Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age

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Background: Persistent childhood asthma is mainly atopy driven. However, limited data exist on the risk factors for childhood asthma phenotypes.

Objective: We sought to identify risk factors at the first severe wheezing episode for current asthma 7 years later and separately for atopic and nonatopic asthma.

Methods: One hundred twenty-seven steroid-naive children with the first severe wheezing episode (90% hospitalized/10% emergency department treated) were followed for 7 years. The primary outcome was current asthma at age 8 years, which was also analyzed separately as atopic and nonatopic asthma. Risk factors, including sensitization, viral cause, and other main asthma risk factors, were analyzed.

Results: At study entry, median age was 11 months (interquartile range, 6-16 months); 17% were sensitized, and 98% were virus positive. Current asthma (n = 37) at 8 years was divided into atopic (n = 19) and nonatopic (n = 18) asthma. The risk factors for current atopic asthma at study entry were sensitization (adjusted odds ratio [OR], 12; $P < .001$), eczema (adjusted OR, 4.8; $P = .014$), and wheezing with rhinovirus (adjusted OR, 5.0; $P = .035$). The risk factors for nonatopic asthma were the first severe respiratory syncytial virus/rhinovirus–negative wheezing episode (adjusted OR, 8.0; $P = .001$), first wheezing episode at age less than 12 months (adjusted OR, 7.3; $P = .007$), and parental smoking (adjusted OR, 3.8; $P = .028$).

Conclusions: The data suggest diverse asthma phenotypes and mechanisms that can be predicted by using simple clinical markers at the time of the first severe wheezing episode. These findings are important for designing early intervention strategies for secondary prevention of asthma. (J Allergy Clin Immunol 2017;140:988-95.)

Key words: *Allergy, atopy, bronchiolitis, child, eczema, rhinovirus, respiratory syncytial virus, sensitization, virus, wheeze, wheezing*

Rhinovirus-induced wheezing, atopic characteristics, and severe illness are currently the most important early risk factors for childhood asthma in young hospitalized wheezing children.[1-5] Persistent childhood asthma is mainly atopy driven.[1,2,4-9] The modified Asthma Predictive Index (API), which is based mainly on atopic characteristics, has been used widely to assess the risk of school-age asthma, regardless of the asthma phenotype.[10,11] There are studies investigating separately risk factors for atopic versus nonatopic asthma at school age.[8,12-14] These studies have shown that classical atopic risk factors and also those considered in the modified API were associated with atopic but not nonatopic asthma.[10] However, the study settings have been heterogeneous, being conducted on birth cohorts, and have not focused on the first wheezing episode. Awareness of which early risk factors predict atopic or nonatopic asthma in later childhood could also provide a novel approach into the mechanisms underlying childhood wheezing and asthma phenotypes.[15] Simple clinical markers would also offer a way to find early intervention strategies to prevent asthma.[16]

The development of viral diagnostics has led to good recognition of rhinovirus-induced early severe wheezing as an important asthma risk factor.[1,4,17-19] In addition, already at the first wheezing episode, cross-sectional studies have linked rhinovirus-induced wheezing to atopic characteristics.[2,3,17-20] However, the asthma risk associated with rhinovirus-induced early wheezing has been included in asthma predictive indices in a limited way. These findings have led to a suggestion that asthma risk could be evaluated and potentially modified by targeted pharmacologic intervention at the time of the first wheezing episode.[1,4,9,20,21] This is noteworthy because it has been shown that oral corticosteroid (OCS) treatment can decrease the risk of recurrent wheezing and asthma in hospitalized children with first-time wheezing affected by rhinovirus, eczema, or both.[1,4,9,18,20]

The aim of this study was to assess risk factors at the first severe wheezing episode in corticosteroid-naive children for school-age (age, 8 years) atopic and nonatopic asthma. Based on the previous literature, we hypothesized that the first rhinovirus-induced wheezing episode predicts later atopic asthma.[1-5,17-19,22,23]

METHODS

Subjects

This study consisted of the Vinku and Vinku2 studies (*vinku* means wheeze in Finnish), which used a similar follow-up protocol carried out in the Department of Pediatrics, Turku University Hospital (Turku, Finland).[1,4,18]

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Abbreviations used
API: Asthma Predictive Index
ICS: Inhaled corticosteroid
OCS: Oral corticosteroid
OR: Odds ratio
RSV: Respiratory syncytial virus

Recruitment for the Vinku study was carried out in 2000-2002,[1,4] and recruitment for the Vinku2 study was carried out in 2007-2010.[18] The original aim of both studies was to evaluate the effect of a 3-day course of oral prednisolone for an acute severe wheezing episode using a randomized controlled trial design. To the current long-term follow-up analysis, we included all the steroid-naive children aged 3 to 23 months with their first severe wheezing episode from both studies (Fig 1).[1,4,18] The exclusion criteria were use of inhaled corticosteroids (ICSs) or systemic corticosteroids before study entry, chronic nonatopic disease, and a need for intensive care.[1,18] The studies were approved by the Ethics Committee of the Turku University Hospital and commenced only after obtaining written informed consent from the guardians.

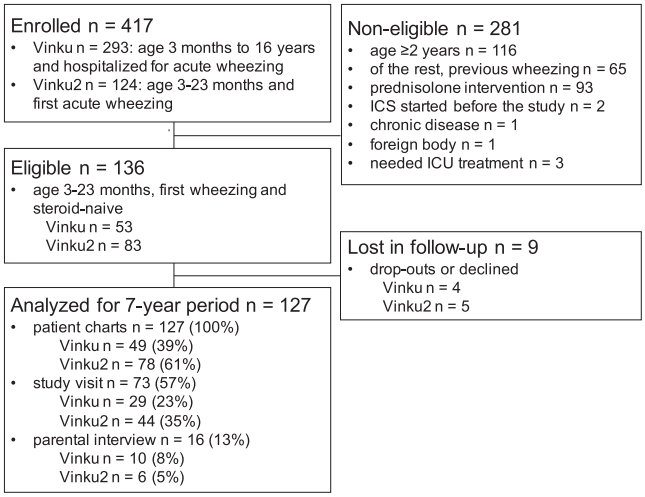

FIG 1. Study flow chart. *ICU*, Intensive care unit.

Study protocol

In both studies, at study entry, venous blood was drawn, and nasopharyngeal aspirate was collected, and then the children were randomized to be given either oral prednisolone or a placebo.[4] Study physicians (TJ, PL, and ML) recruited the patients to both studies and/or prospectively followed them at scheduled visits (2 weeks, 2 months, 12 months, 4 years [Vinku2 only], and 7 years). The children were examined at each visit, and parents were interviewed by using standardized questionnaires at long-term visits (see the parental questionnaire in this article's Online Repository at www.jacionline.org).[1,4,18,24]

For the current analysis, all (100% [127/127]) children were followed from patient charts for asthma symptoms, medications, and laboratory tests for the full 7-year follow-up period (Fig 1 and Table I).[4,9,18] In addition, 57% (73/127) of children attended the 7-year follow-up visit either in the Vinku study in 2007-2008 or in the Vinku2 study in 2014-2015, and parents of 13% (16/127) were interviewed by telephone at age 8 years (Fig 1). The study protocols were registered at ClinicalTrials.gov (Vinku: NCT00494624 and Vinku2: NCT00731575).

Virus, laboratory, and pulmonary function data

At study entry, the nasopharyngeal aspirates for viral diagnostics were drawn by using a standardized procedure.[25,26] The nasopharyngeal aspirates were analyzed for adenovirus; coronaviruses (229E, OC43, NL63, and HKU1); enteroviruses; human bocavirus; human metapneumovirus; influenza A and B; parainfluenza virus types 1 to 4; polyomaviruses WU and KI; rhinovirus types A, B, and C; and respiratory syncytial virus (RSV). In both studies PCR was used to detect all viruses, and additional serology was done for human bocavirus.[18,26,27] Also, the Vinku study used culture, antigen detection, and/or serology for adenovirus, enteroviruses, human metapneumovirus, influenza A and B virus, parainfluenza virus types 1 to 3, rhinovirus types A and B, and RSV.[26,27] Laboratory studies at study entry and age 8 years included allergen-specific serum IgE levels and blood eosinophil counts, which were measured by using routine diagnostics of the Central Laboratory of Turku University Hospital.

Long-term follow-up visit was arranged at age 8 years (Fig 1).[4] Flow-volume spirometry (Jaeger MasterScreen system [Jaeger GmbH, Würzburg, Germany] in Vinku and Medikro Spirometry Software [Medikro Oy, Kuopio, Finland] in Vinku2) was measured in both studies with a bronchodilatation test, as was spirometry, at baseline and 15 minutes after 400 μg of albuterol (Ventoline) administered by means of inhalation through a spacer (Babyhaler; both from GlaxoSmithKline, Brentford, United Kingdom). In Vinku2 a free running test designed to measure bronchial hyperreactivity in children was used, as was spirometry, at baseline and 1, 5, and 10 minutes after exercise testing.[11,28] The registered index was FEV_1. Families were instructed to withhold the child's regular asthma medications with ICSs during the preceding 4 weeks and to withhold salbutamol for 12 hours before spirometry. The test was rescheduled if the child was ill or taking salbutamol for asthma symptoms.

Outcome

The outcome of this study was the risk for current asthma at age 8 years, which was analyzed separately for atopic and nonatopic asthma. Risk factors were assessed at the time of the first severe wheezing episode (Table I).

Children were given a diagnosis of current asthma at age 8 years if they met 1 or more of the subsequent criteria during the preceding 12 months: reports from patient charts of doctor-diagnosed asthma and need for regular use of doctor-prescribed asthma therapy with ICSs for more than a month, use of OCSs for asthma exacerbations, acute asthma attack relieved by repeated use of bronchodilator, and/or hyperreactivity in spirometry defined as reversible airflow obstruction with an increase of 12% or greater in FEV_1 in the bronchodilatation test or a decrease of 15% or greater in the exercise challenge test.[11] Current atopic asthma at age 8 years was defined as asthma with laboratory-verified sensitization (95% [18/19]) or patient chart– and parent-reported allergy symptoms (5% [1/19], Table II). Nonatopic asthma was defined as asthma without these features. Children were in remission if they were without asthma symptoms and therapy within 12 months before the study visit and/or without hyperreactivity on spirometry at the study visit.

Definitions

A wheezing episode was defined as a sharp whistling sound in expiratory breathing together with expiratory distress.[11] Severe wheezing refers to the fact that 90% of the children were hospitalized and 10% were admitted to the emergency department of the tertiary hospital. Any sensitization was defined as positive IgE antibody results against common allergens (cutoff level of 0.35 kU/L for codfish, cow's milk, egg, peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus*; fluoroenzyme immunoassay, CAP FEIA, Phadiatop Combi [Phadia, Uppsala, Sweden]).[4,18] Aeroallergen sensitization was defined as IgE antibodies to any of the latter 8 allergens. Eczema was defined as a physician-made diagnosis with typical symptoms, including pruritus; typical morphology; and chronicity of disease.[11] In this article viral findings were combined into 3 subgroups according to the viral etiology of the first wheezing episode at study entry: the rhinovirus group (rhinovirus alone or with other viruses, with RSV included), the RSV group (RSV alone or with other viruses, with rhinovirus excluded), and the RSV/rhinovirus-negative group (other viruses or no viruses found).[1,4,29]