High Incidence of Recurrent Wheeze in Children With Down Syndrome With and Without Previous Respiratory Syncytial Virus Lower Respiratory Tract Infection

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Background: Respiratory syncytial virus (RSV)-induced lower respiratory tract infection (LRTI) is associated with the subsequent development of recurrent wheeze. In a recent study, we found a high incidence (9.9%) of hospitalization for RSV-induced LRTI among children with Down syndrome (DS), indicating DS as a new risk factor for RSV-induced LRTI. In the current study, we aimed to investigate the development of long-term airway morbidity in children with DS after hospitalization for RSV-induced LRTI.

Methods: A combined retrospective cohort and prospective birth cohort of children with DS with a history of hospitalization for RSV-induced LRTI was studied (n = 53). Three control populations were included: children with DS without hospitalization for RSV-induced LRTI (n = 110), children without DS but with hospitalization for RSV-induced LRTI (n = 48), and healthy siblings of the previous 3 groups mentioned (n = 49). The primary outcome was physician-diagnosed wheeze up to 2 years of age.

Results: The incidence of physician-diagnosed recurrent wheeze in children with DS with a history of hospitalization for RSV-induced LRTI was 36%. Unexpectedly, up to 30% of children with DS without a history of RSV-induced LRTI had physician-diagnosed recurrent wheeze (no significant difference). In children without DS, a physician-diagnosed wheeze was found more frequently in children hospitalized for RSV-induced LRTI than healthy controls (31% vs. 8%, P = 0.004).

Conclusions: In this combined retrospective/prospective cohort study RSV-induced LRTI did not significantly contribute to the risk of recurrent wheeze in children with DS. An unexpected finding was that recurrent wheeze was very common among children with DS.

Key Words: recurrent wheeze, Down syndrome, respiratory syncytial virus (RSV), lower respiratory tract infection

(Pediatr Infect Dis J 2010;29: 39–42)

Respiratory syncytial virus (RSV) is the single most important cause of lower respiratory tract infections (LRTIs) in infants and young children. About 0.5% to 2.0% of infected children require hospitalization, but children with Down syndrome (DS) have an increased risk of being hospitalized for RSV-induced LRTI (9.9%). Between 41% and 72% of young children experienced recurrent episodes of wheezing after RSV-induced LRTI, however, to our knowledge recurrent wheeze in children with DS has not been previously studied.

Study of the pathophysiology of recurrent wheeze after RSV-induced bronchiolitis and the association with asthma in later life have yielded contradictory findings. Most studies show a transient relationship between RSV-induced bronchiolitis and recurrent wheeze, with wheeze no longer being associated with a history of RSV-induced bronchiolitis in school-age children. However, a few reports suggest that RSV is causally associated with the development of persistent asthma. In a recent study, we established that DS is an independent risk factor for hospitalization for RSV-induced LRTI and that children with DS also tended to have more severe disease. The aim of this study was to determine the incidence of recurrent wheeze after RSV-induced LRTI in children with DS.

METHODS

Study Participants

We included a retrospective cohort of children with DS with a history of hospitalization for RSV-induced LRTI (n = 30), who were being monitored by the Down Syndrome Study Group. These children, born between 1988 and 2007, attended the outpatient clinic of the pediatric department of either the VU University Medical Centre Amsterdam or the University Medical Centre Utrecht. Subsequently, a prospective longitudinal birth cohort study of children with DS, born between 2003 and 2005 was included as described in our previous article. This birth cohort consisted of 23 children with DS who had been hospitalized for RSV-induced LRTI. Thus, the total index group consisted of 53 children with DS who had been hospitalized for RSV-induced LRTI (DS+ RSV+). Three control groups were included, to differentiate between DS and hospitalization for RSV-induced LRTI as risk factors for recurrent wheeze (Fig. 1). The first control group (n = 110) consisted of children with DS from the same birth cohort as part of the index group, but without a history of hospitalization for RSV-induced LRTI (DS− RSV−). The second control group (n = 48) consisted of children without DS who had been hospitalized for RSV-induced LRTI (DS+ RSV−). These children were selected from the placebo group of a trial on corticosteroid use for RSV-induced LRTI. A third control group (n = 49) of healthy controls consisted of siblings (aged: 1–4 years) of the children from the other 3 groups studied (DS− RSV−). Children with hospitalization for RSV-induced LRTI had either a positive enzyme immunoassay for RSV, a positive direct immunofluorescence assay for RSV infection of epithelial cells in nasopharyngeal secretions or a positive viral culture for RSV.

Data Collection

A short standardized questionnaire was taken by 1 investigator (B.B.) from the primary physician to inquire whether signs of
airflow limitation had been noted upon physical examination and mentioned in the patient’s chart in at least 2 independent consultations or whether the child had ever been diagnosed with asthma. Second, parents were asked to complete a questionnaire on their children’s health in the first 2 years after hospitalization for RSV-induced LRTI or up to the age of 2 years in the case of controls who had not been hospitalized for RSV-induced LRTI. Extended Dutch versions of the standardized British Medical Council questionnaire and the European Community Respiratory Health Survey questionnaire were used to obtain data on the presence and frequency of wheezing. Information on confounding factors, such as parental smoking habits, a family history of atopic symptoms, gestational age, and number of siblings, were also collected. The primary outcome was physician-diagnosed recurrent wheeze. Secondary outcomes were parent-reported recurrent wheeze and physician-diagnosed asthma. Recurrent wheeze was defined as 2 or more separate episodes of wheeze in a period of 2 years. It was not studied how a diagnosis of asthma was made at this young age. Written parental informed consent was obtained for the collection of all data.

Statistical Analysis

Differences in baseline characteristics were compared using $\chi^2$ analysis. The percentage of physician-diagnosed recurrent wheeze or asthma or parent-reported recurrent wheeze was compared using $\chi^2$ analysis. For children with DS, logistic regression analysis was performed to evaluate the independent determinants of recurrent wheeze or physician-diagnosed asthma, including hospitalization for RSV-induced LRTI, sex, prematurity, patient eczema, number of siblings, parental smoking, and parental history of atopy. All statistical analyses were performed using the software program SPSS for Windows (version 12.0.2; SPSS Inc, Chicago, IL). A $P$ value of 0.05 was considered the limit of significance.

RESULTS

Study Population

Fifty-three children with DS who had been hospitalized for RSV-induced LRTI were compared with children with DS without RSV-induced LRTI ($n = 110$), children without DS who had been hospitalized for RSV-induced LRTI ($n = 48$) and healthy controls ($n = 49$). Baseline characteristics and risk factors for recurrent wheeze are given in Table 1. There were no significant differences in baseline risk factors for recurrent wheeze between the prospective and retrospective cohort of the index group (data not shown). The 2 cohorts were combined as 1 index group. Median age of hospitalization for RSV-induced LRTI in children with and without DS was similar (6 vs. 4.5 months, not significant). The significant difference in the presence of one or more siblings at home in the healthy control group was because this group was made up of the siblings of children in the other 3 groups.

RSV-Induced LRTI Does Not Have a Significant Effect on Recurrent Wheeze in DS

Physician-diagnosed recurrent wheeze in DS+ RSV+ and DS+ RSV− children was 36% and 30% respectively (not significant) (Fig. 2). Similar nonsignificant differences were found for parent-reported recurrent wheeze (42% vs. 32%) and physician-diagnosed asthma (11% vs. 9%, data not shown). No significant

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**FIGURE 1.** Selection of children in the analysis.

**Fig 1:**

**TABLE 1.** Baseline Characteristics and Risk Factors for Recurrent Wheeze

<table>
<thead>
<tr>
<th>DS+ RSV+</th>
<th>DS+ RSV−</th>
<th>DS− RSV+</th>
<th>DS− RSV−</th>
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<tr>
<td>n = 53</td>
<td>n = 110</td>
<td>n = 48</td>
<td>n = 49</td>
</tr>
<tr>
<td>Male sex</td>
<td>32 (60%)</td>
<td>56 (51%)</td>
<td>22 (46%)</td>
</tr>
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<td>Median age</td>
<td>6 (0–27)</td>
<td>4.5 (0–12)</td>
<td>7 (15%)</td>
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<td>Prematurity</td>
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<td>5 (9%)</td>
<td>9 (8%)</td>
<td>9 (19%)</td>
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<td>Parental atopy</td>
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*At time of RSV hospitalization, months (range).

**P < 0.05 for DS+ RSV− versus DS+ RSV+.

***P < 0.01 for DS− RSV− versus all other groups.

DS indicates Down syndrome, RSV, respiratory syncytial virus.

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**FIGURE 2.** Incidence of recurrent wheeze.
The results of this study show that children with DS have a high risk of recurrent wheeze independent of a history of severe RSV-induced LRTI. Previously described factors associated with recurrent wheeze, such as family size, parental smoking, and atopy, did not have a significant effect on the outcome of recurrent wheeze or asthma in children with DS, although this study was not powered to demonstrate more subtle effects. Different pathophysiological mechanisms could underlie the generally increased risk of recurrent wheeze among children with DS. First, airway physiology may be abnormal in children with DS: a high incidence of airway anomalies have been reported, with laryngomalacia and tracheomalacia being the most frequent endoscopic findings, and abnormalities in lung function or airway hyper responsiveness, as well as abnormal thymus development and function, children with DS have a low absolute number of B-cells and T-cells, especially in the first 2 years of life. The defective T-cell or vivo proliferative responses to nonspecific and antigenic stimuli, cytokine production, and NK-cell responses detected in individuals with DS are thought to be involved in the increased susceptibility of these individuals to infectious pathogens. In our study, all the wheezing episodes reported by the parents occurred in combination with a common cold. Therefore, the high incidence of RSV-induced LRTI and recurrent wheeze in children with DS could reflect a generally defective defense against respiratory viral pathogens. In conclusion, we hypothesize that children with DS have a combination of pre-existent lung abnormalities, genetic factors, and immunologic deficits that make them more susceptible to respiratory viruses and subsequently results in a high incidence of both RSV LRTI and recurrent wheeze in a parallel manner rather than a serial one.

This study has potential methodologic limitations. First, this study was not powered to detect small, but relevant effects of RSV-induced LRTI on recurrent wheeze. However, it is emphasized that there were virtually no differences in outcome between children with DS and without RSV-induced LRTI. Second, parent-reported wheeze might be biased because of the subjectivity of reporting symptoms. Recall bias could play a role in the high incidence of recurrent wheeze in the group of children without DS who had been hospitalized for RSV-induced LRTI because the parents of these children had kept a daily log on respiratory symptoms for a different study. For that reason we used physician-diagnosed wheeze as primary outcome, being based on written information from the patient’s chart and therefore not prone to recall bias. Third, we can not exclude the possibility that the high incidence of recurrent wheeze in children with DS who have been hospitalized for RSV-induced LRTI is related to a history of RSV-induced LRTI which did not require hospital admission. Finally, we limited the study to children up to 2 years of age and thus can say nothing about the persistence of wheezing. Prolonged follow-up of children with DS aged 6 to 10 years may provide more insight into the long-term respiratory prognosis of children with DS who have been hospitalized for RSV-induced LRTI.

In conclusion, RSV-induced LRTI does not have a significant effect on the incidence of recurrent wheeze in children with DS. An unexpected finding was the high incidence of recurrent wheeze in children with DS without a history of severe RSV-induced LRTI. It is conceivable that the high incidence of recurrent wheeze and the high incidence of hospitalization for RSV-induced LRTI in children with DS have a common etiology. Abnormal lung function or airway hyper responsiveness, as well as abnormal immunologic maturation, could play a decisive role in the development of long-term airway morbidity in children with DS. Our results prompt future studies on lung development and immunology in DS to give better insight in the pathophysiologic mechanism of RSV LRTI and recurrent wheeze in this specific population.
ACKNOWLEDGMENTS

The authors thank P. Winkler, researcher at the University Medical Centre Utrecht, The Netherlands, for her excellent technical support.

REFERENCES