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FULL LENGTH ARTICLE

The clinical and immunological features of pediatric COVID-19 patients in China

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Abstract In December 2019, the corona virus disease 2019 (COVID-19) caused by novel coronavirus (SARS-CoV-2) emerged in Wuhan, China and rapidly spread worldwide. Few information on clinical features and immunological profile of COVID-19 in paediatrics. The clinical features and treatment outcomes of twelve paediatric patients confirmed as COVID-19 were analyzed. The immunological features of children patients was investigated and compared with twenty adult patients. The median age was 14.5-years (range from 0.64 to 17), and six of the patients were male. The average incubation period was 8 days. Clinically, cough (9/12, 75%) and fever (7/12, 58.3%) were the most common symptoms. Four patients (33.3%) had diarrhea during the disease. As to the immune profile, children had higher amount of total T cell, CD8+ T cell and B cell but lower CRP levels than adults ($P < 0.05$). Ground-glass opacity (GGO) and local patchy shadowing were the typical radiological findings on chest CT scan. All patients received antiviral and symptomatic treatment and the symptom relieved in 3—4 days after admitted to hospital. The paediatric patients showed mild symptom but with longer incubation period. Children infected with SARS-CoV-2 had different immune profile with higher T cell amount and low inflammatory factors level, which might ascribed to the mild clinical symptom. We advise that nucleic acid test or examination of serum IgM/IgG antibodies against SARS-CoV-2 should be taken for children with exposure history regardless of clinical symptom.

Introduction

In December 2019, a novel coronavirus, labeled as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO), has been identified as the causative agent of the Corona Virus Disease 2019 (COVID-19) outbreak in Wuhan, China.[1] This disease rapidly spread to China as well as overseas that WHO declared the pandemic of COVID-19 on 11 March,2020.[2,3] By 17 March 2020, in total of 184976 confirmed cases from 159 countries and areas were reported globally, including 7529 deaths.[4] Although there is still unclear about the early transmission at the initial of SARS-CoV-2 infection, accumulating information verified that this virus can transmitted between human and many subclinical cases exits after intimate contact.[5—8]

Adults infected with SARS-CoV-2 usually present as fever, cough, dyspnea and pneumonia. Elder people with underlying disease or immunocompromised are prone to develop severe situation such as acute respiratory distress syndrome.[9—11] One recent studies that have reported clinical characteristics of 1099 patients with laboratory confirmed COVID-19 and found that 0.9% of patients were aged below 15-year-old, suggesting the incidence of COVID-19 in children is much lower than adults.[12] However, the clinical features of child and adolescents was not reported. The objective of this study was to describe the clinical features of twelve children diagnosed as COVID-19 in Chongqing area. Through this study, we sought to delineate the epidemiology and clinical characteristics of 2019-nCoV infection in children.

Methods and materials

Data collection

A total of twelve patients under 18-year-old whom confirmed as COVID-19 from 28th January, 2020 to 11th February, 2020 were recruited in our study from three hospitals: YongChuan hospital of ChongQing medical university, Chongqing Three Gorges Central Hospital and The Public Health Center, Chongqing. The COVID-19 was diagnosed based on the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (5thedition, National Health Committee) and experts' consensus statement of Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children.[13,14] Epidemiological, clinical, laboratory, and radiological characteristics and treatment data were obtained from electronic medical records. To analyze the immune profile, we collected the laboratory exam of twenty adults at the same time. All data were reviewed by a trained team of physicians before processed to further analysis. This study was approved by Ethics Commission of Chongqing Medical University (KY-2020-01.01). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Laboratory confirmation

Sputum and throat swab specimens collected from patients. RT-PCR targeted the open reading frame1ab and nucleocapsid protein gene of SARS-CoV-2 were performed twice in every 24 h. Patients with consecutive positive nucleic acid tests were confirmed as SARS-CoV-2 infection.

Statistical analysis

Continuous variables were described as means and standard deviations, Categorical variables were expressed as counts or percentage. Continuous variables were compared using independent group *t*-tests or Mann—Whitney test. Statistics significance was accepted at $P \leq 0.05$.

Results

Demographic characteristics

As for Feb 11, 2020, the cumulative number of confirmed cases infected with SARS-CoV-2 in Chongqing city has reached 505, with 12(2.3%) children and adolescents.[15] This study population included these twelve hospitalized peadiatric patients with confirmed COVID-19. The mean age was 14.5 years range from 7 month to 17 years, and six of the patients were male. According to the exposure history, three patients were local residents of Wuhan, one patient had travelled to Wuhan within fourteen days, eight patients contacted with confirmed COVID-19 case. The majority of patients presented as clustered disease. The average incubation period from exposure to onset was eight days range from one day to thirteen days. On admission, ten patients were categorized as mild pneumonia while the other two cases were asymptomatic infection.

Clinical manifestation

The median time from exposure to onset of fever was 8 days and cough was 10 days (Fig. 1). Cough (9/12, 75%) and fever (7/12, 58.3%)were the most common symptoms when patients admitted to hospital. Most patients had mild fever with the peak temperature less than 39 celsius degree.The fever in six patients typically resolve within one week, expect for one case whose fever lasted thirteen days. Seven patients presented with dry cough and the remaining two patients reported productive cough without symptoms of short of breath or dyspnea. In our observation, four patients had diarrhea during the disease. The median time from exposure to onset of diarrhea was eleven days (Fig. 1). For one patient, diarrhea was one of the initial symptoms of infection accompanied with low fever and mild cough, the other three patients developed diarrhea three to four days post hospitalization. Other symptoms observed during the course of disease including upper airway symptom such as nasal and sore throat (2/12), dizziness (2/12) and fatigue (1/12) (Table 1).

The youngest patient was a 7-month-old baby with chief complain of cough for two days. This baby contacted with her aunt who came back from Wuhan thirteen days ago and subsequently, her mother was confirmed as COVID-19 four days ago. The baby had low-grade fever (peak temperature 37.8 °C) and mild cough.The computed tomography (CT) showed bilateral patchy shadowing. The respiratory pathogen test including influenza virus, respiratory syncytial virus, adenovirus, and mycoplasma was negative. The baby was finally confirmed as COVID-19 by RT-PCR detection of virus RNA.

Table 1 Clinical characteristics of twelve paediatric patients infected with SARS-CoV-2.

	Overall, Mean (±SD)
Age, median (25th-75th percentile), y	14.50 (9.25—15.75)
Gender (%)	
Male	6 (50)
Female	6 (50)
Exposure History (%)	
Contact with confirmed case	8(67.7)
Local residents of Wuhan	3 (25)
Travelled to Wuhan	1(8.3)
Fever	7 (58.3)
Febrile days	5.29 ± 4.300
Maximum temperature, °C	38.27 ± 0.411
Cough, No. (%)	9 (75)
Diarrhea, No. (%)	4(33.3)
Upper airway symptom, No. (%)	2(16.7)
Dizziness, No. (%)	2(16.7)
Fatigue, No. (%)	1(8.3)
Hemoglobin, g/L (normal range 120—160)	130.30 ± 13.84
Platelets, × 10^9/L (normal range 125—350)	278.60 ± 133.340
WBC cells, × 10^9/L (normal range 3.5—9.5)	6.33 ± 1.78
ALT, U/L (normal range 7—40)	28.8±16.5
AST, U/L (normal range 14—36)	23.8±7.77
CK-MB,U/L (normal range 0—25)	14.7±8.13
sCr, umol/L (normal range 62—106)	54.5±18.72
BUN,mmol/L (normal range 2.5—6.1)	3.44±0.83
PT, s (normal range 8—14)	13.5±2.15

Abbreviations: WBC: white blood cell; ALT:Alanine aminotransferase; AST: Aspartate aminotransferase; CK-MB: creatine kinase isoenzymes,sCr:Serum creatinine.BUN: bloodUrea nitrogen,PT: prothrombin time.

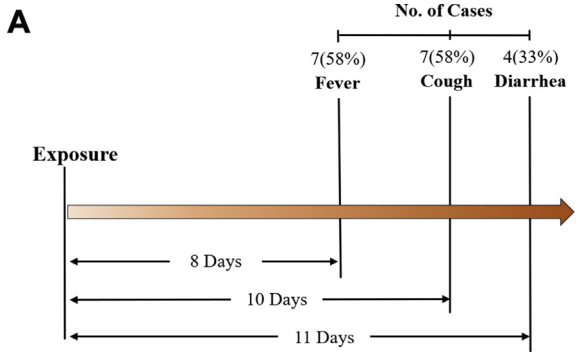

Figure 1 Timeline of from exposure to onset of symptom in SARS-CoV-2-infected paediatric patients.

Laboratory findings and radiology results

For the laboratory findings, most patients (11/12) had normal white blood cell and two patients had lymphopenia. The dynamic changes of clinical laboratory parameters, including white blood cells (WBC), lymphocytes count and platelet, were available for three patients. The data of WBC, lymphocytes and platelet count were tracked from day 2 to day 14 after the onset of the disease, and all three patients showed normal WBC, lymphocytes and platelet

count during the course of disease (Fig. 2A—C). In addition, all patients showed normal biochemical test including liver and renal function test, cardiac enzymes test, coagulation function (Table 1).

Since paediatrics presented mild symptom and less organ disorders according to laboratory exam. We then investigated the immune profile between paediatrics and adults. We compared the amount of T lymphocyte and its subgroups, level of antibodies, serum compliment as well as inflammatory markers in two groups. As a consequence, children had higher total T cell, CD8+ T cell and B cell amount than adults ($P < 0.05$). By contrast, adults showed higher CRP level ($P < 0.05$).We also observed the increasing of IL-6 in adults, but no statistics significance between two groups. There were no difference of antibodies and serum compliment in two groups (Table 2).

All patients underwent CT scan once suspected or confirmed COVID-19. The CT scan results of ten patients are considered abnormal. Similar to adults, ground-glass opacity (GGO) and local patchy shadowing were the most common changes of chest CT scan (Fig. 3A—B). One patient presented as tiny shadow of fibrotic streaks in the right lung, which was considered irrelevant image to COVID-19. Two patients with positive virus RNA detected by RT-PCR had normal chest CT.

Treatment and outcome

All patients applied interferon-α 1b inhalation therapy, 8 of 12 patients received Lopinavir/Ritonavir, and 2 patients received Ribavirin treatment. Patient showed good tolerance to these treatment and no adverse effect observed. No patients received glucocorticoid or antibiotics during treatment. All patients relieved the symptom 3—4 days after admitted to hospital. No case progressed to severe state.

Discussion

As for Feb 11, 2020, the cumulative number of confirmed cases infected with SARS-CoV-2 in Chongqing city has reached 505, with 12(2.3%) paediatric patients. In this study, we retrospective analyzed the clinical features of twelve paediatric patients infected with SARS-CoV-2 from 7-month to 17-years-old. The majority of patients presented as cluster disease. In paediatric patients, there are several different features compared with adult patients. Firstly, this study revealed that the average incubation period of paediatric patients was eight days, which is longer than adults. One recent study reported that the

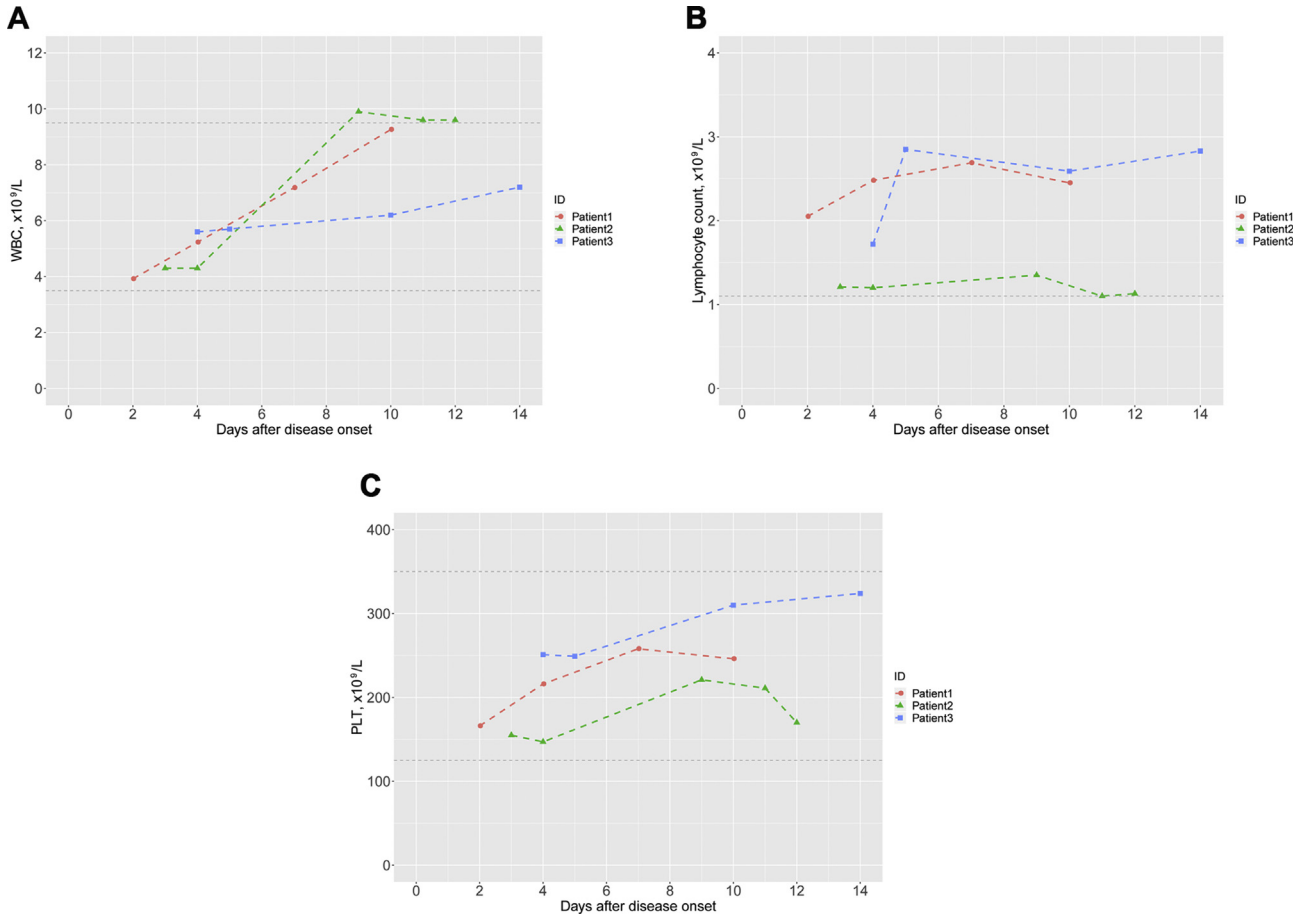

Figure 2 The dynamic changes of clinical laboratory parameters, including WBC **(A)**, lymphocytes **(B)** and platelet count **(C)**, in 3 paediatric patients infected with SARS-CoV-2 based on days after disease onset.

Table 2 The level of T cell and its subgroups, antibodies, compliment 3, and inflammatory markers in paediatrics and adults groups.

	Paediatrics (n = 12)	Adults (n = 20)	p-value
Total T cells (x10^9/L)	2.13 ± 0.72	1.06 ± 0.53	<0.0001[a]
CD4+ T cells (cells/ul)	598.10 ± 215.10	425.50 ± 278.10	0.0596
CD8+ T cells (cells/ul)	442.50 ± 117.50	246.80 ± 144.10	0.0068[a]
Total B cells (x10^6/L)	194.70 ± 75.42	120.9 ± 57.89	0.0284[a]
NK cells(x10^6/L)	208.2±117.4	191.2±87.91	1
IgM(g/L)	1.22±0.39	1.03±0.41	0.2515
IgG(g/L)	10.86±1.44	11.85±4.51	0.9805
C3(g/L)	1.37 ± 0.10	1.35±0.22	0.9416
IL-6 (ng/ml)	8.44 ± 2.65	20.51 ± 5.19	0.0842
CRP (mg/L)	11.51 ± 2.39	23.34 ± 2.84	0.0251[a]
PCT(ng/ml)	0.18 ± 0.066	0.11 ± 0.025	0.3136

[a] Statistics significance.

median incubation period of COVID-19 was three days.[12] Secondly, similar to adults, fever and cough were the dominant symptoms for paediatrics but less severe. In addition, four patients experienced diarrhea during the disease course while diarrhea is rare in adults. In Zhong's study, the incidence of diarrhea was 3.7%, while another study which recruited 138 cases discovered around 10% patients had diarrhea.[11,12] In our observation, diarrhea was the initial onset of one patient and the other three patients developed diarrhea after hospitalization. All four patients received lopinavir/tonavir treatment. It was unclear whether diarrhea associated with drug adverse reaction of lopinavir/tonavir.Thirdly, lymphopenia was not frequently observed in paediatric patients. Only two patients had lymphopenia in our study. However, Zhong et al reported lymphopenia was observed in 82.1% (731/890) of patients. Moreover, Wang et al reported the dynamic changes of lymphocyte count in thirty-three patients including twenty-eight survivors and five nonsurvivors.[11] They reported most patients had marked lymphopenia and non-survivors showed severe lymphopenia over time, which suggested the amount of lymphocyte might related to the severity and poor prognosis of COVID-19.

All the twelve paediatric patients infected with SARS-CoV-2 presented with mild symptoms and no one received ICU care. All patients relieved the symptom three to four days after admitted to hospital. However, 15.73% (173/1099) patients were categorized into severe subgroups based on the recently study. This difference may be due to the immune response to SARS-CoV-2 between children and

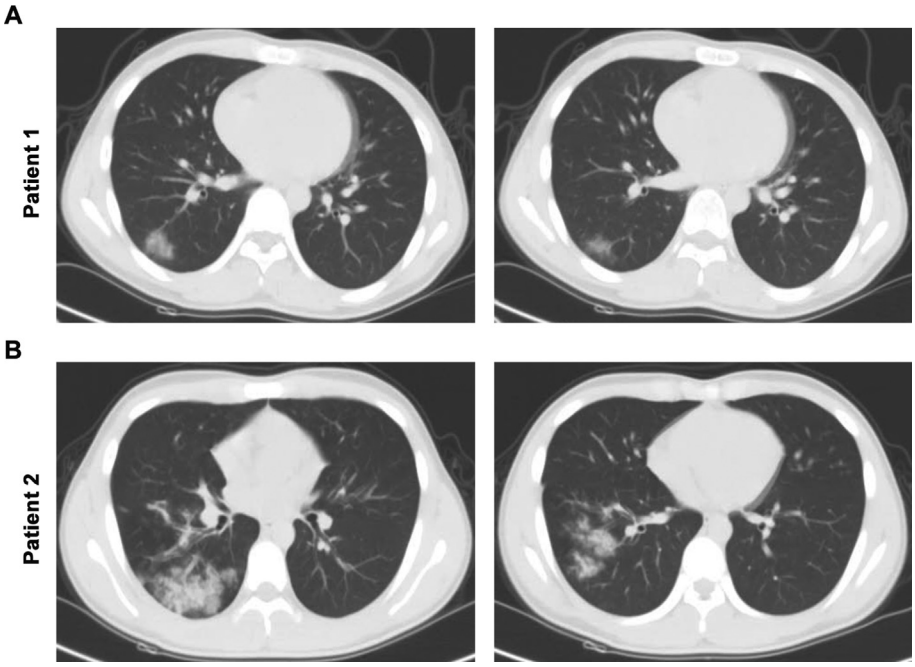

Figure 3 Chest CT images of two patients. **(A)** Patient 1 was a 16 year-old male patient with fever. CT test showed ground-glass opacity in the right lung. **(B)** Patient 2 was a 14 year-old male with fever and cough. CT scan showed ground-glass opacity and local patchy shadowing in the right lung.

adult. Therefore, we compared the immune profiles between paediatrics and adults. Children showed higher level of T cell and its subgroup cells (CD8+ T cells and B cells), but lower IL-6 and CRP level after infection. T lymphocytes exert antivirus function and balance immune response. In SARS-CoV infection, CD8+ T cells were the main inflammatory cells infiltrated into the pulmonary and played a vital role in virus clearance. However, it could also induce immune injury by inflammation cytokines.[16,17] In another study about SARS-CoV, depletion of CD4+ T cells led to reduced capability of lymphocytes recruitment and cytokine production, which resulted in immune mediated delayed clearance of SARS-CoV.[18] SARS-Cov-2 shares high similarity in genome and protein structure with SARS-CoV, the immune response of these two disease might be similar to some extent. IL-6 a key cytokine contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions. It can be promptly and transiently produced in response to infections and involved in the production of acute phase proteins including CRP, proliferation of B-lymphocytes and neutrophils.[19] The serum IL-6 level usually increase during infection and dramatically elevation of serum IL-6 often associated with severe infection.[20,21] Antonio and his colleagues have reported that children with H1N1infection induces an early and significant upregulation of IL-6 expressions. Importantly, IL-6 was significantly correlated with specific clinical findings, such as severity of respiratory compromise and fever.[22] In our study, only two paediatric patients (16%) showed elevated IL-6 level with less than 5 fold increases. The average level of IL-6 in paediatrics was lower than adults, which may be partially responsible for the less severe symptoms in paediatric patients. Additionally, as children usually belong to the second or third-generation infection, the virulence of virus may be decreased when children infected. Interestingly, we didn't tracked further infection transmitted by these patients. This might be due to the immune situation and low viral load for children. Whether children were less capability in disease spreading and the underlying mechanism needs more investigation.

This study have several limitations. First, the small sample size of this study due to low incidence of COVID-19 in children. In this study, we enrolled twelve cases for analysis, which might cause the incomplete understanding the clinical features of this group. Multi-center study recruiting more patients with different age group is required in future. Secondly, since all the clinical data were collected retrospectively, the information, particular the laboratory information, was incompletely in some individuals. Finally, most patients were still hospitalized at the time of manuscript submission. This may affect the judgement of the final outcome and continued observations is needed. Taking together, this study described the clinical features of paediatric patients infected SARS-CoV-2. The paediatrics showed mild symptom and different immune profile. Therefore, paediatric patients are easily to be ignored in practice. We advise that nucleic acid test or examination of serum IgM/IgG antibodies against SARS-CoV-2 should be taken for children with exposure history regardless of clinical symptom.

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Conflict of Interest

The authors declare no conflict of interest.

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