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Coronavirus Disease-19 Among Children outside Wuhan, China

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Abstract:	<p>Summary Background Ongoing outbreak of coronavirus disease-19 (CoVID-19) results in fast increasing patient number in China and many other countries. Published articles on CoVID-19 had focused on reporting the characteristics of adults. The data of children is limited. We aimed to clarify the epidemiological and clinical characteristics of CoVID-19 in children.</p> <p>Methods We prospectively followed up 31 confirmed cases < 18 years of age with SARS-CoV-2 infection in Shenzhen Third People's Hospital between Jan 16, 2020, and Feb 19, 2020. All 31 cases were confirmed as having SARS-CoV-2 in upper respiratory tract specimens by real-time RT-PCR. The epidemiological, demographic, clinical, laboratory, and radiological profiles and treatment outcomes were analysed.</p> <p>Findings All 31 cases had no Huanan seafood market exposure. 29 (93.5%) children are in family clusters. 12 (38.7%) children had no symptoms. Fever were observed in 14 (45.2%) children. The duration of fever was 1–9 days (median:2 [IQR 1-3]) . There were 13 (41.9%) cases had cough. Lymphocytes above the normal range were seen in 17 children, and lymphocytes below the normal range were not seen. 12 (38.7%) children exhibited elevated lactate dehydrogenase levels. Increase of erythrocyte sedimentation rate were seen in 10 (32.3%) patients. Chest CT image were normal in 20 (64.5%) cases, one of which become unilateral pneumonia later in clinical course. 8 (25.8%) patients showed unilateral pneumonia and 1 patient progress for bilateral pneumonia (Table 4.) . 3 (9.7%) patients had bilateral pneumonia. 23 (74.2%) children had been discharged. The other children are afebrile, and their clinical symptoms are decreasing in severity.</p> <p>Interpretation Children are susceptible to infection by SARS-CoV-2. Our preliminary findings show that children develop a milder form of the disease with a less-aggressive clinical course</p>

than do adults.

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Summary

Background

Ongoing outbreak of coronavirus disease-19 (CoVID-19) results in fast increasing patient number in China and many other countries. Published articles on CoVID-19 had focused on reporting the characteristics of adults. The data of children is limited. We aimed to clarify the epidemiological and clinical characteristics of CoVID-19 in children.

Methods

We prospectively followed up 31 confirmed cases < 18 years of age with SARS-CoV-2 infection in Shenzhen Third People's Hospital between Jan 16, 2020, and Feb 19, 2020. All 31 cases were confirmed as having SARS-CoV-2 in upper respiratory tract specimens by real-time RT-PCR. The epidemiological, demographic, clinical, laboratory, and radiological profiles and treatment outcomes were analysed.

Findings

All 31 cases had no Huanan seafood market exposure. 29 (93.5%) children are in family clusters. 12 (38.7%) children had no symptoms. Fever were observed in 14 (45.2%) children. The duration of fever was 1–9 days (median:2 [IQR 1-3]). There were 13 (41.9%) cases had cough. Lymphocytes above the normal range were seen in 17 children, and lymphocytes below the normal range were not seen. 12 (38.7%) children exhibited elevated lactate dehydrogenase levels. Increase of erythrocyte sedimentation rate were seen in 10 (32.3%) patients. Chest CT image were normal in 20 (64.5%) cases, one of which become unilateral pneumonia later in clinical course. 8

(25.8%) patients showed unilateral pneumonia and 1 patient progress for bilateral pneumonia (Table 4.) . 3 (9.7%) patients had bilateral pneumonia. 23 (74.2%) children had been discharged. The other children are afebrile, and their clinical symptoms are decreasing in severity.

Interpretation

Children are susceptible to infection by SARS-CoV-2. Our preliminary findings show that children develop a milder form of the disease with a less-aggressive clinical course than do adults.

Funding

None

Introduction

The coronavirus disease-2019 (CoVID-19) emerged in Dec 2019 in Wuhan, China is believed to be caused by the occasional jump of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from animals to human¹⁻³. While, several epidemiological and clinical investigations indicated that the person-to-person transmission of this infectious disease had occurred and led to the most of cases in China and many other countries⁴⁻⁷. A total of 391 infected individuals were recorded by Feb 13, 2020 in Shenzhen, Guangdong province of China. Of which, the majority of cases (360/391) were adults, while there are 31 children (7.9%) <18 years of age. As current cases reports are focus on adults, here we prospectively monitored a cohort of 31 children with laboratory-confirmed SARS-CoV-2 infection in Shenzhen and

summarized their epidemiologic, clinical, laboratory and radiologic features, as well as the short-term outcomes.

METHODS

Patients

All the 31 laboratory-confirmed children patients (<18 years of age) with CoVID-19, who was hospitalized at Shenzhen Third People's Hospital (Guangdong, China) during Jan 11 to Feb 13, 2020 were included in this study. The study was approved by The Shenzhen Third People's Hospital Ethics Committee.

Specimen Collection and SARS-CoV-2 Testing

The nasopharyngeal and oropharyngeal swab specimens for SARS-Cov-2 diagnosis were collected every 3 days with synthetic fiber swabs, under the guidelines introduced by WHO or China CDC. The collected specimens, stored at 2-8°C, were shipped with ice to the Shenzhen CDC. RNA was extracted and tested by real-time RT-PCR with SARS-CoV-2 specific primers and probes in biosafety level 2 facilities at the Shenzhen CDC following the standard protocol released by China CDC⁴.

Radiologic Investigations

Chest CT were performed in all patients after admission to detected the abnormalities of lungs. Patients will be rechecked by CT before discharge. During transport of the patients to and from the computed tomography suite, strict droplet and contact precautions were observed.

Treatment

Interferon atomization, intravenous ribavirin and oral lopinavir and ritonavir were

used off label. The treatment strategy for children with CoVID-19 was modeled after the initial experience with adult patients. A regimen including interferon, ribavirin or Lopinavir and ritonavir, with or without antibiotic, in various combinations at different stages of the disease were used.

Statistical Analyses

Analyses were conducted with Graphpad prism software, version 6. Data are provided as mean \pm standard deviation (SD) or median with quartile (interquartile Range, IQR). Chi-square test was performed for the comparison of rates between two groups. A two-tailed P value < 0.05 was considered statistically significant.

Role of the funding Source

None.

RESULTS

Patients and Clinical Findings

All the 31 cases came from 28 families without the history of exposure to Huanan seafood market in Wuhan. 29 (93.5%) of 31 CoVID-19 children were in family clusters, with a total of 51 confirmed members. 9 (29%) cases had not been to Wuhan or Hubei province before admission, but 8 of which were in family cluster with family members who had been to Wubei province recently, left 1 case contacted with person from Wuhan before admission. There are 13 (41.9%) male and 18 female (58.1%) in this cohort aged from 1.5 years to 17 years. None of the patients was immunocompromised. 2 (6.5%) patients had underlying diseases, one of which had asthma, and the other had duplicate kidneys. The demographic and epidemiologic characteristics are summarized

in table 1.

The clinical features of the children are presented in table 2. 12 (38.7%) children had no clinical symptoms, 2 children (6.4%) exhibited ≥ 3 features including fever, cough, nasal congestion, runny nose, diarrhea. Fever and cough were the most common symptoms and other symptoms were unusual. Fever were observed in 14 (45.2%) children. The duration of fever was 1–9 days (median:2 [IQR 1-3]). There were 13 (41.9%) cases had cough. Positive signs were not obvious in physical examinations for all children. No children developed skin rash, lymphadenopathy, hepatosplenomegaly, or clinical bleeding.

Neutropenia, lymphocytosis were common among the patients. Lymphocytes above the normal range were seen in 17 children, and lymphocytes below the normal range were not seen. Thrombocytopenia was observed in one case. Initial biochemical results were normal for the majority of children, but 12 (38.7%) children exhibited elevated lactate dehydrogenase levels. Increase of erythrocyte sedimentation rate were seen in 10 (32.3%) patients. Elevation of C reactive protein and procalcitonin were rare. The hematologic and biochemical findings are presented in Table 3.

The primary radiologic abnormality were ground-glass, hazy patchy shadows or high density shadows, mainly in the subpleural field (Figure 1) . Chest CT image were normal in 20 (64.5%) cases, one of which become unilateral pneumonia later in clinical course. 8 (25.8%) patients showed unilateral pneumonia and 1 patient progress for bilateral pneumonia (Table 4.) . 3 (9.7%) patients had bilateral pneumonia.

Treatment and Outcomes

30 of 31 (96.8%) patients were treated with interferon atomization or sprays once a diagnosis of CoVID-19 was suspected or confirmed. Interferon were tapered over 1–2 weeks. Antibacterial agents were excluded without evidence of bacterial infection. Of the 31 patients, 1 (10%) had bilateral involvement. Empirical use of azithromycin was performed in one case when routine blood test show leukocytosis and mycoplasma IgM test was positive. Ribavirin were administered in initial 3 cases for one week and was switched to lopinavir and ritonavir in one case when National Health and Health Commission of China renew the guideline of CoVID-19. In consideration of the mild clinical features, corticosteroids were not used and interferon atomization or sprays was alone performed in 6 cases. One day of oseltamivir was performed in one case before influenza was excluded. Interferon combined with lopinavir and ritonavir were performed in the recent 19 cases. No significant adverse events related to treatment were recorded.

Interferon atomization or sprays were well tolerated in all patients. Among 3 patients who used ribavirin, major short-term adverse effects such as severe haemolytic anaemia had not been observed. Oral lopinavir and ritonavir didn't cause nausea, vomiting, diarrhea, rash in 21 cases who used this medicine, but one had vomiting. No children in this cohort required mechanical ventilation.

23 (74.2%) children had been discharged at the time of presentation. Discharge criteria based on guidelines of China and fulfilled following: temperature remained normal for more than 3 days, respiratory symptoms were relieved, and SARS-CoV-2

nucleic acid of respiratory tract specimens were negative twice in a row (the sampling interval was at least 24 hours). CT reexamination showed lung lesions. Patient were advised to be isolated at home for at least 14 days. Chest CT was also recommended in one month. There was no evidence that he had spread the infection to others by telephone follow-up. The other children are afebrile, and their clinical symptoms are decreasing in severity.

Discussion

CoVID-19 caused by SARS-CoV-2 was first reported in Wuhan of Hubei province, China¹. The first case of a family cluster appeared in Jan 10, 2020 in Shenzhen⁸. The cases are still increasing in China and other countries. It is reported that this emergent infectious disease is more likely to infect older adults with comorbidities, and can result in severe even fatal respiratory diseases such as ARDS⁶. While the reported cases of children were rare. Here, we describe a cohort of 31 patients <18 years (with 28 patients <14 years) who were hospitalized with CoVID-19 in Shenzhen city of China. To our knowledge, it is the largest single-center, pediatric case series so far.

Apart from the common features between adults and children, we had found a few epidemical and clinical characteristics in children which sharply differed from that of the previously described adult patients. For instance, no gender preference was showed in the children patients, as the number of male were significant large than the female's in adult patients with CoVID-19⁶. In contrast to the seldom asymptomatic cases in adult, the children infected with SARS-Cov-2 had a quite high ratio (ca. 1/3) of asymptomatic carriers and all the reminder 2/3 cases were mild-symptomatic. In addition, although

majority of adult cases had mild symptoms, the cases with severe symptoms in adults was not unusual; while there was no any severe case in children. In line with all the children patients developed no severe complications, all of them had good clinical outcomes and were free of SARS-Cov-2 virus when discharged from hospital. This was quite similar to SARS in children⁹. It intrigued us why the SARS-Cov-2 infection did not result in severe complications in children. Regarding to there were some severe even dead adult cases among their family members (data not shown), it seems unlikely that the children having milder complications we observed results from the small sample (just 31 cases) bias. The mechanism of children with COVID-19 had milder symptoms and signs requires further study. But disease severity is not necessarily linked to transmission efficiency and a lack of severe disease manifestations affects our ability to contain the spread of the virus. Since the cytokine storm caused by vigorous immune response against the virus is a major factor for the severity of disease, we also speculated that the children with incomplete immune response may develop mild complications. Of course, these assumptions need to be confirmed by further experimental investigations for the immunopathogenesis. Nevertheless, children are susceptible to SARS-CoV-2 infection, but they seem to develop milder disease. It's worth mentioning that disease severity is not necessarily linked to transmission efficiency. As the patients without symptoms are prone to not seek health care and receive diagnosis, they may spread the virus invisibly. Given the relative high proportion of invisible but dangerous virus-carrier among children patients and almost all children patients were in family clusters, it is necessary to pay more attention in

children with infected family members in case the missing of these asymptomatic patients.

Comparing with reduced absolute value of lymphocytes in most adults, lymphocytes above the normal range were seen in most children. It is suggested 2019-nCoV might mainly act on lymphocytes. Our results suggest that the pathogenesis of SARS-CoV-2 needs further study⁶.

This study has some limitations. First, only 31 patients were enrolled, making it far from assessing the whole clinical spectrum of disease in children. All cases in this study were immunocompetent, making it impossible to clarify the effect of underlying chronic diseases on CoVID-19. Second, the follow-up monitoring time is too short to evaluate the whole clinical course. Monitoring medium-term to long-term outcomes is required.

In conclusion, children are susceptible to infection by SARS-CoV-2. Our preliminary findings show that children develop a milder form of the disease with a less-aggressive clinical course than do adults.

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Dr Chuming Chen and Fuxiang Wang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

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Table 1. Epidemiologic and demographic features of children infected with SARS-CoV-2

Presenting Feature	No. of Patients(%)
Demographic characteristics (N = 31)	
Gender	
Male	13 (41.9)
Female	18 (58.1)
Age	
Mean	7.33±4.35
Median	6.75
Range	1.5-17
Age distribution	
0-4 years	10 (32.2)
5-9 years	13 (41.9)
10-14 years	6 (19.4)
15-17 years	2 (6.5)
Epidemiologic (N = 31)	
Huanan seafood market exposure	0
Family cluster	29 (93.5)
Social contact	1 (3.2)
Hospital contact	0

Table 2. Clinical characteristics of children with CoVID-19.

clinical features	No. of Cases (%)
Fever	14 (45.2%)
Highest temperature, °C	39.7
$\geq 38.5^{\circ}\text{C}$	5 (16.1%)
37.2-38.5°C	9 (29%)
Duration , day	1~9
$\geq 3\text{d}$	5 (35.7%)
$< 3\text{d}$	9 (64.3%)
Cough	13 (41.9%)
Nasal congestion	3 (9.7%)
Sore throat	2 (6.5%)
Chills or rigor	2 (6.5%)
Nasal congestion	3 (9.7%)
Runny nose	2 (6.5%)
Fatigue	2 (6.5%)
Headache	1 (3.2%)
Sputum production	1 (3.2%)

< 3 clinical features	29 (93.5)
0 clinical features	12 (38.7)
1 clinical features	11 (35.5)
2 clinical features	6 (19.4)
≥3 clinical features	2 (6.4%)
3 clinical features	1 (3.2%)
4 clinical features	1 (3.2%)

Table 3. Laboratory features of children with CoVID-19.

Laboratory test	At Admission	During Hospitalization
	N (%)	N (%)
Total white blood cell count of < $5 \times 10^9/L$	12 (38.7)	12 (38.7)
Total white blood cell count of > $12 \times 10^9/L$	1 (3.2)	2 (6.5)
Neutrophils count of < $1.8 \times 10^9/L$	12 (38.7)	14 (45.2)
Neutrophils count of > $6.3 \times 10^9/L$	2 (6.5)	2 (6.5)
Lymphocyte count of < $1.1 \times 10^9/L$	0	0
Lymphocyte count of > $3.2 \times 10^9/L$	8 (25.8)	17 (54.8)
Platelet count of < $125 \times 10^9/L$	1 (3.2)	1 (3.2)
Haemoglobin < 120 g/L	1 (3.2)	3 (9.7)

Alanine aminotransferase > 45 U/L	2 (6.5)	2 (6.5)
Albumin < 40 g/L	0	0
Globulin > 40 g/L	0	0
Creatine kinase > 200U/L	0	2 (6.5)
Lactate dehydrogenase > 250 U/L	3 (9.7)	12 (38.7)
Activated partial thromboplastin time > 43.5s	1 (3.2)	1 (3.2)
Creatinine > 81µmol/L	0	0
Troponin I > 0.006µg/L	0	0
erythrocyte sedimentation rate > 20mm/h	10	10
Procalcitonin > 0.01 ng/mL	1 (3.2)	1 (3.2)
C-reactive protein > 8mg/L	4 (12.9)	4 (12.9)
Interleukin 6 > 7pg/mL	2 (6.5)	3 (9.7)
Blood oxygen saturation > 93%	31 (100)	31 (100)

Table 4. Initial Chest Radiographic Features and Progression During Hospitalization At Admission During Hospitalization

At Admission		During Hospitalization	
Radiographic Findings	No. (%)	Progression	No. (%)
Normal	20 (64.5)	No change	19 (95)
		Unilateral pneumonia	1 (5)
		Bilateral pneumonia	0
Unilateral pneumonia	8 (25.8)	No change	7 (87.5)
		Bilateral pneumonia	1 (12.5)
Bilateral pneumonia	3 (9.7)	NA	NA

Figure 1. Chest computed tomography(CT) images of CoVID-19 in Children.



A. Chest CT scan from case 1, a 10 years and 5 months-old children. B. CT images of case 4, a one year and 6 months-old infant. C. Case 4, 6 years and 4 months-old children. D. Chest CT of case 6, 3 years and 11 months-old young children. Imaging features were ground-glass, hazy patchy shadows or high density shadows, mainly in the subpleural field.