Clinical Features, Diagnosis, Treatment and Short-term Outcome of Severe Acute Respiratory Syndrome (SARS) in Children

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Clinical Features

Symptoms and signs caused by coronavirus-associated atypical pneumonia (or SARS) are non-specific. In adult patients, the commonest presenting clinical features are fever, malaise, chills, rigor, myalgia, headache, dizziness and cough. In children, especially young children and infants in which fever is generally present, the other systemic and respiratory symptoms may not be prominent or are difficult to elicit.

In a series of 43 children aged less than 18 years who were treated at the Princess Margaret Hospital (PMH) in March to April 2003, the following presenting clinical features in percentages are noted (Table 1).

In general, the older the children, the more pronounced are the systemic symptoms like high fever, malaise, chills, rigor, headache and myalgia. Respiratory symptoms like cough, coryza, sore throat, sputum production and dyspnoea are often absent although the disease primarily involve the lungs. Initial symptoms in infants and young children may be deceptively mild but they do not necessarily run a mild clinical course. A period of close observation following the onset of fever usually will clarify the picture and lead to a more definitive diagnosis.

Table 1 Presenting clinical features in 43 children aged less than 18 years with clinical diagnosis of SARS (information only accurate up to 20 April 2003)

	% (N=43)
Fever	100
Cough	65
Malaise	58
Sputum production (Phlegm)	42
Coryza	40
Myalgia	37
Headache	35
Chills and/or rigor	33
Nausea and/or vomiting	28
Sore throat	16
Diarrhoea	16
Dizziness	12
Dyspnoea	9
Anorexia	7
Abdominal pain	7
Lethargy	7
Chest pain	2

As the presenting clinical features are non-specific, even in adults, additional clues like a contact history, abnormal chest radiograph and sometimes characteristic though not pathognomonic, initial laboratory findings are extremely helpful in clinching a diagnosis. Suggestive laboratory abnormalities include one or more of the following: decreased white cell and lymphocyte counts, decreased platelet count, elevated liver enzymes, creatine kinase and lactate dehydrogenase levels. This underscores the importance of a good history taking, appropriate investigations and a period of close clinical observation in the diagnostic process.

Diagnosis

Four aspects of diagnosis are essential in the overall work-up of a suspected case of SARS.

1. Clinical

The presenting clinical features plus symptoms and signs that evolve as the illness progresses will usually clarify the picture and lead to a better differential diagnosis. The list of differential diagnoses to consider includes community acquired pneumonia caused by bacteria, viruses, mycoplasma and chlamydia. Common respiratory viruses that can cause pneumonia include influenza A and B, parainfluenza types 1, 2, and 3, respiratory syncytial virus (RSV) and adenovirus. Pneumonia caused by the novel coronavirus (SARS-CoV) is a new clinical entity which does not have a pathognomonic feature. That makes its diagnosis often difficult especially during seasonal epidemics of other respiratory viruses like influenza, RSV and adenovirus. Laboratory investigations are always indicated to exclude the diagnosis of bacterial, other viral, mycoplasmal and chlamydial pneumonias.

In the absence of an epidemic or outbreak situation, the diagnosis of coronavirus-associated atypical pneumonia (or SARS) is often by an educated exclusion of other causes of pneumonia.

2. Epidemiological

In a series of 43 children diagnosed and treated at PMH in March to April 2003, more than 80% of patients have a definite contact history (Table 2).

The importance of meticulously eliciting a contact history in helping the diagnostic process cannot be overemphasised as children are usually the victim of an infectious disease, as in this case, instead of the source of infection.

3. Radiological

A chest radiograph (CXR) is an indispensable investigation and very often the CXR needs to be repeated as frequently as the change in clinical condition warrants. However, no characteristic radiographic findings exist for SARS. The appearances of focal or diffuse consolidations are not unique and many other causes of atypical pneumonia can produce the same picture. Nevertheless, if a contact history is forthcoming, the suspicion will certainly be heightened. Increased vigilance for the possibility of SARS is the key to radiological diagnosis. If the condition is not suspected, the diagnosis will never be made.

When the diagnosis of SARS is highly suspicious, based on clinical features and an epidemiologic link, and yet the CXR findings are not definite (e.g. early in the course of illness or pneumonic infiltrates are obscured by the cardiac silhoutte), a computed tomography (CT) of the chest will be of immense help.

Again, the CT findings of SARS are non-specific and cannot pin-point the exact aetiology or the infectious agent. However, in the presence of a contact history and additional suggestive laboratory findings, the utility of CT when suggestive CXR findings are lacking cannot be underestimated.

Table 2 Sources of contact in 43 children aged less than 18 years with clinical diagnosis of SARS (information only accurate up to 20 April 2003)

	No. (N=43)	%
Amoy Gardens point source outbreak	27	63
Hospital contact	4	9
Social contact	3	7
Household contact	2	5
Unknown	7	16

4. Microbiological

The purpose of microbiological investigations is three-fold – exclusion of common pathogens causing community acquired pneumonia (e.g. *Streptococcus pneumoniae*), exclusion of less common pathogens causing atypical pneumonia (e.g. influenza virus), and confirmation of SARS through identification of SARS-CoV using reverse transcriptase polymerase chain reaction (RT-PCR) for viral genetic material (RNA), paired serology for antibody response and viral culture for isolation of the live virus.

RT-PCR is a rapid diagnostic tool which complements clinical and radiological diagnosis. However, the first generation RT-PCR assay is far from perfection in terms of sensitivity although it has high specificity.

In the PMH series, the sensitivity of the test in diagnosing SARS was only 50% when nasopharyngeal secretions were used as specimens. Use of stool specimens for the test may improve the sensitivity and should be done together with respiratory specimens. A negative RT-PCR result may not mean the absence of disease (false negativity). Hence the test cannot be used for excluding the diagnosis of SARS or for decision making in early discharge of patients suspected of suffering from SARS.

An increase in specific antibody titre against the SARS-CoV in the convalescent serum of a patient with a suspected diagnosis of SARS essentially confirms the diagnosis. However, rise in antibody titre is delayed and may not be evident for as long as 3-4 weeks after the onset of fever. Hence, serological diagnosis is in general retrospective and often cannot benefit treatment decision.

Likewise, recovery of the live virus by viral culture of respiratory secretions or stool is time consuming and labour intensive. Although it is the gold standard of diagnosis in virology, the utility of the test in SARS is undermined by the apparent difficulty in growing the virus in special cell lines or tissue culture media using sophisticated technique in advanced laboratories. Again, diagnosis made by viral culture is in general retrospective, appears to be less sensitive, and often will not help management decision in the acute phase of illness when patients are in dire need of prompt diagnosis to target treatment.

The diagnostic approach to SARS in children will only improve with accumulated clinical experience and the development of very sensitive and specific rapid diagnostic tools, which is the prime focus of ongoing intense research.

Treatment

No specific therapy was available when SARS first appeared in medical history and the aetiological agent was not even known. The need for coverage of a suspected viral cause had led to inclusion of the most broad-spectrum antiviral agent available then on the market, ribavirin, in the initial treatment regimen. Subsequently, it was perceived that the pathogenesis of the atypical pneumonia had a strong immunologic component, and then corticosteroid was also included in the treatment protocol to suppress the overactive immune response, with well documented success. Very soon, a cocktail comprising of oral or intravenous ribavirin, and various dose combinations of different corticosteroids (e.g. Prednisolone, hydrocortisone and methylprednisolone) has become standard therapy. The usual course of ribavirin treatment lasted for 1-2 weeks, and that of corticosteroid 2-4 weeks. However, as the epidemic unfolded, it was soon realized that some adult patients did not respond to the combination of ribavirin and steroid, or initially responded but later relapsed in the third week of illness. Novel therapy for salvage of these unfortunate adult patients who failed to respond to repeated doses of pulse methylprednisolone and suffered from uncontrolled immunologic destruction of their lung tissues became the prime focus of clinical research. Use of immunomodulating agents like Pentaglobin (IgM), intravenous immunoglobulin (IVIG), cyclophosphamide, thalidomide, anti-TNF-alpha (Infliximab) etc. emerged on the research agenda of investigative compounds. Similarly, other antiviral agents, including interferon-alpha, were considered in the face of growing evidence of lack of in vitro and clinical efficacy of ribavirin for the treatment of coronavirus infection. Agents like protease inhibitors (e.g. Kaletra, which is a combination of ritonavir and lopinavir, originally marketed for treatment of HIV infection) showed initial promise, and clinical efficacy was forthcoming when used in combination with ribavirin in situations where repeated high doses of methylprednisolone had clearly failed. The use of neutralising antibody contained in the plasma of convalescent patients with laboratory confirmed SARS was also attempted with encouraging results in terms of immediate mortality and discharge at 22 days from onset of fever, provided that the convalescent patient plasma was administered before 16 days from onset of fever.

All in all, new modalities of treatment, both antiviral and immunomodulating, have become the focus of ongoing intense research to unravel the therapeutic futility faced by clinicians in their fight against SARS. For survivors of SARS who required mechanical ventilation or have significant pulmonary complications, long-term follow-up of their lung functions is indicated (e.g. for monitoring of pulmonary fibrosis). Of course, prevention is always the best cure. A vaccine that induces both individual and herd immunity will be the ultimate answer to conquering the dreadful coronavirus, which is emerging as a pandemic global threat to human existence.

Last but not least, children who are hospitalised with SARS may require prompt professional psychosocial intervention during their prolonged stay in hospital with a life-threatening ailment and treatment with drugs that may cause psychological adverse effects, and especially when one or both of their parents have died from SARS. Clinical psychologists can better explain the role of psychological support and management in children with SARS.

Outcome

In our experience, children with SARS will recover with good supportive care and specific drug treatment, although adolescents and very young infants may be at risk of severe illness and may require intensive care. A simplified summary of the treatment and outcome of 43 children hospitalised at Princess Margaret Hospital in March-April 2003 is presented in Table 3.

Table 3 Treatment and outcome of 43 children with SARS hospitalised at PMH in March-April 2003 (information only accurate up to 20 April 2003)

	No. (N=43)	**%**
Death	0	0
Oxygen therapy	8	19
- CPAP via nasal prong	1	2
- noninvasive ventilation (BiPAP)	1	2
- intubation and mechanical ventilation	1	2
- nasal cannula only	6	14
Pulse methylprednisolone therapy	10	23
Intensive care	5	12