Exercise induced bronchoconstriction in childhood asthma

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Chapter 2

Equal virulence of rhinovirus and respiratory syncytial virus in infants hospitalised with lower respiratory tract infection

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Published as brief report

ABSTRACT

Respiratory syncytial virus (RSV) and rhinovirus (RV) are predominant viruses associated with lower respiratory tract infection (LRTI) in infants. We compared the symptoms of LRTI caused by RSV and RV in hospitalised infants. RV showed the same symptoms as RSV, so on clinical grounds, no difference can be made between these pathogens. No relation between CT-value and length of hospital stay was found.
INTRODUCTION

Lower respiratory tract infection (LRTI) is the most frequent cause of hospitalisation in infancy and is most commonly caused by viruses\textsuperscript{1-4}. The respiratory syncytial virus (RSV) is the predominant virus classically associated with severe LRTI, needing hospitalisation in infancy\textsuperscript{1-4}. Besides RSV, the rhinovirus (RV) is an important cause of LRTI\textsuperscript{1-5}. Few studies have described the clinical pattern of RV LRTIs as compared to RSV LRTIs, but the results are inconsistent\textsuperscript{2-4}.

Little is known about the relation between the viral load and the clinical pattern of LRTIs in infants. Previous studies in hospitalised infants have only investigated RSV viral load and disagree on the relation between viral load and disease severity\textsuperscript{1,6}. The relationship between RV viral load and disease severity in hospitalised children has not been studied.

The objective of this study is to compare the prevalence and clinical pattern of viral pathogens in infants hospitalised for a LRTI. Secondary objective is to analyse the relation between viral load and disease severity.

METHODS

Patients and samples

Study data were prospectively collected from infants up till age 2, hospitalised in 2006 and 2007 with LRTI at a large teaching hospital in the Netherlands. A LRTI was diagnosed on clinical grounds with symptoms of rhinorrhea, cough, respiratory distress or wheezing with or without fever. Infants could be reincluded with a second LRTI.

Nasopharyngeal washings were taken from each patient upon admission. Viral pathogens were identified by using a multiplex Real Time -Polymerase Chain Reaction (RT-PCR). Viral load was determined by the number of amplification cycles needed for a positive PCR test (cycle threshold, CT)\textsuperscript{7}. CT-values of 40 and lower demonstrating a characteristic amplification plot, were considered positive. There is a significant inverse linear relationship between viral load and CT-value\textsuperscript{7}. Correlation between CT-values and length of hospital stay was analysed.

Clinical pattern

Clinical symptoms were assessed by a clinician and documented using a questionnaire. Data collection included; age, rectal temperature, rhinorrhea, respiratory distress, dietary intake, need for oxygen therapy (evaluated via transcutaneous oxygen saturation), infiltrative abnormalities in chest radiographs (analysed by a radiologist), administration of antibiotics and length of hospital stay.
Statistical analysis

We used a Chi-Square test, Fishers exact test, Mann-Witney U test and independent samples t-test (if normally distributed) to determine differences between groups. Correlations were calculated using Spearman correlation. A 2 sided value of $p<0.05$ was considered statistically significant. Analyses were performed with the Statistical Package for the Social Sciences (SPSS®) for Windows® version 15 (IBM, Chicago, IL, USA).

RESULTS

We included 120 infants with a LRTI requiring hospitalisation. Nasopharyngeal washings were tested positive with RT-PCR in 98 of the 120 cases (81.7%). Eleven infants had a dual infection (9.2%). RSV and RV were the most frequent viral pathogens; RSV was detected in 58 infants (48.3%), RV in 27 infants (22.5%) (table 1).

Table 1. Viral pathogens identified in the hospitalised infants.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Frequency</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory syncytial virus</td>
<td>58</td>
<td>48.3</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>27</td>
<td>22.5</td>
</tr>
<tr>
<td>Human Metapneumovirus</td>
<td>6</td>
<td>5.0</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>7</td>
<td>5.8</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>5</td>
<td>4.2</td>
</tr>
<tr>
<td>Influenza 3 virus</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Para Influenza 2/4 virus</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Para Influenza 1 virus</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Negative RT-PCR</td>
<td>22</td>
<td>18.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>131</strong></td>
<td></td>
</tr>
</tbody>
</table>

* 11 (9.2%) dual infections, consisting of RSV+RV (3/11), RSV+adenovirus (6/11), RV+hMP (2/11)

Clinical characteristics

We compared the clinical characteristics of the two most prevalent viral causes of LRTI; RSV (N=49) and RV (N=22). Dual infections were not included in the analysis. Median age at hospitalisation was 3.2 months (0.3-22.3), with no differences between both groups ($p=0.49$). Patients with a RSV infection tended to have more need for oxygen therapy compared to the patients with a RV infection, but the difference was not significant ($p=0.18$). No significant differences were found between the RSV and RV groups regarding fever, respiratory distress, reduced dietary intake, abnormalities in chest radiographs, administration of antibiotics and duration of hospital stay (table 2).
Three patients had an unknown status of oral food intake. Chest radiography was performed in 24 patients (15 in the RSV group, 9 in the RV group).

<p>| Table 2. Clinical symptoms of RSV and RV. |</p>
<table>
<thead>
<tr>
<th>RSV (N=49) [%]</th>
<th>RV (N=22) [%]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)*</td>
<td>2.6 (0.3-16.1)</td>
<td>3.6 (0.6-22.3)</td>
</tr>
<tr>
<td>Hospital stay (days)*</td>
<td>4 (2-18)</td>
<td>4 (2-15)</td>
</tr>
<tr>
<td>Fever</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Need for oxygen therapy</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>Abnormalities in chest radiographs</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Administration of antibiotics</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>Reduced dietary intake</td>
<td>71</td>
<td>55</td>
</tr>
</tbody>
</table>

*Age and length of hospital stay are displayed in median (minimum-maximum). Abbreviations used: RSV: respiratory syncytial virus, RV: rhinovirus

CT-value and clinical pattern
There was a statistically significant, but very weak correlation between CT-value and length of hospital stay (mean CT-value 28.5±4.9, median hospital stay 4 days (1-26), r=0.19, p=0.04). In the RSV LRTI group this correlation is significant but weak (r=0.28, p=0.05). In the RV LRTI group no correlation between CT-value and hospital stay was found (r=0.13, p=0.58).

CT-value in the 22 infants hospitalised with a RV LRTI was significant higher than in the 49 infants with a RSV LRTI (mean CT-value RV: 29.3±4.0, RSV: 25.4±4.2, p<0.01).

DISCUSSION
The main conclusion of this study is that we observed no significant difference in the clinical pattern of LRTI caused by RSV and RV. This implies that on clinical grounds, no difference can be made between RSV and RV infection. Also, no relation between CT-value and length of hospital stay was found.

Several studies have compared the clinical pattern of RV and RSV infection in infants hospitalised with a LRTI, yet the results are inconsistent. Midulla et al. compared the clinical pattern of RV and RSV infections in infants aged <12 months, hospitalised for bronchiolitis. They described a milder clinical pattern in infants with a RV infection, compared to RSV infection. In contrast, Papadopoulos et al. described that RV LRTI was associated with a more severe disease compared to RSV in infants aged <18 months, hospitalised with a LRTI. Korppi et al. retrospectively performed PCR on nasopharyn-
geal aspirates of infants aged <23 months, hospitalised because of wheezing. They concluded that RV-associated wheezing and RSV bronchiolitis have similar clinical patterns, but infants differed with regard to age, presence of atopic dermatitis and eosinophilia during infection. Our study showed that there were no significant differences in clinical pattern between hospitalised infants with RSV and RV infection, although infants with a RSV infection tended to have more need for oxygen therapy compared to the infants with a RV infection. This finding is consistent with the study of Korppi, in which lower saturation values in infants with RSV infection were observed.

The inconsistent results of previous studies can be due to differences in study population, age and criteria for hospitalisation. Moreover, prevalence and virulence of viral pathogens causing LRTI can vary regionally and can change over seasons and years.

In our study, a virus was detected in 81.7 % of the included infants, showing that the major causative pathogens of LRTI in infancy in our region were covered with the used multiplex RT-PCR. Other studies detected a virus in up to 73.3% of hospitalised children. Our results show that RSV (48.3%) was the most common pathogen, followed by RV (22.5%), which is consistent with other studies.

The viral load was evaluated by looking at the CT-value. The diagnostic value of the CT-value is unclear. Fodha et al. describe a positive correlation between RSV viral load and disease severity (determined by respiratory rate, duration of hospitalisation and need for intensive care unit admission), in hospitalised infants. In non-hospitalised infants, a relation between RSV viral load and disease severity (determined by a severity scoring model) was found as well. In contrast, there seems to be no association between RV viral load and disease severity. Also in our study, no relation between CT-value and length of hospital stay was found in infants with a RV LRTI. In the studied infants with a RSV LRTI, there is a significant, but weak correlation between CT-value and length of hospital stay. Mean CT-value was significantly higher in infants hospitalised with a RV LRTI compared to infants with a RSV LRTI, indicating a lower viral load in infants with a RV LRTI. The clinical implication of this finding remains unclear.

Several remarks can be made about our study. The design of our study was cross-sectional, prohibiting the analysis of the dynamics of the viral load in relation to the clinical pattern. Clinical symptoms of infants with a dual infection were not analysed because of the small number of dual infections and the heterogeneity of this group.

The results of our study are of clinical importance, as they show that the clinical pattern of infants hospitalised with an RV infection can be as severe as an RSV infection. Consequently, the need for identification of both pathogens is equally important, and medical management of infants hospitalised with one of these infections should be the same. Appropriate isolation measures to counter intramural transmission are as important in RV infections as in RSV infections. Many hospitals use immunofluorescence assay (IFA) to identify pathogens causing LRTI. IFA, although a rapid and sensitive test
for RSV, does not detect other predominant viral airway pathogens, such as RV. With the availability of RT-PCR, sensitive and specific detection of viral pathogens has become possible. The identification of a virus during a LRTI can aid the clinician to refrain from the use of antibiotics. Specific identification of pathogens causing LRTI is also important for the follow-up of children hospitalised with a LRTI, as LRTIs in infancy may play an important role in the development of asthma and/or atopic disease.

In conclusion, this study shows that the clinical pattern of infants hospitalised with a LRTI due to RSV and RV does not significantly differ. In addition, no relation between CT-value and clinical pattern is found in these infants. Further research needs to be done to study the relationship between the dynamics of the CT-value and the clinical pattern, especially in RV LRTIs.
REFERENCES
