Pediatr Allergy Immunol 2004: 15: 206–209
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PEDIATRIC ALLERGY AND IMMUNOLOGY

Childhood severe acute respiratory syndrome, coronavirus infections and asthma

Van Bever HP, Chng SY, Goh DY. Childhood severe acute respiratory syndrome, coronavirus infections and asthma.
Pediatr Allergy Immunol 2004: 15: 206–209. © 2004 Blackwell Munksgaard

Severe acute respiratory syndrome (SARS) is a new infectious disease caused by a novel coronavirus. Children appear to be less susceptible to the SARS coronavirus, although the other non-SARS coronaviruses can cause respiratory infections in adults and in children of all ages. The exact reasons as to why SARS preferentially affects adults, and not children, are still unknown. Many hypotheses exist and need to be explored. During the outbreak of SARS, there did not appear to be an increase in asthma exacerbations in children.

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Key words: childhood severe acute respiratory syndrome; coronavirus; asthma

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Accepted 24 November 2003

Severe acute respiratory syndrome (SARS) is a new infectious disease purported to have begun in the southern Chinese province of Guangdong in November 2002. It has now been established that SARS is caused by a novel coronavirus (SARS-CoV) that had previously not been described (1). Although the majority of patients with SARS recover, SARS can have a severe clinical course and may result in death. Children appear to be less susceptible to SARS both in numbers and severity (2). Many aspects of this new disease are however still unknown. Predicting further evolution of SARS and its impact upon childhood health is largely speculative at the moment. Like many other viral infections of the airways, SARS may perhaps become a permanent respiratory tract pathogen with which we will have to deal with and which will become part of our routine differential diagnoses for acute respiratory symptoms. Perhaps, it may even be possible, although unlikely, that SARS may be eradicated in the near future. At present, the future of SARS is certainly an enigma, and far more studies are needed to unravel the mysteries of this new disease, its origin and its future.

Coronaviruses and children

The human coronaviruses HCoV-229E in serogroup I and HCoV-OC43 in serogroup II are the second most important cause of the common cold after rhinoviruses (3, 4). Infections by coronaviruses are usually limited to the upper airways and are clinically indistinguishable from other upper respiratory infections caused by numerous other viruses. The clinical manifestations of coronavirus infections are essentially those of the so-called 'common colds', that need little or at most symptomatic treatment (5). In some cases, however, lower respiratory infections can occur, causing bronchitis, bronchiolitis and even pneumonia. To the best of our knowledge, acute respiratory distress syndrome (ARDS) induced by coronaviruses has never been described (6). On the contrary, coronaviruses can also induce non-respiratory symptoms such as abdominal pain and acute diarrhea.

Coronaviruses affect both children and adults. In the epidemic that occurred 2 years ago in the north of France, 41% of the subjects were younger than 15 years (5). In a study on hospitalized patients with acute respiratory infections, it was demonstrated that rhinovirus and coronavirus were both associated with lower respiratory tract illnesses in all age groups. In children <5 years, the predominant clinical syndromes were pneumonia and bronchiolitis; while in older children and young adults, exacerbations of asthma were the predominant manifestation (7). In a recent study on infants hospitalized for acute

wheezing, rhinoviruses were found to be the most important triggers (33%) and were associated with the development of asthma. In that study on wheezy infants, coronaviruses could not be identified (8). These results are in concordance with those of a study from Hungary, showing that antibody levels to coronavirus OC43 reached a peak between 15 and 19 years of age, while rates of positive sera were lowest before 1 year of age (9).

In a study evaluating healthy children and possible carrier status, rhinovirus was identified in 18% of healthy children and enterovirus RNA in 11% of healthy children. Coronavirus RNA was however not identified in any of the children and hence it is suggested that healthy children may not carry the virus (10).

In summary, from the literature on coronaviruses and children, it seems that the non-SARS coronaviruses can cause upper and lower respiratory infections in adults and in children of all ages. Wheezing during infancy was not associated with coronavirus infection and healthy carriers of coronaviruses are unlikely amongst children.

SARS in childhood

In adults, SARS can be a deadly disease. Clinically, the disease is characterized by fever, dyspnea, lymphopenia, and rapidly progressive changes on radiography, resulting in ARDS and death (11–13). It has now become obvious that SARS has different features in children (2) compared with adults.

The incidence of SARS is lower in children (see Fig. 1). In Singapore, SARS mainly affects adults between 20 and 60 years of age. If SARS does occur in children, symptoms are usually mild and indistinguishable from other lower respiratory infections. In Singapore, none of the children diagnosed with SARS required intensive care and none developed ARDS. The experience in Hong Kong has been similar (2).

The exact reasons as to why SARS preferentially affects adults, and not children, are still unknown. Many hypotheses exist and need to be explored. The fact that children developed a milder form of illness is not unique to infection with the SARS coronavirus, as a number of other respiratory infections behave in the same way, such as influenza, infections with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*, and even varicella. One possible explanation is that children may enjoy cross-immunity persisting after recent exposures to other coronaviruses. Cross-protection from childhood vaccination [e.g. measles, mumps and rubella (MMR) vaccine] has also been postulated in the popular press (14), but no scientific data on the subject are available. However, if children were protected by MMR vaccination, it would be expected that younger non-vaccinated children would develop severe SARS but this has not been the case. Furthermore, there is no reason why adults should not also be protected by MMR vaccination.

Another possibility can lie in the strength of the specific immune response to the SARS coronavirus, which is known to vary with age. In those patients suffering from severe SARS (20%), a biphasic clinical pattern was noted (15). After an initial phase of fever and respiratory symptoms, these patients experience spontaneous improvement. However, after 8 days a second phase starts, which is characterized by more severe respiratory symptoms (i.e. ARDS) and diarrhea (see Fig. 2). It has been shown that the second phase is unrelated to viral replication, but may be related to immunopathological damage (15). In children, it seems that the second phase

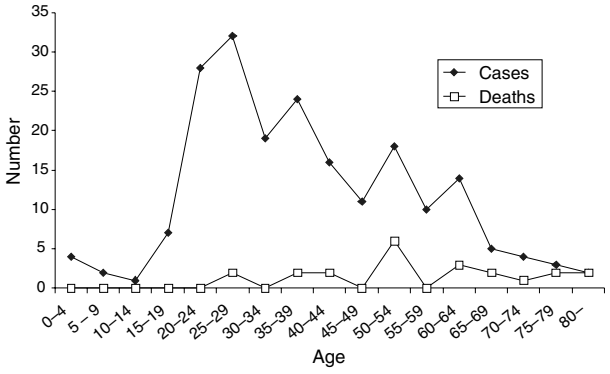

Fig. 1. Probable SARS cases and deaths in Singapore, during March 1 to April 28, 2003 (n = 200). (Source: Ministry of Health, Singapore).

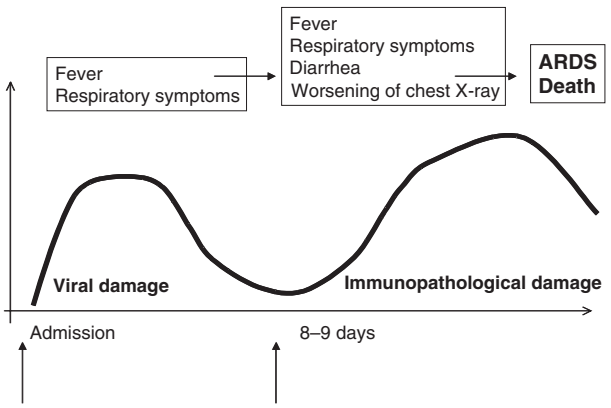

Fig. 2. The biphasic pattern of severe SARS.

does not occur, which can be the result of low immune response to the virus. Children can develop the mild first phase, but seem to be protected against the severe second phase of ARDS.

An explanation for this is unknown at the moment, but it could be the result of differences in macrophages features between adults and children. From an anatomopathological study on postmortem lung samples of SARS patients, a giant-cell infiltrate was seen with a pronounced increase in macrophages (CD68-positive cells) in the alveoli and the interstitium of the lungs (16). This infiltrate is different from the infiltrate seen in non-SARS ARDS, which comprises activated neutrophils (and has increased levels of interleukin 8), and which can occur in both adults and children (17). Therefore, it seems that activated macrophages play an important role in severe SARS. The lack of activation of macrophages by SARS-CoV could be the reason why children do not develop severe SARS (i.e. ARDS during the second phase). A possibility could be that children lack expression of the receptors for SARS-CoV on their macrophages. Although, children are vulnerable to non-SARS coronaviruses, it could be that the SARS-CoV uses different receptors. It has been shown that the first step in HCoV-229E infection is binding of the trimeric 200-KDa viral spike glycoprotein (S) to its receptor on human cells, identified as human aminopeptidase N (hAPN, CD13) (18). SARS-CoV likely uses other receptors to penetrate into macrophages. It would be of worth to focus research on the differences in macrophage features between adults and children during infection with SARS-CoV.

SARS and childhood asthma

During the outbreak of SARS in Singapore, there did not appear to be an increase in asthma exacerbations in children (this was likewise confirmed by our colleagues in Hong Kong). On the contrary, the incidence of acute respiratory infections and acute asthma attacks (triggered by respiratory viruses) declined dramatically. We saw little of the usual influenza and respiratory syncytial virus infections. We attribute the decrease in acute respiratory infections and acute asthma attacks to the changes Singaporeans have had to make to their lifestyle. These changes included the closure of schools for a period of time, stepped-up public hygiene measures and the wearing of facemasks.

Worldwide, several health care workers have been reported to develop SARS after caring for patients with SARS. These health care workers were present during aerosol-generating procedures performed on patients with SARS, suggesting that aerosol-generating procedures may increase the risk of SARS transmission (19). Procedures capable of stimulating cough and promoting the generation of aerosols include administration of aerosolized medication treatment, diagnostic sputum induction, bronchoscopy, airway suctioning and endotracheal intubation. As a result, in our institution, we only use bronchodilators delivered by metered dose inhalers with spacer devices instead of nebulizers in the treatment of acute asthma exacerbations.

It appears that SARS-CoV does not induce bronchial hyperreactivity or eosinophilic inflammation in children to an extent to induce asthma attacks in children. In contrast, non-SARS coronaviruses, have been linked to acute asthma in children (20, 21) and can induce eosinophilic inflammation of the lower airways (22, 23).

However, as SARS is a new epidemic, we should be careful with our conclusions. In Singapore, effective measures were instituted that prevented the spread of SARS within the community. It may be possible that should the virus be spread to a larger scale than what has been experienced among children (e.g. in schools), SARS-CoV triggered asthma exacerbations may occur.

Conclusion

SARS appears to be a disease primarily afflicting adults. The reasons for this are still unknown. A much dreaded possibility is that it could in the future similarly affect children. For now, at least, we can infer from our observations that SARS does not have a significant impact on childhood asthma, and that there is no indication to radically change treatment strategies for asthmatic children. There are however many urgent questions that are in need of answers: Why does SARS preferentially affect adults? Are there differences in immune response between adults and children to SARS? What is the future behavior of SARS? Will there be new mutations of this virus with increasing virulence and infectivity?

A new unexpected disease has occurred. As a result of intensive and collaborative worldwide research, enormous progression has been made in the understanding of this condition within a very short period of time. Much more work is needed, however, in our continued battle with our new enemy.

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Appendix

Recently, a metallopeptidase, angiotensin-converting enzyme 2 (ACE2), isolated from SARS coronavirus (SARS-CoV)-permissive Vero E6 cells, that efficiently binds the S1 domain of the SARS-CoV S protein, was identified as the receptor of the SARS-CoV (1–3). Inhibition studies of binding by antibodies developed against peptides from S, suggest that the receptor-binding domain is located between amino acid residues 303 and 537. These results also confirm that ACE2 is a functional receptor for the SARS virus and may help in the elucidation of the mechanisms of SARS-CoV entry and in the development of vaccine immunogens and entry inhibitors (4).

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