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Original Articles

Radiological and Pulmonary Function Outcomes of Children With SARS

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Summary. We examined the radiological and pulmonary function outcomes of children affected with severe acute respiratory syndrome (SARS) at 6 months from diagnosis. Twenty-one female and 26 male Chinese patients (median age, 13.6 years; interquartile range, 9.9–16.0) were studied. In each subject, high-resolution computed tomography (HRCT) of the thorax and pulmonary function were assessed. All children were asymptomatic and had a normal clinical examination. Mild pulmonary abnormalities were detected on HRCT in 16 (34.0%) subjects, including residual ground-glass opacification (n = 5), air trapping (n = 8), and a combination of ground-glass changes and air trapping (n = 3). The need for oxygen supplementation ($P = 0.02$) and lymphopenia during the course of illness ($P = 0.012$) were significant risk factors in predicting abnormal HRCT. There were no significant lung function differences between those with and without HRCT abnormalities. Despite complete clinical resolution, a considerable proportion of children affected with SARS had abnormal HRCT findings at 6 months. These abnormalities were more prevalent in those with severe disease. It is important that careful follow-up be carried out to assess the clinical significance and persistence of such abnormalities. **Pediatr Pulmonol. 2004; 38:427–433.**

Key words: severe acute respiratory syndrome; outcome; lung function; high-resolution computed tomography.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is a new infectious disease that struck Hong Kong without any warning and rapidly spread to affect many other countries. A novel virus, the SARS-associated coronavirus, was found to be the etiological agent.[1–3] Fatality rates in adults affected with SARS were reported to exceed 10%, and pulmonary complications in the form of pulmonary fibrosis and bronchiectasis may be as high as 20%.[4] We previously reported on the presenting clinical and laboratory features of children affected with SARS. In contrast to adults, the clinical course and radiological changes of children affected were generally much milder, and the duration for resolution was shorter.[5,6] However, complications in terms of permanent radiological changes and pulmonary function abnormalities are not known.

Viral pneumonia has been reported to lead to long-term pulmonary sequelae, namely bronchiectasis and fibrosis in children.[7,8] Functional abnormalities may also be observed, such as bronchial hyperreactivity, chronic cough, and asthma.[9,10] The occurrence of sequelae is

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unpredictable, and a careful assessment of clinical and radiological outcomes is therefore important.

The aims of this follow-up study were 1) to delineate the radiological and pulmonary outcomes in children at 6 months after an acute episode of SARS, and 2) to correlate the development of pulmonary complications with clinical indices and laboratory abnormalities during the course of illness. We used high-resolution computed tomography (HRCT) of the thorax and pulmonary function tests as our assessment tools.

METHODS

Study Patients

Children and adolescents, now recovered from SARS, previously received hospital treatment at 1 of the 5 pediatric departments in Hong Kong (Prince of Wales Hospital, United Christian Hospital, Princess Margaret Hospital, Queen Elizabeth Hospital, and Pamela Youde Nethersole Eastern Hospital). Those who satisfied the following inclusion criteria were recruited for this study: 1) seroconversion to SARS coronavirus, 2) age less than 18 years at time of diagnosis, 3) 6 months since diagnosis of SARS was made, and 4) no acute upper respiratory tract infection illness for 2 weeks prior to the study. Written informed consent was obtained from parents, and age-appropriate assent was provided by subjects. The study was approved by the Institutional Ethics Review Board of the Chinese University of Hong Kong.

Clinical and Laboratory Data

Clinical and laboratory data at diagnosis and during the course of illness were collected using a standardized data extraction form that captured a wide range of information, including: demographic characteristics, past medical history, symptoms at presentation (chills and rigor, myalgia, cough, sore throat, malaise, headache, runny nose, diarrhoea, dizziness, and others), duration of fever and hospitalization, need for oxygen supplementation, ventilation, and intensive care unit admission. The medications (antibiotics, ribavirin, and systemic corticosteroids) received by patients were also documented. Laboratory data were also documented, including total white cell count, absolute neutrophil count, absolute lymphocyte count, platelet count, lactic dehydrogenase and creatine phosphokinase levels on admission, and the most deranged result during the course of illness.

Clinical Assessment

Each child was thoroughly examined on the day of assessment, and weight and standing height were measured with a calibrated weighing scale and stadiometer by standard anthropometric methods.[11] Each individual then went through the following radiological and pulmonary investigations.

High-Resolution Computed Tomography of the Thorax

Scanning was done with the subject in supine position, using a low radiation dose technique.[12,13] We employed 50–80 mA and 0.6–1 sec (34–80 mAs) with thin collimation (1 mm) and a high-spatial-frequency reconstruction algorithm at 7-mm intervals from the lung apices to the bases. Each scan was obtained during breathhold at end inspiration and at end expiration. Images were photographed at conventional lung window settings (window center, −700 to −600 HU; window width, 1,000–1,500 HU).

A pediatric radiologist (W.C.) who was blinded to the clinical and pulmonary status of the subjects evaluated the CT scans. Scans obtained during inspiration were evaluated for the presence of residual parenchymal abnormality (ground-glass appearance, consolidation, and interstitial thickening) and fibrosis (parenchymal band and bronchiectasis). Expiratory scans were evaluated for the presence of focal air trapping. Ground-glass opacification was defined as increased lung parenchymal attenuation that did not obscure the underlying vascular architecture.[14] Consolidation was defined as opacification in which the underlying vasculature was obscured.[14] All images were examined for interstitial abnormalities which included intra- and interlobular, septal, or peribronchovascular interstitial thickening. Parenchymal bands and traction bronchiectasis were considered evidence of fibrosis.[15,16] The diagnosis of focal air trapping in a lobe was based on the presence of focal areas of abnormally low attenuation within the lung parenchyma on the expiratory scan that were not present on the inspiratory scan.

Pulmonary Function Test

Pulmonary function tests were carried out by the same team of supervised technicians, according to the recommended standard.[17] Spirometry was measured by the Medical Graphics Pulmonary Function System with BreezeSuite Software (Medical Graphics Corp., St. Paul, MN). The best of at least three technically acceptable values for forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), maximum midexpiratory flow rate (MMEFR), and flow-volume curves was selected. Total lung capacity (TLC) was measured by body plethysmography (MedGraphics Elite Series™ Plethysmograph) and expressed in liters (BTPS). Diffusion capacity of carbon monoxide (DLco) was measured by the single breath technique. Pulmonary function results were expressed as percentages of predicted normal values.[18]

Statistical Analysis

The demographic data, laboratory results, and percent predicted lung function parameters were expressed as medians with interquartile ranges. Potential risk factors were first evaluated individually by chi-square test and Mann-Whitney test for association with abnormal HRCT. Risk factors with $P < 0.25$ were then analyzed by multivariate logistic regression analysis, using a forward stepwise selection strategy. When two or more potential risk factors were highly correlated, the factor that was clinically important was selected for entry.

Subjects were divided into four groups according to HRCT findings (normal, air trapping, ground-glass opacification, and combination of air trapping and ground-glass changes). The Kruskal-Wallis test with the Mann-Whitney post hoc test were used to explore the relationship of lung function parameters among these four groups.

SPSS for Windows (Release 11.0, SPSS, Inc., Chicago, IL) was used in the analyses, and the level of significance was set at 5% for all comparisons.

RESULTS

Study Patients

The study involved five regional pediatric units that together looked after 80 serologically confirmed SARS children, which accounted for 86% of all pediatric SARS cases in Hong Kong. We were given consent to collect clinical and laboratory data on 47 patients. All participated in the radiological and pulmonary assessment at between 6–8 months from diagnosis. None of the patients required readmission following discharge from the hospital for SARS. There were 21 female patients and 26 male patients; their median age was 13.6 years (interquartile range (IR), 9.9–16.0). None of the patients reported any respiratory or exercise intolerance symptoms, and all had a normal clinical examination. All patients were ethnic Chinese. Two patients suffered from allergic rhinitis, for which they received antihistamine on an as-required basis. Two patients had a past history of febrile convulsion. Three patients suffered from asthma, two were receiving regular inhaled corticosteroids, and one was receiving as-required inhaled bronchodilator.

Clinical and Laboratory Findings

The median duration of fever for the course of illness was 7 days (IR, 7–8), and the median duration of hospital stay was 21.5 days (IR, 20–26; range, 12–45 days). The most common symptoms at presentation were fever (in 98% of patients); cough (56.4%); malaise (54.5%); chills (40.0%); runny nose (31%); and myalgia (29.1%). Less common symptoms included diarrhea (23.6%), headache (21.8%), rigor (21.8%), loss of appetite (21.8%), dizziness (18.2%), vomiting (12.7%), sore throat (11.0%), sputum production (5.5 %), and dyspnea and abdominal pain (each present in one patient). The median maximum temperature recorded was 39.4°C (range, 36.9–40.5°C). None of the patients were hypoxic on admission, but 11 subsequently developed oxygen dependency during the course of illness. Five patients were admitted to the intensive care unit (ICU) and two required mechanical ventilation; one was managed on bilevel positive airway pressure ventilation, and the other required endotracheal intubation. No fatalities were recorded.

On admission, the median total white blood count was 5.3×10^{-9}/l (IR, $4.3–7.2 \times 10^{-9}$/l). The median neutrophil count was 12.3×10^{-9}/l (IR, $9.3–16.8 \times 10^{-9}$/l). The median lymphocyte count was 0.6×10^{-9}/l (IR, $0.4–1.0 \times 10^{-9}$/l). Lymphopenia (absolute lymphocyte count, $<1{,}000/mm^3$) was seen in 38% of subjects on admission, and during the course of illness, 64% developed lymphopenia. The platelet count remained normal in most cases. The highest LDH level reached was 1,548 U/l, and the highest CPK seen was 1,787 U/l.

Treatment

As there was no consensus treatment guideline at the early phase of the outbreak, there was variation in the choice and duration of treatment with antibiotics and second-line therapy between different hospitals. Initial treatment included a macrolide antibiotic (clarithromycin, azithromycin, or erythromycin) and cephalosporin, levofloxacin, or amoxicillin/clavulanate to target common pathogens causing community-acquired pneumonia. All patients received ribavirin; the range of treatment duration was from 7–17 days. Thirty-eight patients were given oral prednisolone; the range of treatment duration was from 3–23 days. Twenty-one patients were given intravenous hydrocortisone; the duration of therapy was from 3–16 days. Nineteen patients were given pulse intravenous methylprednisolone.

Findings on High-Resolution Computed Tomography of the Thorax

Pulmonary abnormalities were detected on HRCT in 16 (34.0%) subjects (Table 1). Abnormal HRCT findings were residual ground-glass opacification (n = 5, 31.2%), air trapping (n = 8, 50%), and a combination of ground-glass changes and air trapping (n = 3, 18.8%). All HRCT changes were mild in extent. Three of the 5 patients who had ground-glass changes on HRCT also had evidence of fibrosis involving a small segment of a single lobe. All three cases with combined air trapping and residual ground-glass changes on HRCT required oxygen supplement during the course of illness, and two of them required ventilatory support.

TABLE 1— Clinical Details and Radiological Findings in Children With Abnormal HRCT[1]

Subject number	Age (years)	Sex (male/ female)	Hospital stay (days)	Duration of fever (days)	Oxygen supplement given (yes/no)	Ventilatory support given (yes/no)	Ground-glass changes	Air trapping	Fibrosis
1	13.6	F	21	7	Y	N	−	+	−
2	9.8	M	22	8	N	N	−	+	−
3	15.9	F	21	7	Y	Y	+	+	−
4	12.4	M	26	7	Y	N	−	+	−
5	13.4	F	30	7	N	N	+	−	+
6	15.0	M	43	18	N	N	−	+	−
7	18.2	M	35	9	Y	N	+	−	−
8	17.0	M	21	7	N	N	−	+	−
9	16.9	F	28	8	N	N	+	−	+
10	13.5	F	18	7	Y	N	−	+	−
11	13.8	F	24	6	Y	N	+	+	−
12	16.6	M	17	9	N	N	+	−	−
13	18.0	M	43	5	N	N	+	−	+
14	13.6	M	28	7	N	N	−	+	−
15	15.9	F	21	8	Y	Y	+	+	−
16	11.7	F	32	7	N	N	−	+	−

[1]M, male; F, female; +, finding present on HRCT; −, finding absent on HRCT; Y, yes; N, no.

Based on the presence or absence of abnormal HRCT findings, the cohort of subjects was classified into two groups (Table 2). There were significant intergroup differences observed in age distribution ($P = 0.037$), duration of hospitalization ($P = 0.048$), requirement of oxygen supplementation ($P = 0.003$), lymphocyte count on admission and the most abnormal result during the course of illness ($P < 0.0001$), and the need for hydrocortisone

TABLE 2— Comparison of Subjects' Characteristics Stratified According to HRCT Results[1]

	Abnormal HRCT (n = 16)	Normal HRCT (n = 31)	*P* value
Sex (M/F)	6 (37.5%)/10 (62.5%)	20 (64.5%)/11 (35.5%)	0.078
Age (years)	14.4 (13.4–16.9)	12.5 (5.9–15.2)	0.037
Hospital stay (days)	26 (21–32)	21 (20–24)	0.048
Duration of fever (days)	7 (7–8)	7 (6–8.3)	0.939
Maximum temperature (°C)	40 (39.1–40)	39.2 (38.6–39.9)	0.090
Oxygen supplement	7 (46.7%)	2 (6.5%)	0.003
Ventilatory support	2 (13.3%)	0 (0%)	0.101
Cough	9 (60%)	17 (56.7%)	1.00
Malaise	11 (73.3%)	13 (43.3%)	0.68
Chills	6 (40%)	11 (36.7%)	1.00
Runny nose	5 (33.3%)	10 (33.3%)	1.00
Myalgia	6 (40%)	7 (23.3%)	1.00
Total WBC at admission	5.3 (4.2–6.2)	5.3 (4.3–7.4)	0.385
Lym count at admission	0.9 (0.6–1.0)	1.3 (1.0–1.8)	<0.0001
Lowest recorded lym count	0.4 (0.1–0.8)	0.9 (0.6–1.1)	<0.0001
Neutro count at admission	3.9 (3.2–4.7)	2.8 (2.2–5.1)	0.260
Highest recorded neutro count	12.1 (10.4–15.2)	12.5 (7.8–19.0)	0.887
LDH at admission	480.0 (270.3–738.3)	371.0 (256.0–563.0)	0.533
Highest recorded LDH	752.5 (401.8–957.0)	588.0 (321.3–859.5)	0.399
CPK at admission	78.5 (70.8–106.3)	92.0 (67.0–144.0)	0.316
Highest recorded CPK	167.0 (66.5–467.8)	243.0 (88.8–355.8)	0.587
Use of systemic steroids			
Hydrocortisone	11 (68.8%)	8 (25.8%)	0.004
Prednisolone	14 (87.5%)	20 (64.5%)	0.168
Methylprednisolone	10 (62.5%)	6 (19.4%)	0.003

[1]WBC, white blood count; Lym, lymphocyte; Neutro, neutrophil; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; numerical data, median (interquartile range); categorical data, frequency (%).

($P = 0.004$) and methylprednisolone ($P = 0.003$). Forward stepwise logistic regression revealed that oxygen supplementation ($P = 0.02$) and the most abnormal lymphocyte count ($P = 0.012$) were the two most significant factors associated with abnormal HRCT.

Findings on Pulmonary Function Test

Thirty-eight patients underwent a full pulmonary function test. Four were found to have abnormal lung function: two with mild obstructive deficit (FEV_1/FVC 78% and FEV_1/FVC 79%), and two with mild restrictive deficit (TLC and FVC 76% and 75% predicted, respectively; TLC and FVC 77% and 70% predicted, respectively). Of the four patients, only one who had restrictive deficit on lung function also had a concomitant HRCT abnormality. Patients with a past medical history of asthma had normal pulmonary function.

The pulmonary results stratified according to HRCT findings are shown in Table 3. There were no significant differences in lung function between subjects with either air trapping or residual ground-glass opacification, those with combined abnormalities, and those with normal HRCT scans.

DISCUSSION

In this study, we demonstrated that HRCT abnormalities at 6 months after acute SARS infection were prevalent. Even though all subjects from our cohort were clinically asymptomatic with relatively normal lung function, pulmonary sequelae on HRCT were found in 34%. We attempted to investigate whether there were any possible risk factors leading to the pulmonary sequelae on HRCT. The factors identified were the need for oxygen supplementation and a low lymphocyte count during the course of illness.

Inflammatory damage to the small airways is the most common injury sustained by the human lung.[19] Viral infection causing significant pulmonary sequelae, especially small airway disease, is often reported after adenovirus and mycoplasma infection.[20] HRCT has become the investigation of choice for the detection and evaluation of air-space and airway diseases, especially those associated with small airway damage.[21] The abnormal findings on HRCT in the present study included residual ground-glass opacification and air trapping. Ground-glass opacification is a predominant feature seen during the acute stage of SARS. It is a nonspecific radiological appearance commonly found in children suffering from infective pneumonia of any etiology, and in most cases, it is reversible and does not lead to significant lung function deficit.[22] Air trapping is secondary to collateral air drift into the alveoli beyond the narrowed or obstructed bronchus or bronchiole.[23] It causes decreases in pulmonary blood flow, and leads to gradual atrophy of the involved portion of the lung tissue.[24]

Air trapping on HRCT was found in 15% and 37% of children with a history of *Adenovirus* and *Mycoplasma* pneumonia, respectively.[24,25] Residual lung function abnormalities were also reported in association with air trapping demonstrated on HRCT. Mok et al.[26] found long-term impairment of small airway function, and Sabato et al.[27] showed persistent spirometric abnormalities, even in asymptomatic children, at 3 years following *Mycoplasma* pneumonia. Our cohort of children whose HRCT revealed air trapping remained clinically asymptomatic with normal lung function. In fact, we were unable to demonstrate any significant lung function differences between subjects with isolated HRCT changes, a combination of changes, and those with normal HRCT findings. This discrepancy may be explained by the mild abnormalities found on their HRCT, even though we did not attempt to grade the severity of involvement within affected lung segments. Chang et al.,[13] in a follow-up study, found a proportion of children with postinfectious small airway damage to have normal lung function. Poor correlation was also demonstrated between the extent of HRCT abnormalities and lung function test results.[28]

Lymphopenia was found to be a significant risk factor for abnormal HRCT in our study. It is possible that patients

TABLE 3— Lung Function Stratified According to HRCT Findings[1]

	Normal HRCT	Residual ground glass	Air trapping	GG + AT	*P* values
Count	22	5	8	3	
% predicted FVC	93.5 (88–101)	82.0 (73.3–92.3)	96.0 (78–108.5)	93.0 (73–108)	NS
% predicted FEV_1	89.5 (81–94)	82.0 (72.5–87.5)	90.5 (74.3–102.8)	97.0 (79–103)	NS
FEV_1/FVC	89.0 (80–96)	90.0 (86.3–94.8)	85.5 (80–93)	97.0 (88–99)	NS
% predicted FEF_{25-75}	88.0 (64–111)	81.0 (65–94.5)	83.0 (57.8–107)	105.0 (102–126)	NS
% predicted TLC	101.0 (92.8–108.3)	93.0 (88.5–102.8)	96.5 (90.5–114.3)	96.0 (91–102)	NS
% predicted DLco	119.0 (91.5–141.5)	106.0 (103.8–119.8)	106.0 (91.0–1125.0)	98.0 (91.0–102.0)	NS

[1]Results, median (IR); GG, ground glass; AT, air trapping; HRCT, high-resolution computed tomography of thorax; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; FEF_{25-75}, forced expiratory flow rate over middle 50% of FVC; TLC, total lung capacity; DLco, carbon monoxide diffusion capacity corrected; NS, not statistically significant

with the lowest lymphocyte count manifested a more intense immunopathological response, with a tendency toward pulmonary sequelae. Children with more severe bronchiolitis from respiratory syncytial virus (RSV) infection were shown to have significantly lower absolute lymphocyte counts than those with mild disease.[29] In adults affected with SARS, T-cell lymphopenia was found to predict adverse outcomes.[30] The actual mechanism for lymphopenia is still unknown. It is possible that in severe SARS, a combination of heightened immune response-enhancing lymphocyte apoptosis and direct viral invasion and destruction of lymphocytes cumulatively cause the end result of lymphopenia.[30,31] The other significant predictor for abnormal HRCT findings is the requirement of oxygen supplementation. This is likely to be another marker of more severe disease, rather than a causative factor in lung damage.

There are certain limitations to our study. First, there was no control group or subjects admitted with lower respiratory tract infection other than SARS during the same time period for comparison. Although data from a comparison group would provide further confirmation of the abnormalities detected in our SARS cohort, we considered it unreasonable to subject normal children or those who recovered from typical common pneumonia to unnecessary radiation. Our HRCT study protocol involved a low-dose technique which aimed to minimize radiation exposure for participants. Second, our study was a cross-sectional assessment of lung function and radiological features. To better understand the progress and natural history of the abnormalities identified in this cohort, it would be ideal and essential to undertake a longitudinal study to assess the changes in the various parameters over time. We plan to carry out such a longitudinal follow-up study. Third, we were only able to recruit 47 subjects for this study from the initial cohort of 80 children. However, on reviewing hospital admission records and discharge summaries, the demographic characteristics of the attendants and nonattendents were similar, and all those who refused assessment were clinically milder cases. Thus, it was unlikely that we missed significant lung function and radiological abnormalities from those who refused assessment.

In summary, this study showed that despite complete clinical resolution with normal lung function, a considerable proportion of children with history of SARS coronavirus-associated pneumonia have abnormal findings on HRCT, suggestive of small airway damage. These radiological changes were significantly predicted by a need for oxygen supplementation and lymphopenia during the course of illness. It is important that careful follow-up be carried out to assess the longitudinal changes and tracking into adulthood of such abnormalities. It is equally important to assess the clinical relevance of such radiological changes, to allow for better understanding of the disease and for prognostic counselling of the families.

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