Molecular Study of Respiratory Syncytial Virus, Human Rhinovirus and Human Metapneumovirus, Detected in Children With Acute Wheezing

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ABSTRACT

Background: Viruses are known to cause the majority of acute respiratory infections. A great deal of evidence indicates that the etiology of most cases of wheezing in children, like asthma or bronchiolitis, is also linked to such respiratory infections.

Objectives: We assessed the prevalence of three common viruses including; respiratory syncytial virus (RSV), human rhinovirus (HRV), and human metapneumovirus (hMPV), in children with acute wheezing.

Patients and Methods: Ninety six wheezy children, 48 males (50%) and 48 females (50%) under the age of 5 years, were enrolled in the study. All patients visited as outpatients or inpatients when referred to the Mofid Children's Hospital, in Tehran, from September 2009 to March 2010. A nasopharyngeal sample was taken from each child's nostril and the three viruses were detected by a molecular polymerase chain reaction method (PCR).

Results: Out of 96 patients, 63 cases (64.8%) had a positive PCR test for at least one virus. Prevalence of each virus including RSV, HRV and hMPV alone or in combination were 44 (45.8%), 13 (13.5%) and 6 (6.3%), respectively. There were no significant relationships between; age, prematurity, fever, respiratory distress and the existence of any kind of virus in the nasopharynx.

Conclusions: Our study revealed that the prevalence of these three viruses in the nasopharyngeal secretions of children suffering from acute wheezing was similar to other studies. The results of this study concluded; PCR assay is a widely available and rapid method to detect the viral etiology which induces wheezing in children in Iran, and the study also provides a baseline for future studies about the clinical importance of this relationship.

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1. Background

Respiratory viruses are known to cause most acute respiratory infections (ARI) (1). The major viruses are: respiratory syncytial virus (RSV), human rhinovirus (HRV), Parainfluenza virus, Influenza virus, Adenovirus, Enterovirus, and recently known viruses such as, human Metapneumovirus (hMPV), and human bocavirus (2, 3). Accumulated evidence indicates that the etiology of most cases of asthma, namely virus induced asthma, is linked to such respiratory infections (4, 5). Respiratory infections by RSV, HRV and hMPV have been implicated in the induction of wheezing and the exacerbation of asthma (6).

Epidemiologic data suggests that about 70% of infants have experienced an RSV infection by the age of one year, and 100% by the age of two years (7). RSV is known to be a major causative agent of acute wheezing in children and may be strongly associated with asthma development later in life (8).

HRV was long believed to be the most frequently detected pathogen in the common cold, but recently it has been reported that there is also a higher prevalence of this virus in children with exacerbated asthma symptoms, than in those with well controlled disease (9, 10).

hMPV was first identified in 2001, and was reported to be one of the organisms of ARI in children (11, 12). Many epidemiologic studies have shown that, hMPV similar to RSV, is associated with bronchiolitis and recurrent wheezing in children (13-15).

2. Objectives

Epidemiological surveys on the prevalence of the causative viruses in children suffering from ARI and acute wheezing in Iran are limited. Therefore, we conducted our study to detect RSV, HRV and hMPV using polymerase chain reaction (PCR) on the nasopharyngeal secretions of children under 5 years of age, referred to one of the main children’s hospitals in Tehran with acute wheezing illness.

3. Patients and Methods

A total of 96 children experiencing wheezing symptoms, under the age of five years, were enrolled in the present descriptive study. All of the children who were referred to the Mofid Children’s Hospital with an ARI diagnosis and severe wheezing, during the cold months from September 2009 to March 2010, were seen as either outpatients or inpatients. Predefined exclusion criteria included; patients with acute wheezing and a diagnos-
4. Results

We detected RSV, HRV and hMPV in the nasopharyngeal samples from 96 Iranian children, 48 males (50%) and 48 females (50%) with acute wheezing of whom 55 (57%) were referred as outpatients and the remaining 41 (43%) as inpatients. There were 33 (34%) patients who were diagnosed with acute bronchitis and 63 (67%) had a diagnosis of bronchial asthma. The prevalence of each virus including RSV, HRV and hMPV alone or in combination in the nasopharyngeal samples is shown in Table 2. Age distribution of the patients was; 59 patients (61.5%) under 1 year, 26 patients (27%) between 1 to 2 years, and 11 patients (11.5%) between 2 to 5 years.

Having a previous history of premature birth due to a high prevalence of RSV infection, was seen in 14 patients (14.6%), half of them gave a positive sample for RSV. Low grade fever (axillary temperature < 38.5°C) was seen in 58 patients (60.4%), moderate to high grade fever (axillary temperature ≥ 38.5°C) in 23 patients (24%) and the remaining 15 patients (15.6%) did not have a fever.

There were 42 patients (43.7%) who experienced respiratory distress and 54 patients (56.3%) that did not have any difficulty breathing. There were no significant relationships between the items above such as; age, prematurity, fever, respiratory distress and the existence of any kind of virus in the nasopharynx.

Table 2. Primers for PCR Used in This Study

<table>
<thead>
<tr>
<th>Virus Primer</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV/forward</td>
<td>5-TGG ACA AGT TGT TGA GGT TTA TGA ATA TGC-3</td>
</tr>
<tr>
<td>RSV/reverse</td>
<td>5-TCC TAT TTT GGT AGG CAT TCT-3</td>
</tr>
<tr>
<td>HRV/forward</td>
<td>5-GCA CTT CTG TTT CCC C-3</td>
</tr>
<tr>
<td>HRV/reverse</td>
<td>5-CGG ACA CCC AAA GTA G-3</td>
</tr>
<tr>
<td>hMPV/sense</td>
<td>5-CAT GCC CAC TAT AAA AGG TCA G-3</td>
</tr>
<tr>
<td>hMPV/primer L6</td>
<td>5-GGA ACA AGT TGT TGA GGT TTA TGA ATA TGC-3</td>
</tr>
<tr>
<td>hMPV/sense primer L7</td>
<td>5-A CCC CAG TCT TTC TTG AAA-3</td>
</tr>
</tbody>
</table>

Abbreviations: hMPV, human metapneumovirus; HRV, human rhinovirus; respiratory syncytial virus, RSV; respiratory syncytial virus

5. Discussion

We detected three major viruses in the samples obtained from 96 Iranian children with acute wheezing during seven months; RSV, HRV and hMPV. These three viruses were detected in about two thirds of the patients (65.8%), with RSV being the dominant virus (45.8%). Many studies have suggested that RSV is a major candidate as an inducer of acute wheezing in children, and some of these children may go on to develop bronchiolitis or pneumonia (16, 17).

Elhajja et al., demonstrated that RSV was the major etiology of bronchiolitis in children especially between 3-6 months and the combination of RSV and HRV was seen in 26% of the patients (18). Papadopoulos et al., demonstrated the presence of these viruses in 931 children under three years with acute wheezing; RSV was seen in 28.5%, HRV in 18.3% and hMPV in 6% of patients (19).

Although HRV has long been the most frequently detected pathogen in the common cold (9), Kotanimi-Syrijan et al. were the first to recognize that HRV was also associated with early wheezing as a risk factor for asthma (20). Other subsequent studies have confirmed that HRV is an important risk factor for recurrent wheezing in children (5, 21). In contrast to RSV, the initial data suggests that HRV may be a potential determinant for the response to prednisolone treatment in wheezing children (22, 23). These findings emphasize the importance of searching for HRV in addition to RSV as a potential etiologic of bronchiolitis.

Several research groups have reported that hMPV is also an etiologic agent of wheezing illness in children (24, 25) and in a study by García-Garcia et al., this virus was found to be the third most frequent virus after RSV and HRV in children under two years of age, with first incidence and recurrent wheezing (26). Moattari et al., in the only Iranian study, reported that in 120 children suffering from wheezing, hMPV was seen in about 20 patients (16.5%) (27). In spite of some previous studies that have emphasized that hMPV occurred predominantly in older children (28), in our study there was no significant age distribution between RSV and hMPV patients.

Although many other respiratory viruses can be detected by RT-PCR which can also induce wheezing in children, owing to budget restrictions, our study was limited to the detection of only: 1) RSV, the most common pathogen causing wheezing. 2) HRV, the virus that is probably the second most common etiology of wheezing induced by viruses. 3) hMPV, the novel virus that can be an important virus in the induction of wheezing.

We hope that with the advent of sensitive molecular testing, the clinical importance of pathogen detection becomes an increasingly practical method. For example is there any relationship between viral etiology of wheezy child and it’s specific treatment?

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Authors’ Contribution

[will be filled by author]

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A Molecular Study of Three Main Viruses

Khanbabaie GT et al.

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