ORIGINAL ARTICLE

VIRUSES ASSOCIATED WITH ACUTE EXACERBATION OF BRONCHIAL ASTHMA AMONG CHILDREN IN UNIVERSITY MALAYA MEDICAL CENTRE

Rakhee Yadav

1. Hospital Tengku Ampuan Rahimah, Jalan Langat, 41200, Klang, Selangor Darul Ehsan, Malaysia

Abstract

Viruses have known to be an important cause of asthmatic exacerbations. A cross sectional study to identify the prevalence of virus in acute exacerbation of asthma in University Malaya Medical Centre (UMMC). In this study 103 known asthmatic children between the ages of 2-12 years were analysed for presence of virus. The throat swabs and nasopharyngeal aspirates were taken and analysis was done for identification of virus. Among the children 60% had a family history of asthma, 39% allergic rhinitis and only 17% had eczema. Majority (80%) of these children were diagnosed with asthma before the age of 5. At least 70% were under follow up for their asthma, 32% in UMMC paediatric asthma clinic, 20% by private paediatricians and 17% by a general practitioner and 31% had no follow up. More than half (52%) of them had partially controlled asthma and 54% presented with moderate exacerbation of asthma. The main presenting complaints were coryza (84%) and shortness of breath (88%). About 59% of the patients were treated as out-patients. Twenty two percent (22%) had viruses detected during their exacerbation. The virus identified were mainly rhinovirus (15%), respiratory syncytial virus (5%) and bocavirus plus metapneumovirus (2%). Majority of the patients were treated as outpatient (58%) and only two patients were admitted in the paediatric intensive care unit.

Key words: bronchial asthma, exacerbation, severity, virus isolation

Corresponding Author: Rakhee Yadav, 14 Jalan USJ 3/1f, 47600 Subang Jaya, Selangor, Malaysia
Email: rakheey@yahoo.com

Introduction

Asthma is an important cause of chronic respiratory disease worldwide. In the latest International Study of Asthma and Allergies in Childhood (ISAAC III), it is estimated that the prevalence of asthma in Malaysia has increased from 6.4% to 9.4% in children aged 6-7 years and from 9% to 13% in children aged from 13-14 years. Asthma control is very important in preventing asthma morbidity and mortality. As part of the Global Initiative for Asthma (GINA) guidelines in maintaining well-controlled asthma is the prevention of asthmatic exacerbations. Exacerbation of childhood asthma is a common acute presentation in general practices and emergency departments.
departments in the developed world. The majority of these children are not hospitalized but the exacerbation is associated with significant cost and morbidity. Despite many studies, the cause of most exacerbations of asthma remains controversial. Exacerbations can be defined as the presence of either one of the following based on the Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations:

A definition of a mild asthma exacerbation is not justifiable with present methods of analysis, because the symptoms or changes in flow rates during these episodes will be only just outside the normal range of variation for the individual. The definition of a moderate asthma exacerbation should include one or more of the following: deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization. ER visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids. The definition of a severe asthma exacerbation for clinical trials should include at least one of the following:

(a) Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.

(b) A hospitalization or ER visit because of asthma, requiring systemic corticosteroids.

In children, most of the exacerbation is associated with viral infections and these are probably the most difficult to treat as these exacerbations are not responsive to oral corticosteroids. Respiratory viruses are known major contributor to morbidity and mortality worldwide. Recent work in asthma has implicated human rhinoviruses as an important cause of asthmatic exacerbations but a variety of respiratory viruses are known to cause acute respiratory infections, including the common cold, bronchiolitis and pneumonia in humans.

In children, most of the exacerbation is associated with viral infections and these are probably the most difficult to treat as these exacerbations are not responsive to oral corticosteroids. Respiratory viruses are known major contributor to morbidity and mortality worldwide. Recent work in asthma has implicated human rhinoviruses as an important cause of asthmatic exacerbations but a variety of respiratory viruses are known to cause acute respiratory infections, including the common cold, bronchiolitis and pneumonia in humans.

The major pathogens that are known to be responsible are Respiratory Syncytius (RSV), Human Rhinovirus (HRV), Human Metapneumovirus (HMPV), Human Parainfluenza virus (HPIV), Enterovirus (EV), Influenza viruses (InfV), Adenoviruses (AdV), and Human Boca virus (HBoV). The mechanisms responsible for viral-induced exacerbations remain uncertain. Proposed mechanisms include direct infection of the lower respiratory tract, the inflammatory response to viruses, increases in bronchial responsiveness and up-regulation of intercellular adhesion molecule-1 expression in bronchial epithelium.

Respiratory viruses are also well recognized as major triggers of acute exacerbations of asthma in children and adults, resulting in frequent outpatient visits and hospitalisations. Although a connection between upper respiratory infections and asthma has long been recognised, the potential importance of the association was probably underestimated until relatively recently when it was shown that 85% of asthma attacks in children and 44% in adults are precipitated by upper respiratory infections. An increasing body of evidence supports the hypothesis that these infections cause a greater degree of morbidity in asthmatic subjects than in the
healthy population, emphasizing a discrepancy in the antiviral response of asthmatics. There is very little published data regarding the presence of different types of viruses in asthmatic children in Malaysia. The objective of this study is to determine the types of viruses implicated in acute exacerbation of bronchial asthma in children presenting to University Malaya Medical Centre (UMMC) and to determine if there was an association between virus isolation and the severity of asthmatic exacerbation.

Materials and methods

A cross-sectional study conducted over a one year period, from November 2010 until November 2011 in University Malaya Medical Centre (UMMC). All children between the ages of 2 years to 12 years with acute exacerbation of bronchial asthma in the Paediatric Trauma & Emergency (UMMC), General Paediatric Wards and Paediatric Intensive Care Unit of UMMC were included in the study. A face to face interview using a questionnaire was used in the study and convenience sampling was used in the selection of the patients. One hundred and three (103) patients were interviewed and throat swab samples for virology were collected from all of them. The sample size calculated was 84 patients using a confidence level of 95%, margin of error 10%, population size of 624 and response distribution 50%. The inclusion criteria were all children between 2 to 12 years of age with acute exacerbation of bronchial asthma who had been previously diagnosed with bronchial asthma and the exclusion criteria was children below 2 years or above 12 years of age, children whose parents or guardians refused consent for the study and also children diagnosed with asthma but presenting for other reasons without any exacerbation of asthma.

For children above 6 years old a nasal and throat swab was taken by the doctor. For the younger children a nasopharyngeal aspirate was taken by the nurses during suction. Only sterile Dacron/polyester swabs with plastic shafts were used. Calcium alginate swabs or swabs with wooden sticks were not used as they could contain substances that inactivate some viruses and inhibit PCR testing. Staff nurses conducted the suction and aspiration of nasopharyngeal aspirations using the routine sterile method with suction tubing connected to a mucous extractor and a suction pump with pressure of 50-100 mmHg. The samples were sent to the virology laboratory for identification.

Statistical analysis was carried out using SPSS version 20 (PASW) and Microsoft Excel database. A p value of < 0.05 was taken as significant. Descriptive analysis was performed on the data that was obtained and Chi square test was used to determine association between categorical variables.

Results

During the study period there were 767 number of visits for asthma exacerbations in children between 2-12 years range in the UMMC Paediatric Trauma & Emergency Unit and the wards. Overall there were a total of 624 patients seen and only 124 patients were recruited for the study using a convenience sampling. However the data from 21 children was incomplete and so only 103 children were included in the study. Most of the patients were Malays 76 (74%), followed by Indian 18 (17%) and the Chinese were 9 (9 %). There were more males 60 (59%) than females 43 (41 %). About 48% were between 2-5 years of age, 30% were 6-9 years of age and 22% were
10-12 years of age. Only 42 (41%) of these children were ever breast fed and 56 (54%) had at least one parent who smoked.

**Figure 1. Atopy among Immediate Family members of the patient**

The family history of atopy such as asthma, allergic rhinitis and eczema in the immediate family members of the index patients showed that 59% of patients had more than one family member with asthma, 29% with allergic rhinitis and 17% with eczema.
Table 1. Family history of atopy

<table>
<thead>
<tr>
<th>History of atopy</th>
<th>p value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>0.86</td>
<td>0.92 (0.21-4.16)</td>
</tr>
<tr>
<td>Mother</td>
<td>0.68</td>
<td>1.61 (0.42-6.19)</td>
</tr>
<tr>
<td>Sibling</td>
<td>0.47</td>
<td>0.79 (0.17-3.65)</td>
</tr>
<tr>
<td>&gt;1 member</td>
<td>0.60</td>
<td>1.00 (0.42-2.37)</td>
</tr>
<tr>
<td>None</td>
<td>0.60</td>
<td>0.91 (0.14-6.14)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>0.48</td>
<td>0.21 (0.02-1.76)</td>
</tr>
<tr>
<td>Mother</td>
<td>0.23</td>
<td>0.76 (0.09-5.88)</td>
</tr>
<tr>
<td>Sibling</td>
<td>0.37</td>
<td>0.22 (0.02-2.39)</td>
</tr>
<tr>
<td>&gt;1 member</td>
<td>0.64</td>
<td>1.81 (0.65-5.05)</td>
</tr>
<tr>
<td>None</td>
<td>0.64</td>
<td>0.12 (0.01-1.43)</td>
</tr>
<tr>
<td>Eczema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mother</td>
<td>0.89</td>
<td>-</td>
</tr>
<tr>
<td>Sibling</td>
<td>0.04</td>
<td>-</td>
</tr>
<tr>
<td>&gt;1 member</td>
<td>0.13</td>
<td>0.29 (0.07-1.15)</td>
</tr>
<tr>
<td>None</td>
<td>0.14</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1 shows that asthma was the most common atopic condition amongst family members. However, family history of atopy was not associated with severity of asthmatic exacerbation as can be seen in the table below (p>0.05).

Figure 2. Age at diagnosis of asthma

![Age at diagnosis of asthma](image)
Figure 2 illustrates the age at first diagnosis of asthma in index patients. About 80% of the patients were diagnosed before the age of five years. There was only one patient diagnosed at one year of age and that patient had a strong family history of asthma with a history of recurrent wheezing in infancy. Only 21% of patients were diagnosed after the age of five years.

Overall, 69% had minimal follow up, whether it was with a general physician or private paediatrician. About one third (32%) of the patients had regular follow up in the UMMC paediatric asthma clinic. Thirty one percent (31%) of patients did not have any follow up and some of these patients bought the asthma medications regularly from private pharmacist, practicing a self-care.

In terms of asthma control about 29% were controlled, 52% were partly controlled and 19% were uncontrolled. Most of the patients were from the partly controlled group with less than one third being controlled. It was noticed that 22% of patients were seen with acute exacerbation of asthma. Majority (78%) of the patients had no virus detected but virus was detected in 22% of the patients. Rhinovirus was detected in 15%, RSV in 5% and bocavirus with human metapneumovirus in 2%. Interestingly, both cases of bocavirus had co-infection with human metapneumovirus.

Figure 3. Virus isolation over the various ages

Figure 3 shows that rhinovirus is present throughout the different ages in childhood. Whereas RSV was only seen in children below the ages of six, the combination of bocavirus with human metapneumovirus was seen in two children, two and six years old.
Figure 4. Virus isolation and severity of exacerbation

![Bar chart showing virus isolation and severity of exacerbation](image)

Figure 4 describes the severity of exacerbation for each virus isolated. The two patients with combined bocavirus and human metapneumovirus both were of the mild category. Rhinovirus had mostly moderate severity but two of the six patients with severe exacerbation had rhinovirus isolated. RSV was associated with mainly moderate exacerbations of asthma (n=4).

Patients were asked about the presenting complaints during these asthmatic exacerbations. Although none were significantly associated with severity of asthma about eighty four percent (84%) of patients complained of cough and cold (coryzal symptoms) (Table 2).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes</th>
<th>No</th>
<th>P value</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>49 (48%)</td>
<td>54 (52%)</td>
<td>0.75</td>
<td>1.14 (0.49-2.63)</td>
</tr>
<tr>
<td>Coryza</td>
<td>86 (84%)</td>
<td>17 (16%)</td>
<td>0.84</td>
<td>0.89 (0.29-2.74)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>91 (88%)</td>
<td>12 (12%)</td>
<td>0.83</td>
<td>0.87 (0.25-3.02)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>58 (56%)</td>
<td>45 (44%)</td>
<td>0.31</td>
<td>0.65 (0.29-1.48)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (4%)</td>
<td>99 (96%)</td>
<td>0.25</td>
<td>3.97 (0.376-41.99)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (11%)</td>
<td>92 (89%)</td>
<td>0.90</td>
<td>0.92 (0.24-3.47)</td>
</tr>
</tbody>
</table>

Most of the patients (73) said that the cause of their current asthma exacerbation was an upper respiratory infection which related to the coryzal symptoms reported by patients as their chief complaint. The second most common trigger reported was cold weather or cold drinks. (13). Only 5% of patients had exercise induced exacerbations.

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More than half (58%) of the patients were discharged from the Paediatric T & E Unit after presenting with exacerbation of asthma. Among those admitted 43 (42%), only two patients were admitted to the paediatric intensive care unit for 3 and 4 days respectively. There were no deaths noted among patients admitted.

Chest X rays were done for 32 (82%) patients. Of those done, 9 (8%) were reported normal, 19 (18%) reported as pneumonia and 2 (2%) with bronchiolitis.

**Discussion**

This study identifies viruses isolated from children presenting with acute exacerbation of bronchial asthma in UMMC. Although there are no such studies in Malaysia similar studies have been done overseas. In this study 80% of the children were diagnosed with asthma before the age of 5 years and only 29% of them were controlled. It was also noticed that 59% of the children had at least one member of the family who had asthma. About one third (32%) had regular follow up and about one third of them (31%) had no follow up at all. Viruses were isolated in 22% of the patients who presented with acute exacerbation of asthma. However, the presence of virus in other studies was much higher (51% and 53%) as reported elsewhere.

The low pick up rate in this study could be due to convenience sampling and the smaller patient population in this study. Rhinovirus was seen in 15%, RSV was seen in 5% and Bocavirus with human metapneumovirus in 2%. In other studies the presence of rhinovirus was much higher 35%, 52%, 40% and 63%. Bocavirus is a new virus that has recently been found to be associated with asthmatic exacerbations. It was also noticed in this study that rhinovirus was seen in the whole age range (2-12 years) whereas RSV was seen only in children below 6 years. In terms of severity, those patients infected with rhinovirus showed moderate to severe asthmatic exacerbations. The presenting complaint of these patients was mainly coryza (84%). Majority of the patients were treated as out-patients (58%) and only two patients were admitted in the paediatric intensive care unit. Viral isolation among patients with asthma exacerbations did not predict severity and outcome of asthma exacerbation in this study.

**Conclusion**

Twenty two percent of children with asthma exacerbation in UMMC were associated with viral infections (p >0.05). At least 70% were under follow up for their asthma, and 31% had no follow up. More than half (52%) of them had partially controlled asthma and 54% presented with moderate exacerbation of asthma. The virus identified were mainly rhinovirus, respiratory syncytial virus, and bocavirus with metapneumovirus.

**Acknowledgement**

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