirmed,[5] with 3169 deaths in China and 1130 deaths outside China. With the development of the pandemic, increasing number of children, even infants and newborns, are being infected by 2019-nCoV. Until now, only a few reports of the infection in children have been made. As far as we know, this is the second largest number of cases with 2019-nCoV infection in children.

METHODS

Patients

For this retrospective study, 25 children were recruited from January 19 to March 12, 2020 at the 4 government-designated hospitals (Chongqing Public Health Medical Center, Chongqing Three Gorges Central Hospital, People's Hospital of Yongchuan District, Qianjiang Central Hospital). All the children in close contact with a confirmed patient were observed for 14 days and tested with 2019-nCoV real-time reverse transcription-PCR (RT-PCR) tests, in which the confirmed cases with RT-PCR positive were all hospitalized in the above 4 hospitals not only for clinical illness warranting medical care, but also for observation.

Data Collection

Epidemiological, demographic, clinical, laboratory, chest computed tomography (CT) scan, management and outcome data were collected through a review of medical records. Clinical outcomes were followed up until March 12, 2020. Laboratory confirmation of 2019-CoV was done in District Center for Disease Control, respectively. All the real-time RT-PCR tests used the same protocol described previously.[6]

Clinical Classification

We classified the cases according to the recommendations on "Recommendation for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition)" and "Diagnosis, treatment and prevention of 2019 novel coronavirus infection in children: expert's consensus statement"[7,8] as follows:

1. Asymptomatic infection: Children tested positive for 2019-nCoV, but without manifestations of clinical symptoms or abnormal chest imaging findings between the time of their RT-PCR positive test.
2. Mild cases: Children with only fever, cough, pharyngeal pain, nasal congestion, fatigue, headache, myalgia or discomfort, etc. and without signs of pneumonia by chest imaging or of sepsis.
3. Common cases: Children with or without fever, respiratory symptoms such as cough; and chest imaging indicating pneumonia, but not reaching the criteria of severe pneumonia.
4. Severe cases: Meeting any of the following criteria: (1) increased respiratory rate: ≥70 times/min (<1 year), ≥50 times/min (≥1 year) (after ruling out the effects of fever and crying); (2) oxygen saturation <92%; (3) hypoxia: assisted breathing (moans, nasal flaring and 3 concave sign), cyanosis, intermittent apnea; (4)

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*Intensive Care Unit, Ministry of Education Key Laboratory of Children Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Pediatrics, Children's Hospital of Chongqing Medical University, China, †People's Hospital of Yongchuan District, China, and ‡Qianjiang Central Hospital, China.

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Address for correspondence: Feng Xu, PhD, or Chenjun Liu, PhD, Intensive Care Unit, Children's Hospital of Chongqing Medical University, No. 136 Zhongshan second road, Yuzhong District, Chongqing, 400014, China. E-mail: xufeng9899@163.com or liucwd@163.com.

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disturbance of consciousness: somnolence, coma, or convulsion; (5) food refusal or feeding difficulty, with signs of dehydration.

5. Critical cases: Those who meet any of the following criteria and require ICU care: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) combined with other organs failure.

The classification was made according to the most severe stages of the disease course.

Treatment

All children were admitted to the designated hospital for isolation and treatment. (1) General treatment: ensuring sufficient calories and water intake; maintaining water-electrolyte balance and homeostasis; monitoring vital signs and oxygen saturation; keeping respiratory tract unobstructed and inhaling oxygen when necessary. (2) Antiviral treatment: there was no confirmed effective antiviral treatment, so interferon, ribavirin and lopinavir/ritonavir (LPV/RTV) were used variously in the 4 government-designated hospitals.

Statistical Analysis

Categorical variables were described as frequency rates and percentages. Continuous variables were described as mean ± SD if normally distributed or as median with interquartile range if not. For comparisons between 3 groups, analysis of variance for normally distributed data or Kruskal-Wallis Test for abnormal distribution data was adopted. A *P*-value of less than.05 was considered significant. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 19.0 software (2010; SPSS Inc., Chicago, IL).

RESULTS

Presenting Characteristics

Twenty-five children that infected with 2019-nCoV at the 4 government-designated hospitals of Chongqing were included. The median age was 11.0 (6.3–14.5) years (range 0.6–17.0 years), and 14 of them were males. All children were related with a family cluster outbreak, including 7 children (28%) with a travel or residence history in Hubei Province. There were 8 asymptomatic cases, 4 mild cases, 13 common cases, and none severe and critical cases. The common symptoms were fever [6 (24%)], cough [13 (52%)], sore throat [3 (12%)], rhinorrhea [3 (12%)], rhinobyon [3 (12%)], diarrhea [1 (4%)] and fatigue [1 (4%)]. Only 1 child had underlying disease (the Down's syndrome with Ventricular Septal Defect, 8 mm, without surgery) (Table 1).

Laboratory Parameters

In the 25 cases, 21 cases (84%) had normal white blood cell counts, while only 2 cases (8%) more than 10×10^9/L and 2 cases (8%) less than 4×10^9/L. The absolute lymphocyte counts were normal in all the children. Most cases had normal IL-6 (10 in 15cases, 66.7%), $CD4^+$ T lymphocyte (23cases, 92%) and the $CD8^+$ T lymphocyte (23cases, 92%), except 5 cases with IL-6, 2 cases with $CD4^+$ and $CD8^+$T lymphocyte increased mildly, respectively. All the children's liver function test, renal function test, procalcitonin, and immunological function test were normal (Table 2).

Comparisons of laboratory results, such as White blood cell counts, Absolute lymphocyte counts, CRP, IL-6, $CD4^+$ T lymphocyte and $CD8^+$ T lymphocyte, between asymptomatic cases, mild cases and common cases presented no significant difference as seen in Table 3.

Chest Computed Tomography scan

All the children had a chest CT scan, with 13 cases being abnormal. Among them, 7 cases had ground-glass opacity, either single or multiple, especially in the lung periphery; 2 cases had patchy consolidation or a strip shape; 4 cases had a blurred bronchovascular bundle (Fig. 1).

Treatment Effect of Different Antiviral Drugs

All the patients were treated with interferon atomization, among these, in 6 cases this was combined with Ribavirin, and in 12 cases combined with LPV/RTV. There was no significant difference of the days from onset to RNA turning negative (RTNT), the days of nucleic acid turning negative after treatment (RTNT0), and the hospital stay days between the groups of interferon, interferon plus ribavirin and interferon plus LPV/RTV (Table 4).

Prognosis and Outcome

The quarantine release standard was described previously.[7] In this study, all the children were cured. The average hospital stay

TABLE 1. Baseline Characteristics

	n	Percentage (%)
Age, median, years	11.0 (6.3, 14.5)	
Sex		
Male	14/25	56
Female	11/25	44
CCP	25/25	100
Signs and symptoms		
Asymptomatic	8/25	32
Fever	6/25	24
Cough	13/25	52
Sore throat	3/25	12
Running nose	3/25	12
Nasal obstruction	3/25	12
Diarrhea	1/25	4
Weakness	1/25	4
Clinical classification		
Asymptomatic	8/25	32
Mild cases	4/25	16
Common cases	13/25	52
Symptom duration (d)	13.0(8.0–25.0)	
RTNT (d)	15.20 ± 6.54	
Hospital stays (d)	15.24 ± 6.55	

The signs and symptoms were recorded all over the course of the disease including before and during hospitalization.

CCP indicates close contact with 2019-CoV patients; DS, duration of symptoms; RTNT, the time from onset to nucleic acid turning negative.

TABLE 2. Laboratory Findings

	n	Percentage (%)
White blood cell count, $\times 10^9$/L		
<4	2	8
4–10	21	84
>10	2	8
Lymphocyte count, $\times 10^9$/L		
Normal	25	100
hsCRP (1–11 mg/L)		
1–11	22	88
>11	3	12
IL-6 (0–5.4 pg/mL)		
Normal	10/15	66.7
Increased	5/15	33.3
CD4+T lymphocyte count (610–1446)		
Normal	22	88
Increased	3	12
CD8+T lymphocyte count (282–749)		
Normal	23	92
Increased	2	8

hsCRP indicates high-sensitivity C-reactive protein.

TABLE 3. Laboratory Data Comparisons According to Illness Severity

	Asymptomatic cases (n = 8)	Mild cases (n = 4)	Common cases (n = 13)	*P*
WBC (×10⁹/L)	6.36 (5.13–8.75)	7.22 (5.67–12.80)	6.08 (4.33–6.79)	0.429
Lymphocyte count (×10⁹/L) (n = 15)	2.37 ± 1.01 (n = 4)	3.90 ± 2.42 (n = 5)	2.73 ± 1.00 (n = 6)	0.174
CRP (mg/L)	0.09 (0.03–1.09)	1.76 (0.42–2.27)	2.10 (0.33–13.18)	0.058
CD4+ T cell count	714.00 (626.50–885.75)	800.50 (639.00–1541.00)	617.00 (428.00–1118.50)	0.600
CD8+ T cell count	601.50 (428.25–908.00)	661.50 (470.00–1261.00)	610.00 (468.50–836.00)	0.837

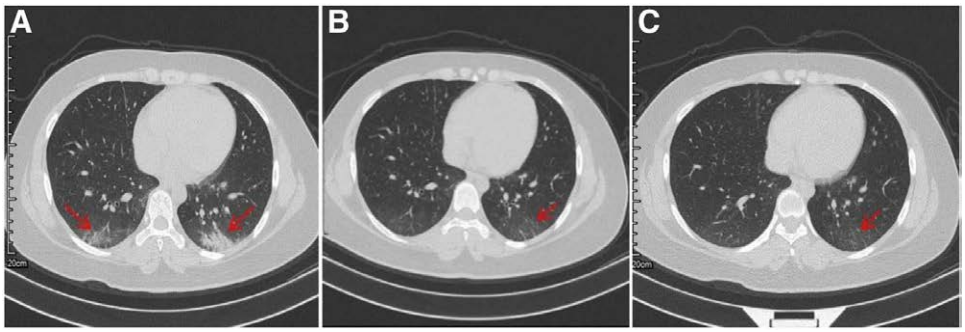

FIGURE 1. Changes in chest CT images of a female 15 years old infected with 2019-nCoV. A: On admission, much patchy ground-glass opacity in the lung periphery. B: Four days after treatment, some ground-glass shadow but significantly less than in (A). C: Seven days after treatment, some ground-glass shadow and nearly the same as in (B).

TABLE 4. Clearance Time of Virus and Hospital Stays of Different Treatment

	A (n = 7)	B (n = 6)	C (n = 12)	*P*
RTNT0 (d)	9.57 ± 4.11	10.83 ± 3.37	13.50 ± 7.19	0.340
RTNT (d)	13.0 (10.0–17.0)	11.0 (9.8–19.0)	17.0 (10.50–22.0)	0.394
Hospital stays (d)	12.86 ± 5.18	15.5 ± 4.85	16.5 ± 7.94	0.522

RTNT indicates the time from onset to nucleic acid turning negative; RTNT0, the time of nucleic acid turning negative after treatment; A, interferon; B, interferon plus ribavirin; C, interferon plus Lopinavir or ritonavir.

was 15.24 ± 6.55 days and the duration days of symptoms in the symptomatic group were 13.0 (8.0–25.0) days.

DISCUSSION

The mortality and morbidity of 2019-nCoV infection we observed in children was lower than that in adults. As of March 12, 2020, there were totally 576 people infected with 2019-nCoV in Chongqing; accordingly, the mortality of 2019-nCoV infection in Chongqing was about 18.4 per million. Relatively, there were 5.66 million children under the age of 15 in 2019; hence, the morbidity in children was about 4.4 per million, accounting for 4.3% of the patients in Chongqing during the same period, and with no deaths. Obviously, the mortality and morbidity of 2019-nCoV infection in children was far lower than that in adults. Only 5 (20%) children were under the age of 5. This is in contrast to influenza where mortality forms a U-shaped pattern, and death rates are higher in young children and the elderly.[9,10] It remains a mystery why the mortality and morbidity are lower in children, especially young children, as compared to adults. It is possible that since there are other coronavirus-induced upper respiratory tract infections every year, and children are susceptible groups, this may provide some immunity to the 2019-nCoV. However, with increasing of age, this immunity may be gradually lost. Alternatively, prior exposure in adults may make adults at higher risk of an enhanced detrimental immune response.

The clinical symptoms of children infected with the novel coronavirus are different from those of adults and nonspecific compared to the common cold. First, according to this data, children with 2019-nCoV infection mainly had cough (52%), fever (24%), runny nose (12%), sore throat (12%), stuffy nose (12%), diarrhea (12%), fatigue (12%) and other symptoms, and the general symptoms lasted about 14 days among the symptomatic group. The incidence of fever is much lower in children group than in adults,[2,3,6] indicating that it is not feasible to screen out 2019-nCoV infections only by measuring temperature alone, especially in children.

The CT manifestations in children are milder than those in adults and the positive rate of CT diagnosis is not high. Most of the CT lesions are located in the subpleural area of the bottom of the lung, which is considered to be a typical imaging feature of 2019-nCoV pneumonia. But, in the early stage of adult 2019-nCoV pneumonia, there are multiple small patch shadows, striping shadows and stromal changes, which are obvious in the lung exoskeleton, and then develop into multiple ground glass shadows and infiltrating shadows in double lungs. In severe cases, lung consolidation and "white lung" may occur. There were only 13 cases of chest CT abnormal, but not seriously and mainly showing patchy ground-glass shadow. Xiong et al[11,12] believed that the severity of lung disease was positively correlated with the 2019-nCoV load detected in the respiratory tract.

There were no statistical differences of lab results between cases with different illness severity, which may indicate lack of specificity of biochemical change in children infected with 2019-nCoV. However, it may also result from our small sample size due to the relatively low morbidity of coronavirus infections in children.

There is no antiviral drug having been proved valid for 2019-nCoV infection. Various clinical effects of antiviral drugs are being evaluated. In this study, it was found that there was no difference in nucleic acid of 2019-nCoV turning negative time between the 3 groups of interferon, interferon plus ribavirin and interferon plus LPV/RTV. However, the number of cases is too small to verify the difference between these 3 groups of treatment in this study and further studies with increased number of cases should be made.

Clustering is an important epidemiological feature of this outbreak, and close family contact is the main mode of 2019-nCoV infection in children.[13,14] All the cases were infected in family cluster mode, with 7 cases having a history of travel or residence in Wuhan.

This study has several limitations. First, the cases number is too small. Second, this study is a retrospective article, and hard to collect and analyze the data. Third, it is hard to call the patients for further information, since we shall concern about patients' privacy and the mental trauma of the family or patients caused by the epidemic.

CONCLUSIONS

The morbidity of 2019-nCoV infection in children is lower than in adults and the clinical manifestations and inflammatory biomarkers in children are nonspecific and are milder than that in adults. Although chest CT scan is helpful for early diagnosis in common cases, RNA-PCR test is still the most reliable diagnostic method, especially for those asymptomatic patients. In our series, children's infection was mainly caused by family exposure so family daily prevention is the main way to prevent 2019-nCoV infection. The reasons why do children have lower morbidity and mild inflammation and symptoms need further studies.

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