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Patient Report

Severe acute respiratory syndrome coronavirus infection in children

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Severe acute respiratory syndrome (SARS) was coined by the World Health Organization (WHO)[1] to describe an unusual form of severe pneumonia that first appeared in Guangdong Province, China, in November 2002. On 12 March 2003, the WHO issued a global alert on SARS.[2] At the time of writing, there were 1755 confirmed cases of SARS with 299 deaths in Hong Kong.[3] A treatment regime of ribavirin and systemic corticosteroid was reported in adults and children.[4–6] A novel coronavirus was suggested to be the cause of SARS.[4,7] It was proposed to be named after the late Dr Carlo Urbani who alerted the WHO to 'something strange and different' on 5 March 2003.[7] We report here five children and teenagers who showed evidence of SARS coronavirus infection.

We analyzed, retrospectively, five children who were found to have pneumonia with evidence of the SARS coronavirus infection, that is, positive reverse-transcriptase – polymerase chain reaction (RT-PCR) and/or serological evidence of infection. Details of RT-PCR and serological tests have been published previously.[4] Clinical features, investigation results, treatment and outcome are listed in Table 1.

Case 1

The first case was a 15-year-old girl. There was no SARS contact nor history of travel to southern China. She was admitted on 17 March 2003 after 4 days of fever, cough and chills. The highest temperature was 39.3°C. She had no respiratory distress during the whole period of hospitalization. Chest X-ray initially showed right upper lobe segmental consolidation. She had lymphopenia of 0.7×10^9/L on admission, which normalized on Day 5. She was initially treated with erythromycin. As the fever persisted, intravenous amoxycillin/clavulanic acid was started on Day 5. The fever settled 8 days after admission and she was discharged on Day 9 with amoxycillin/clavulanic acid. The result of the nasopharyngeal aspirate for SARS coronavirus RT-PCR was found to be positive after discharge. The immunofluorescence assay for SARS coronavirus antibody titre also showed a significant rise from <25 to 1600 for SARS coronavirus. There was no recurrence of fever or cough. The repeated chest X-ray taken 1 month later was normal.

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Case 2

The second case was a 2-year-old girl who presented on 4 April 2003 with high fever for 2 days, cough and malaise. There was no respiratory distress. Chest radiograph at presentation showed right lower zone interstitial infiltrates. Her father had been to mainland China in late February, following which he developed high fever, cough, malaise and myalgia for a week with spontaneous recovery. Radiographic examination of the father's chest showed bilateral interstitial infiltrates. He refused further investigations since his symptoms had already subsided and he was well afterwards. The child was started on oral clarithromycin and amoxicillin initially. The fever persisted and intravenous cefuroxime and oral ribavirin were commenced. Coronavirus was identified on Day 3 of admission from her nasal pharyngeal aspirate by RT-PCR. Ribavirin was changed from oral to intravenous administration and oral prednisolone at 2 mg/kg per day was also started. Her fever subsided on Day 3 of admission, 24 h after commencement of ribavirin. Her condition remained stable. No progressive changes were evident on follow-up chest radiographs. Liver functions and hematological picture remained normal except lymphopenia at presentation. The lowest lymphocyte count was 0.9×10^9 on Day 3 of admission. There were no adverse effects from steroids or ribavirin. She was discharged after 21 days of hospitalization and has remained well at subsequent follow-up visits. The steroid therapy was weaned off over 3 months.

Table 1 Clinical features, investigation results, treatment and outcome of children infected by the severe acute respiratory syndrome coronavirus

Case no.	1	2	3	4	5
Age (years)	15	2	15	Post-conceptional 38 weeks	13
Gender (M/F)	F	F	F	M	M
Clinical features					
Highest body temperature (°C)	40.5	38.6	39.6	38 .5	38.9
Duration of fever (days)	12	5	5	1	7
Respiratory distress	No	No	No	Yes	No
Runny nose	No	No	No	No	No
Cough	No	Yes	Yes	Yes	Yes
Sore throat	No	No	No	No	No
Chills/rigors	Yes	No	Yes	No	Yes
Myalgia	No	No	No	No	Yes
Headache	No	No	No	No	No
Others	No	Malaise	No	Hypothermia	Malaise
Close contact history with SARS	Nil	Father(?)	Nil	Nil	Nil
Laboratory findings					
Lowest Lymphocyte count ($\times 10^9$/L)†	0.7 (Day 7)	0.9 (Day 4)	0.8 (Day 4)	2.4 (Day 4)	1.8 (Day 4)
Lowest platelet count ($\times 10^9$/L)†	151 (Day 7)	197 (Day 4)	161 (Day 4)	404 (Day 4)	137 (Day 8)
Highest serum (range: 165–395)†	NA	353 (Day 3)	249 (Day 4)	1143 (Day 3)	277 (Day 9)
Highest serum ALT (U/L) (range: < 33)†	NA	19 (Day 3)	12 (Day 3)	312 (Day 3)	25 (Day 9)
D-dimer (mcg/mL) (normal < 0.2 μg/mL)†	NA	0.5–2.0 (Day 6)	0.5–2.0 (Day 3)	0.3 (Day 4)	2.0–8.0
Radiological findings					
Initial chest radiograph	Right upper zone air-space consolidation	RLZ interstitial haziness	Right upper zone air-space change and right middle zone interstitial haziness	Right lower zone air-space consolidation	Bilateral interstitial haziness
Treatment and outcome					
Oral ribavirin	No	Yes	Yes	No	Yes
IV ribabirin	No	Yes	No	Yes	No
Oral prednisolone/IV hydrocortisone	No	Yes	No	No	No
Ventilatory support	No	No	No	CPAP 5 cm water	No
Maximum oxygen requirement	21%	21%	21%	45% oxygen	21%
SARS coronavirus RT-PCR†‡	NPA + ve (Day 4)	NPA + ve (Day 3)	NPA – ve (Day 1)	NPA + ve	NPA-ve Stool + ve (Day 3)
SARS coronavirus serology ‡	From <25–1600	Negative	From <25–200	From <25–200	From <25–200
Outcome	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery

†Number of days after onset for specimens collection; ‡Performed by Government Virus Unit, Hong Kong SAR Government. Primers used in RT-PCR assay were COR-1 and COR-2.[9]

ALT, alanine aminotransferase; CPAP, continuous positive airway pressure; NA, not available; NPA, nasopharyngeal aspirate; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS, severe acute respiratory syndrome.

Case 3

The third case was a 15-year-old girl who was admitted on 5 April 2003. She presented with a 1 day history of fever (39°C), chill and cough. There was no history of SARS contact nor history of travel outside Hong Kong. The only abnormal physical finding was inspiratory crackles over the right chest. Fever persisted despite amoxycilin and clarithromycin. It was changed to intravenous cefotaxme and oral ribavirin 3 days after admission. Fever resolved within 24 h. No systemic corticosteroid was given. She made a full recovery.

Case 4

The fourth case was a 56-day-old male premature infant, born at 30 weeks gestation. He was admitted to the pediatric department of another hospital on 6 April for respiratory distress with tachypnea and subcostal insucking. On admission, the rectal temperature was 35.8°C. No other abnormal signs were found. Pulse oximetry revealed a low oxygen saturation, 84%, in room air. Chest radiograph showed consolidation of the right lower zone. He was treated for bacterial pneumonia with intravenous ampicillin, cefotaxime and erythromycin and oxygen. A fever of 38.5°C was detected on Day 3 of hospitalization. He was transferred to the Department of Paediatrics, Kwong Wah Hospital, Kowloon, Hong Kong, for intensive care because of progressive respiratory distress with increasing oxygen requirement. After admission to the intensive care unit, nasal continuous positive airway pressure (CPAP) with pressure of 5cmH_2O and 2 L/min oxygen were given. Oxygen saturation increased from 94 to 96% and tachypnea was improved with less subcostal insucking. He was weaned off nasal CPAP after 12 h. Supplemental oxygen was discontinued after 5 days in intensive care. He was transferred back to another hospital for convalescent care. The nasopharyngeal aspirate for SARS coronavirus was found to be positive and ribavirin was started in view of the positive RT-PCR result and young age although he was clinically well.

Case 5

The fifth case was a 13-year-old boy admitted on 4 April. He presented with 3 days of high fever, cough, malaise, myalgia and diarrhea. He also complained of chills and rigors. He had no history of contact to SARS. Chest Xray showed bilateral interstitial infiltrate. Oral amoxycillin and clarithromycin were started on admission. The fever persisted and amoxycillin was replaced by intravenous cefotaxime on Day 2 of admission. However, his symptoms did not respond and chest radiograph on Day 3 showed progressive changes to bilateral lobar involvement. Ribavirin was added on Day 4 of admission. The fever subsided after 2 days of oral ribavirin. No systemic cortisteroid was given. SARS coronavirus was isolated from a stool sample but not from nasal pharyngeal aspirate. His condition remained satisfactory and he was discharged after 21 days. No adverse effect was noted with the use of ribavirin. He remains well after the 1 month follow-up. Subsequent chest radiographs were normal but SARS coronavirus remained detectable from his stool sample up to 1 month after the illness.

Discussion

In line with a previous report from Hong Kong,[5] children had less severe symptoms than adults in the current series. However, SARS coronavirus had a more adverse impact on neonates as illustrated by our case who required CPAP and 40% oxygen. This was similar to the observation in animals.[8] However, this neonate only required a brief period of non-invasive CPAP and improved without ribavirin and systemic corticosteroid, in contrast to the experience in adults.[6] Similar to previous reports in adults and children,[5,6] fever was a ubiquitous feature during the course of SARS in the current series. Fever in adolescents (range of highest temperature, 38.9 to 40.5°C) were significantly higher than toddlers/infants (range of highest temperarure, 38.5 to 38.6°C). The duration of fever was also longer in adolescents (5–12 days) than toddlers/infants (1–5 days). The lactate dehydrogenase level was much higher in the severe neonatal case who required intensive care. This was similar to that reported by Lee *et al*.[6]

In the current series, all three adolescents had a rather benign course in marked contrast to previous case series that reported oxygen dependency in four out of five adolescents. The reason behind the difference was not clear. It is noteworthy that all current cases had no contact history of SARS, unlike the previously reported cases. It was interesting to note that the only adolescent, who was not given ribavirin, had a much longer duration of fever than the two who were treated with ribavirin (12 days vs 5–7 days). In contrast to previous reports,[5,6] history of contact was positive in only one out of five cases. Hence, absence of contact history has a low negative predictive value even in a time of major outbreak, and absence of contact history should not dissuade one from adopting full precaution in dealing with febrile patients in Hong Kong. The transmission route(s) of these patients without contact history remain elusive.

This case series suggests that SARS coronavirus is milder in children and adolescents. Further studies are required to confirm the effectiveness of ribavirin in shortening the duration of fever in adolescents even though the current series suggested that duration of fever appeared to be shorter in those treated with ribavirin.

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