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A case series report of hospitalized children with severe acute respiratory syndrome coronavirus-2 infection in Jinan, China

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Abstract

In December 2019, the outbreak of novel severe acute respiratory syndrome coronavirus-2 infection was reported in Wuhan, China. The disease has spread rapidly throughout China and the rest of the world. It not only occurred in adults but also in some children. So, in this report, we aimed to clarify the epidemiological, clinical, laboratory, and radiological characteristics; treatment; and outcomes of children infected with severe acute respiratory syndrome coronavirus-2 in Jinan, China, and found that children with severe acute respiratory syndrome coronavirus-2 infection are non-specific and are milder than adults. Asymptomatic infections were common. Chest computed tomographic scanning is helpful for diagnosis. While myocardial creatine kinase–myocardial band was prone to increase in these cases. The prognosis of most cases was better.

Keywords

Children, severe acute respiratory syndrome coronavirus-2, infection, outside Hubei

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Introduction

A novel coronavirus pneumonia (NCP), occurred in Wuhan, Hubei Province, China, in December 2019.[1,2] The disease has rapidly spread from Wuhan to other areas. Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds and that cause respiratory, enteric, hepatic, and neurologic diseases.[3,4] Six coronavirus species including four viruses: 229E, OC43, NL63, and HKU1 are prevalent and typically cause common cold symptoms in immunocompetent individuals,[5] two strains: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are zoonotic in origin and have been linked to sometimes fatal illness.[6] SARS-CoV[7–9] and MERS-CoV[10,11] have caused more than 10,000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.[12,13] The 2019 novel coronavirus (SARS-CoV-2) is a distinct clade from the betacoronaviruses associated with human SARS and MERS identified by full-genome sequencing and phylogenic analysis.[14] The SARS-CoV-2 has features typical of the coronavirus family and was classified in the betacoronavirus 2b lineage, has close similarity to bat coronaviruses, and has been postulated that bats are the primary source.

Until now, coronavirus diseases 2019 (COVID-19) pandemic spreading almost all countries of the world. But no promising vaccines or drugs are available that could be recommended on a large scale.[15] In adults with SARS-CoV-2 infection, some cases may result in SARS; however, the current trend suggests that children may get infected but are less symptomatic with less fatality.[16] Therefore, it found that a novel syndrome affecting asymptomatic COVID-19 children, presenting as ahyperinflammatory syndrome which is like Kawasaki disease shock syndrome.[17] This report was to describe the epidemiological, clinical, laboratory, and radiological characteristics; treatment; and outcomes of children with SARS-CoV-2 infection hospitalized in Jinan, outside Hubei, China. We hope that it may provide a reference for the accumulation of SARS-CoV-2 infection cases in children.

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Cases

Data collection

Children with SARS-CoV-2 infection were admitted to Jinan Infectious Disease Hospital of Shandong University from 26 January to 20 February 2020 (a total of 47 patients with SARS-CoV-2 infection in Jinan area, including 10 (21.3%) children). We have obtained written informed consent from the legally authorized representative of the minor patient, including patient assent. Jinan Infectious Disease Hospital, located in Jinan, Shandong Province, is one of the major tertiary teaching hospitals and is responsible for the treatments for COVID-19 assigned by the government. All patients with SARS-CoV-2 infection enrolled in this report were diagnosed according to World Health Organization interim guidance.[18] This case series was approved by the institutional ethics board of Qilu Children's Hospital and Jinan Infectious Disease Hospital of Shandong University.

Laboratory confirmation of SARS-CoV-2 was done in two different institutions: the Jinan CDC and the Shandong Province CDC. Throat-swab specimens, obtained from all patients at admission, were maintained in viral-transport medium. SARS-CoV-2 was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR). Epidemiological, clinical, laboratory, radiological characteristics; treatment; and outcomes data were collected, and patients' demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings, chest computed tomographic (CT) scans, and treatment measures were recorded. Other respiratory viruses including influenza A virus (H1N1, H3N2, and H7N9), influenza B virus, respiratory syncytial virus, parainfluenza virus, adenovirus, and Mycoplasma were also examined with real-time RT-PCR. Sputum were obtained at admission for identification of possible causative bacteria. The date of disease onset was defined as the day when the symptom was noticed. We present continuous measurements as mean (mean (M) ± standard deviation (SD)) if they are normally distributed or median (interquartile range (IQR)), if they are not and categorical variables as count (%). For laboratory results, we also assessed whether the measurements were outside the normal range. SPSS (version 16.0) was used for all analyses.

Table 1. Baseline characteristics and clinical characteristics of children with SARS-CoV-2 infection.

Patients (n = 10)	
Baseline	
Age, median (M ± SD) (years)	5.48 ± 4.12
Female	7 (70%)
Male	3 (30%)
Related to people from Wuhan	7 (70%)
No explicit related to people from Wuhan	3 (30%)
Signs and symptoms at admission	
Fever	5 (50%)
Cough	2 (20%)
Expectoration	1 (10%)
Fatigue	1 (10%)
Headache	2 (20%)
Sore throat	1 (10%)
Rhinorrhoea	2 (20%)
Muscle ache	0
Anorexia	0
Dyspnea	0
Chest pain	0
Diarrhoea	0
Nausea and vomiting	0
Dizziness	0
Abdominal pain	0
Comorbidities	0
Myocardial injury	6 (60%)
ARDS	0
Acute renal injury	0
Acute respiratory injury	0
Septic shock	0
Chest CT findings	0
Chest normal	2 (20%)
Bronchitis	3 (30%)
Multiple mottling and ground-glass opacity	5 (50%)
Treatment	
Antiviral treatment	10 (100%)
Antibiotic treatment	3 (30%)
Nutrition myocardial	3 (30%)
Glucocorticoids	0
Intravenous immunoglobulin therapy	0
Mechanical ventilation	0

ARDS: acute respiratory distress syndrome; CT: computed tomography; SARS-CoV-2 = 2019 novel coronavirus.
Data are n (%), n/N (%), and mean (SD).

Characteristics of SARS-CoV-2-infected children

A total of 10 children infected with SARS-CoV-2 were included, two of them were identical twins. In total, 10 (100%) patients were family cluster infection, his or her father or mother was diagnosed with COVID-19, that is, seven (70%) related to father or mother had a history of exposure to Wuhan or contacted with people of Wuhan and three (30%) had no explicit related to people from Wuhan, but two patients' father had travelled to multiple places and one of patients' mother is a supermarket assistant. The mean age of patients was (5.48 ± 4.12) years, the smallest was 11 months, the oldest was 14 years, including 7 (70%) females and 3 (30%) males (Table 1).

On admission, five (50%) patients had fever, two (20%) had cough, one (10%) had expectoration, one (10%) had fatigue, two had headache, one (10%) had sore throat, and two (20%) had rhinorrhea, but had no other symptoms including muscle ache, anorexia, dyspnea, chest pain, diarrhoea, nausea and vomiting, dizziness, abdominal pain, and

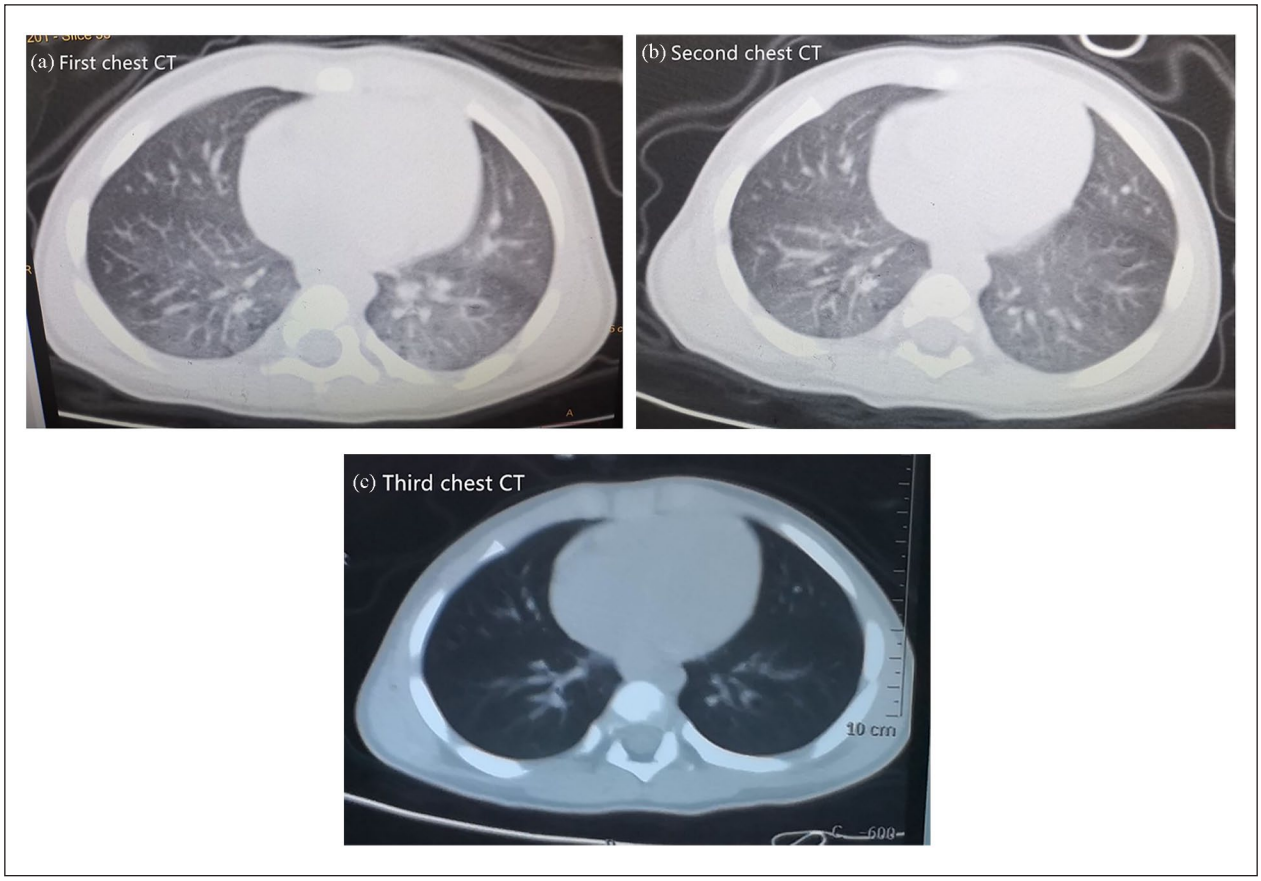

Figure 1. (a) Chest computed tomographic images obtained on 7 February 2020 show ground-glass opacity in both lungs on admission day, (b) images taken on 13 February 2020 show the partly absorption of bilateral ground-glass opacity after the treatment, and (c) images taken on 20 February 2020 show the completely absorption of bilateral ground-glass opacity after the treatment.

rash in skin. Six (60%) myocardial creatine kinase–myocardial band (MB) was elevated, but no patients had other comorbidities include acute respiratory distress syndrome (ARDS), acute renal injury, acute respiratory injury, and septic shock. According to chest CT, 2 (20%) patients showed chest normal, 3 (30%) patients showed bronchitis, and 5 (50%) patients showed multiple mottling and ground-glass opacity (Table 1, Figure 1).

On admission, white blood cell counts of 10 patients were (6.35 ± 2.78) × 10^9/L, below the normal range in 1 (10%) patient and above the normal range in 1 (10%) patient. Neutrophils were (1.85 ± 0.60) × 10^9/L, 4 (40%) patients had neutrophils below the normal range. Lymphocytes were (4.03 ± 2.26) × 10^9/L, below the normal range in 5 (50%) patients and above the normal range in 1 (10%) patient. Monocytes were (0.35 ± 0.12) × 10^9/L. Platelets were (244.20 ± 89.69) × 10^9/L, below the normal range in 1 (10%) patient. Haemoglobin was (125.90 ± 7.85) g/L, below the normal range in 2 (20%) patients. Prothrombin time was (12.10 ± 0.62) s. Activated partial thromboplastin time (33.30 ± 5.30) s, below the normal range in 1 (10%) patient. D-dimer was (0.30 ± 0.21) μg/mL. Most patients had abnormal myocardial zymogram, which showed the elevation of creatine kinase–MB in 6 (60%) patients, the elevation of creatine kinase in 2 (20%) patients, and the elevation of lactate dehydrogenase in 8 (80%) patients. Alanine aminotransferase was (15.70 ± 4.32) U/L. Aspartate aminotransferase was (31.20 ± 7.04) U/L, above the normal range in 1 (10%) patient. Blood urea nitrogen, creatinine, and glucose were in normal range. Regarding the infection index, procalcitonin was above the normal range in 2 (20%) patients, C-reactive protein above the normal range in 2 (20%) patients, Interleukin-6 above the normal in 3 (30%) patients. Erythrocyte sedimentation rate and serum ferritin were in normal range (Table 2). *Mycoplasma* positive were found in 3 (30%) patients, but did not find other respiratory viruses in any of the patients. *Staphylococcus aureus* was cultured in 1 (10%) patient's sputum (Table 2). Cellular and humoral immunity were found in normal among all patients (Table 2).

Treatment and outcomes

In treatment, all patients were treated in isolation. In total, 10 (100%) patients received antiviral treatment, including alfa-interferon (20–30 μg every 12 h, atomized inhalation, 10 patients), oseltamivir (45 mg every 12 h, orally, one patient),

Table 2. Laboratory findings of children infected with SARS-CoV-2 on admission to hospital.

Patients (n = 10)	Normal range	
Blood routine		
White blood cell count ($\times 10^9$/L)	3.5–9.5	6.35 ± 2.78
Increased		1 (10%)
Decreased		1 (10%)
Neutrophils count ($\times 10^9$/L)	1.8–6.3	1.85 ± 0.60
Increased		0
Decreased		4 (40%)
Lymphocytes count ($\times 10^9$/L)	1.1–3.2	4.03 ± 2.26
Increased		1 (10%)
Decreased		5 (50%)
Monocytes count ($\times 10^9$/L)	0.1–0.6	0.35 ± 0.12
Increased		0
Decreased		0
Platelets count ($\times 10^9$/L)	125–350	244.20 ± 89.69
Increased		0
Decreased		1 (10%)
Haemoglobin (g/L)	120.0–140.0	125.90 ± 7.85
Decreased		2 (20%)
Coagulation function		
Prothrombin time (s)	8.8–13.8	12.10 ± 0.62
Increased		0
Decreased		0
Activated partial thromboplastin time (s)	26–42	33.30 ± 5.30
Increased		0
Decreased		1 (10%)
D-dimer (μg/mL)	0–0.5	0.30 ± 0.21
Increased		0
Blood biochemistry		
Creatine kinase (U/L)	26–140	
Increased		2 (20%)
Decreased		0
Creatine kinase–MB (U/L)	7–25	35.40 ± 17.45
Increased		6 (60%)
Lactate dehydrogenase (U/L)	109–245	317.00 ± 88.57
Increased		8 (80%)
Myoglobin (μg/L)	10–46	11.60 ± 4.65
Increased		0
Alanine aminotransferase (U/L)	0–40	15.70 ± 4.32
Increased		0
Aspartate aminotransferase (U/L)	0–40	31.20 ± 7.04
Increased		1 (10%)
Blood urea nitrogen (mmol/L)	2.9–8.2	4.51 ± 1.40
Increased		0
Creatinine (μmol/L)	50.4–98.1	44.94 ± 5.62
Increased		0
Glucose (mmol/L)	3.2–6.0	5.04 ± 0.39
Increased		0
Decreased		0
Infection-related biomarkers		
Procalcitonin (ng/mL)	0.00–0.05	0.05 ± 0.02
Increased		2 (20%)
C-reactive protein (mg/L)	0.068–8.2	2.30 ± 4.25
Increased		2 (20%)
Interleukin-6 (pg/mL)	<1.50	3.32 ± 5.90
Increased		3 (30%)
Erythrocyte sedimentation rate (mm/h)	0.00–15.0	4.60 ± 2.63
Increased		0
Serum ferritin	13–400	55.16 ± 16.33
Increased		0
Co-infection		
Other viruses		0
Mycoplasma		3
Bacteria		1 (10%)
Immune biomarkers		
Total T lymphocytes percentage (T%)	56–86	70.66 ± 4.74
Increased		0
Decreased		0
Helper/induction T lymphocyte percentage (CD4 + T%)	33–58	39.95 ± 9.18
Increased		0
Decreased		0
Inhibition/cytotoxic T lymphocyte percentage (CD8 + T%)	13–39	26.86 ± 4.97
Increased		0
Decreased		0
Helper/inhibitory T lymphocyte ratio (CD4 + T/CD8 + T)	0.71–2.78	1.58 ± 0.62
Increased		0
Decreased		0
Immunoglobulin G (g/L)	2.32–14.11	9.05 ± 3.08
Decreased		0
Immunoglobulin A (g/L)	0–0.83	0.94 ± 0.57
Decreased		0
Immunoglobulin M (g/L)	0–1.454	1.19 ± 0.30
Decreased		0

Data are n (%), n/N (%), and mean (SD). Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range. SARS-CoV-2 is a 2019 novel coronavirus.

ribavirin (0.12 g every 24 h, intravenously, two patients), and lopinavir tablets (500 mg twice daily, orally, one patient). The duration of antiviral treatment was 5–14 days (Table 1). Three patients were given antibiotic treatment (Table 2); 2 (20%) patients were treated with a single antibiotic and 1 (10%) patient was given combination therapy. The antibiotics used generally covered common pathogens and some atypical pathogens; the antibiotics used were cephalosporins and/or azithromycin against *Staphylococcus aureus* and *Mycoplasma*. The duration of antibiotic treatment was 3–12 days. Three (30%) patients were treated with fructose sodium diphosphate (0.2–0.5 g every 8 h, orally). No patients were treated with glucocorticoids and immunoglobulin. No

patients used non-invasive or invasive ventilator mechanical ventilation to assist breathing (Table 1). Under treatment, all cases had gradually recovered and till been discharged.

Discussion

This descriptive report on the epidemiology and clinical characteristics of children with SARS-CoV-2 infection in Jinan presents the latest partial status of children with SARS-CoV-2 infection outside Hubei, China. All children were related with a family cluster outbreak. Most related to their father or mother had a history of exposure to Wuhan or contacted with people of Wuhan. Minority had no explicit related to Wuhan or people from Wuhan, but two patients' father had travelled to multiple places, one patient's mother is a supermarket assistant, and they have the chance of getting infected. The most common symptoms were fever; second, were cough, headache, and rhinorrhea; the third symptoms including expectoration, fatigue, and sore throat. However, some infected children had no symptoms but must be taken seriously because they can infect others.

In all cases, the white blood counts of most cases were normal. Neutropenia and lymphopenia were found in some cases. Platelets counts and Haemoglobin decreased in one or two patients. Activated partial thromboplastin time decreased only in one patient. However, the elevation of creatine kinase–MB were found in 60% patients, it showed that SARS-CoV-2 is liable to cause myocardial creatine kinase–MB to increase. The infection index of procalcitonin, C-reactive protein, and interleukin-6 slightly elevated in two or three cases. The respiratory co-infection pathogens, *Mycoplasma* positive in three patients. *Staphylococcus aureus* was cultured in one patient' sputum. But in all patients, the cellular and humoral immunity were found in normal. In chest CT, 30% cases showed bronchitis and 50% cases showed multiple mottling and ground-glass opacity. According to clinical manifestations, all patients could be categorized into different clinical types, including 50% common cases, 30% mild cases, and 20% asymptomatic cases. The most common impairment of organ function is myocardial, but no severe or critical cases were identified. All patients received antiviral treatment, including ten patients were treated with alfa-interferon, one patient with oseltamivir, two patients with ribavirin, and one patient with lopinavir tablets. Three patients were given antibiotic treatment. Three patients were treated with fructose sodium diphosphate to nourish myocardium. After treatment, all children gradually recovered and discharged. The median hospital stay was 10 days (IQR = 7.0–14.0).

The SARS-CoV-2 infection was clustering onset, is more likely to affect older males with comorbidities, and can results in severe and even fatal respiratory diseases such as respiratory distress syndrome. The symptoms of adult cases with SARS-CoV-2 infection were obvious in 1–2 weeks, and the elimination time of virus could last for 3–4 weeks or longer. Compared with adults, the symptoms of children with SARS-CoV-2 infection were significantly lighter, recovery was faster, elimination time of virus was shorter, and prognosis was better. In a relatively short period, some scientists have successively confirmed that the presence of angiotensin-converting enzyme 2 (ACE2) proteins was necessary for the entry of SARS-CoV-2 into cells.[19,20] SARS-CoV-2 seems to have evolved into a kind of virus that can hijack II alveolar epithelial cells, so to facilitate the proliferation and spread of virus[21] or the intracellular response induced by ACE2 in alveolar epithelial cells in children is lower than that in adults, which is also a topic worthy of discussion. The virus can interfere with the renin–angiotensin–aldosterone system (RAAS) and affects podocytes and tubular epithelial cells, resulting in kidney injury. Renal involvement in children with COVID-19 is rare compared to adults.[22] However, COVID-19 seems to affect childhood and adolescence scarcely. However, allergic and immunodeficient children and adolescents need adequate care in this period.[23] The white blood cell counts and the absolute number of lymphocytes were mostly normal in most children with SARS-CoV-2 infection, and the depletion of lymphocytes did not occur, which may be related to the imperfect natural immune development, may lead to the low level of subsequent adaptive immune response, and may be one of reasons to explain the mild clinical characteristics in children. But its specific mechanism need further research. While this report has several limitations: First, only 10 children infected with SARS-CoV-2 confirmed were included. Second, there are only common and mild cases in this report, no severe cases, which is not representative of children with SARS-CoV-2 infection. However, the data in this report permit an early assessment of the epidemiological and clinical characteristics of children with SARS-CoV-2 infection outside Wuhan, China.

Conclusion

The clinical manifestations in children with SARS-CoV-2 infection are non-specific and are milder than that in adults. Asymptomatic infections were not uncommon. Chest CT scanning is helpful for diagnosis and treatment. While myocardial creatine kinase–MB was prone to increase in these case series. Outside Hubei, children's infection is mainly caused by family cluster outbreak and most cases related to Wuhan, but some cases are not clearly related to Wuhan. So, family daily prevention is the main way to prevent SARS-CoV-2 infection in children.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

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Informed consent

The authors confirm that in the Author Declaration Form, we have obtained written informed consent from all legally authorized representatives prior to study initiation. The written informed consent from legally authorized representatives of the subject in the Author Declaration Form, which as in the main document, we confirm that this information is consistent everywhere in this article.

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