Transient Tachypnea of the Newborn is Associated with an Increased Risk of Hospitalization Due to RSV Bronchiolitis

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Running head: Transient Tachypnea of the Newborn and RSV

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Abstract

Background: Transient tachypnea of the newborn (TTN) is a self-limiting respiratory disorder, resulting from a failure to clear the lungs of perinatal fluid. As similar pathophysiological features are present in children with respiratory syncytial virus (RSV) bronchiolitis, we hypothesized that these two conditions may be connected.

Methods: This was a population-based cohort study that included all children born in term (≥37 weeks of gestation) without congenital malformations in Finland between 1996 and 2015. Children diagnosed with TTN (ICD-10 code P22.1) after birth and children hospitalized due to RSV bronchiolitis (ICD-10 code J21.0) during first year of life were identified from the Medical Birth Register and National Hospital Discharge Register, respectively, and the data were linked. Logistic regression was used to analyze the association between these two conditions.

Results: Of the 1,042,045 children included in the study cohort, 16,327 (1.57%) were diagnosed with TTN at birth and 12,345 (1.18%) were hospitalized due to RSV bronchiolitis during the first year of life. The rate of RSV hospitalization was higher in children with a history of TTN compared to children without TTN diagnosis (260/16,327 [1.59%] vs. 12,085/1,025,718 [1.18%], respectively; P value <0.0001). After adjusting for gestational age at birth, mode of delivery, gender, birth weight, multiple births, older siblings, and maternal smoking, TTN was associated with increased risk for RSV hospitalization (OR 1.31; 95% CI 1.16-1.48).

Conclusions: TTN diagnosis after birth was associated with increased risk for RSV hospitalization during the first year of life.
Key words: Transient tachypnea of the newborn; Respiratory syncytial virus; Bronchiolitis; Risk factor
Background

Transient tachypnea of the newborn (TTN) is a self-limiting condition characterized by respiratory distress, which spontaneously clears in approximately 1-3 days (1). Estimated incidence of TTN after term deliveries (37-42 weeks of gestation) is 0.6% (2, 3). It has been associated with elective cesarean section, low gestational age at birth (GA), male gender, and low birth weight (2). While traditionally considered an isolated case of delayed activation of Na+-driven pulmonary fluid transport (4) without risk for recurrence or residual deficit of pulmonary function, the condition has also been associated with the development of childhood asthma and wheezing symptoms (5-7). The reason for this association has remained unclear, and the results of studies assessing the association between TTN and genetic polymorphisms (8, 9) and TTN and maternal asthma (10, 11), for example, have been inconsistent.

Respiratory syncytial virus (RSV) is the most common pathogen causing bronchiolitis in children (12). In developed countries, 2-3% of children <1 year of age are hospitalized due to RSV bronchiolitis (13, 14), and it is among the most common causes of hospitalization in infants. RSV infects primarily respiratory epithelial cells and, by causing respiratory tract fluid accumulation, results in a disease that ranges in severity from a mild upper respiratory tract infection to, at worst, a pulmonary disease leading to respiratory failure (12). Several risk factors for RSV hospitalization have been identified, such as premature birth, chronic pulmonary disease, and congenital heart disease, among the most important ones (12). However, most of the children hospitalized due to RSV are previously healthy (13, 14), and the factors contributing to increased disease severity in these children remain unclear.

Studies in animal models and cell cultures have shown that RSV decreases alveolar fluid clearance by inhibiting the Na+-driven pulmonary fluid transport (15, 16). As similar
pathophysiology is associated with TTN (4), we hypothesized that these two conditions of epithelial ion transport dysfunction might be connected, and that infants with a history of TTN might have an increased risk of severe RSV infection. In this population-based cohort study, we combined data from Finnish national registries to assess the risk of hospitalization due to RSV bronchiolitis in children with a history of TTN.

Methods

Study design

This was a population-based cohort study including all live children born in Finland during the study period from January 1996 to December 2015. Data on GA, mode of delivery, sex, birth weight, multiplicity, parity, maternal smoking, pregnancy-related maternal diagnoses (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes O14, O15, O20 and O21), and infant TTN diagnoses (ICD-10 code P22.1) were obtained from the Medical Birth Register (MBR). The MBR is a population-based registry that collects data on all live births and stillbirths at 22 weeks’ gestation or later and on infants who weigh 500 g or more, and it is complete after linkages to live births (Central Population Register) and stillbirths and infant deaths (Cause-of-Death Register). In addition, the National Hospital Discharge Register (NHDR) was used to identify all children in the study cohort discharged from hospital with a diagnosis of RSV bronchiolitis (ICD-10 code J21.0). NHDR is a registry that collects data on all patients discharged from hospital care in Finland. Data from these two registries were linked using a personal identity code, that is, a unique personal identifier assigned to each person living in Finland. No ethical permission was required for this study since it was based on register-based data and no registered person was contacted.

Statistical methods
To rule out the potential confounding effect of prematurity, we excluded all children born <37 weeks of gestation. In addition, children born with congenital anomalies (ICD-10 Q-diagnoses) were excluded. Included children were followed from birth to 1 year of age. Chi square test was used to compare the rates of RSV hospitalizations between children with and without history of TTN. To analyze the association between TTN diagnosis at birth and RSV bronchiolitis hospitalization during the first year of life, we performed a logistic regression analysis and calculated odds ratios (ORs) with 95% confidence intervals (CI) for RSV hospitalization. First, we performed univariate analyses for all the collected variables (GA, mode of delivery, sex, birth weight, multiplicity, parity as a proxy of the number of older siblings, maternal smoking during pregnancy, and pregnancy-related maternal diagnoses). In the final multivariate model, we included and adjusted the analysis for variables that were statistically significant in the univariate analyses (GA, mode of delivery, sex, birth weight, multiplicity, parity, and maternal smoking). We also performed subgroup analyses stratifying children according to the age at the time of RSV diagnosis (<6 months and 6-12 months). We calculated 95% CIs using the Wald method. All statistical analyses were performed with SAS software (version 9.3).

Results

During the study period, 1 163 414 children were born in Finland. Of these children, 69 518 were excluded from this study due to prematurity (<37 weeks of gestation) and 51 851 due to congenital anomalies (any ICD-10 Q-diagnoses). Of the remaining 1 042 045 children, 16 327 (1.57%) were diagnosed with TTN at birth and 12 345 (1.18%) were hospitalized due to RSV bronchiolitis during the first year of life. The rate of RSV hospitalization was higher in children with a history of TTN compared with children without TTN diagnosis (260/16 327 [1.59%] vs. 12 085/1 025 718 [1.18%], respectively; *P* value <0.0001). After adjusting for GA, mode of
delivery, gender, birth weight, multiple births, older siblings, and maternal smoking, TTN was associated with increased risk for RSV hospitalization (OR 1.31; 95% CI 1.16-1.48, Table 1). The association was statistically significant in both children aged <6 months (OR 1.24; 95% CI 1.08-1.42) and children aged 6-12 months (OR 1.65; 95% CI 1.26-2.18) at the time of RSV diagnosis.

Discussion
In this population-based registry study, we found an association between TTN diagnosis at birth and hospitalization due to RSV bronchiolitis during the first year of life. To our knowledge, this is the first report of association between these two conditions. In addition to identifying a novel risk factor for RSV hospitalization, we believe our findings raise concerns about the transitory nature of TTN and suggest that impaired alveolar fluid transport may be a more significant feature of RSV pathogenesis than previously thought.

There are previous reports on the connection of TTN and childhood asthma and wheezing symptoms during the first seven years of life (5-7), but the mechanisms of these associations have remained unclear. One potential explanation is the existence of a common genetic predisposition between these two conditions. However, studies assessing the role of maternal asthma in the development of TTN have provided inconsistent results (10, 11). Few studies have reported associations between genetic polymorphisms and TTN, specifically genes encoding for beta-adrenergic receptor (9) and progesterone receptor (17), while no such association was found with surfactant protein B polymorphisms studied (8). Maternal asthma is also a risk factor for RSV bronchiolitis (18, 19) and on the other hand, RSV bronchiolitis increases the risk for recurrent wheezing and childhood asthma (12). Therefore, our finding fits well with the existing literature, but further studies are needed to elucidate the underlying mechanisms and to better
understand the causality and interactions between genetic predisposition, TTN, RSV bronchiolitis, and recurrent wheezing/childhood asthma.

Our findings suggest that TTN is an independent risk factor for RSV hospitalization during the first year of life. It increases the risk for hospitalization to levels of well-characterized risk factors for RSV bronchiolitis, including maternal smoking during pregnancy, cesarean delivery and male gender (19). Consequently, TTN could be included in the assessment of risk profile for RSV hospitalization in an individual child. However, until the specific mechanisms for the association are elucidated further, it remains unclear whether it represents shared underlying risk factors (genetic or other) or if causality exists between TTN and RSV bronchiolitis. Causality between these two conditions could provide an indication for prophylactic treatment opportunities aiming at decreasing the risk for RSV hospitalization.

The strengths of this study include population-based national register material enabled by the register-based study design and detailed perinatal data available from MBR. A large sample size allowed us to take into account and adjust the analyses for several confounding factors, which further strengthens our findings. This study also has limitations. As in any register-based study, our study is as reliable as the registries employed. The MBR is a population-based registry that was established in 1987 and collects data on all live births and stillbirths. The NHDR was established in 1969 and collects the data on all patients discharged from inpatient care in Finland. Both registries have been validated through numerous epidemiological studies (20). In our study, RSV bronchiolitis was defined as an ICD-10 diagnosis of J21.0 at discharge and no data on RSV viral detection were available. However, it is likely that with most of the children with J21.0 diagnosis, viral confirmation was done either with antigen detection tests that were widely used in Finland during the whole study period, or with polymerase chain reaction (PCR)-based assays.
whereas other diagnoses were used in the context of bronchiolitis without RSV detection. Furthermore, in children <1 year of age, RSV accounts for >70% of bronchiolitis cases (12, 21). For these reasons, we believe that the lack of virologic data did not cause significant bias in our results. We excluded all children with congenital anomalies (any ICD-10 Q diagnosis) in order to avoid potential bias caused by including children with congenital heart diseases, chronic pulmonary conditions and other congenital anomalies that could increase the risk for RSV bronchiolitis. However, children diagnosed with other, non-congenital diseases during the follow up period were not excluded. Last, the analyses were not adjusted for maternal asthma as these data were not available.

In conclusion, we report a novel association between TTN at birth and RSV bronchiolitis during the first year of life. Our finding raises concerns about the transitory nature of TTN. We suggest that this association may be explained by defects in Na+-driven pulmonary fluid transport. Further studies are warranted to better understand underlying mechanisms.
References


10. Mendola P, Mannisto TI, Leishear K, Reddy UM, Chen Z, Laughon SK. Neonatal health of infants born to mothers with asthma. *Journal of Allergy and Clinical Immunology*. 2014;133:85-+


TABLE 1. Adjusted odds ratios and rates of hospitalizations due to RSV bronchiolitis during the first year of life in children with and without history of TTN stratified by age at the time of RSV diagnosis

<table>
<thead>
<tr>
<th></th>
<th>0-12 months</th>
<th>0-6 months</th>
<th>6-12 months</th>
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<tbody>
<tr>
<td>RSV bronchiolitis hospitalizations, n (%)</td>
<td>12 345 (1.18)</td>
<td>10 249 (0.98)</td>
<td>2096 (0.20)</td>
</tr>
<tr>
<td>Rate of RSV bronchiolitis hospitalizations in children with TTN diagnosis, %</td>
<td>1.59</td>
<td>1.27</td>
<td>0.32</td>
</tr>
<tr>
<td>Rate of RSV bronchiolitis hospitalizations in children without TTN diagnosis, %</td>
<td>1.18</td>
<td>0.98</td>
<td>0.20</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.31 (1.16-1.48)</td>
<td>1.24 (1.08-1.42)</td>
<td>1.65 (1.26-2.18)</td>
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RSV, Respiratory syncytial virus
TTN, Transient tachypnea of the newborn
OR, Odds ratio
CI, Confidence interval