Wheeze in preschool children: the predictive value of episodic viral wheeze and multiple-trigger wheeze in the development of childhood asthma.

Published: 25-04-2019
Last updated: 12-04-2024

We aim to investigate the predictive value of the wheezing phenotypes EVW and MTW at preschool age (based on prospectively reported symptoms of wheezing, dyspnoea and cough or based on clinical assessments) and the predictive value of viral upper…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON48853

Source
ToetsingOnline

Brief title
WHEEP follow-up study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
wheeze

Research involving
Human

Sponsors and support

Primary sponsor: Amphia Ziekenhuis

Source(s) of monetary or material Support: Stichting Astmabestrijding;Wetenschapsfonds Amphia Ziekenhuis

Intervention

Keyword: Asthma, Episodic viral wheeze, Multiple trigger wheeze, Preschool children

Outcome measures

Primary outcome

The primary outcome measure is the predictive value of the preschool wheezing phenotype (diary based as wel as clinically based) in the development of childhood asthma.

Secondary outcome

The sensitivity and specificity of the following asthma predictive scores in our cohort will be evaluated: the Asthma Predictive Index (API) and the Prevention and Incidence of Asthma and Mite Allergy risk score (PIAMA).

Another secondary outcome measure is the predictive value of viral upper respiratory tract infections at preschool age in the development of asthma. The results of nasal swabs, collected in the previous study, will be compared to asthma status at the age of 6 to 8 years.
Moreover, we will study differences in microbiome at preschool age between children who develop childhood asthma and children who do not. In order to compare the microbiome at preschool age to the microbiome at the age of 6 to 8 years, throat swabs will be collected.

Study description

Background summary

Recurrent wheezing is common in preschool children. It shows more often a transient course over time than it results in the more persistent pattern of asthma in children over 6 years of age (1, 2). Based on these differences, the common perception is that preschool wheezing disorders are a heterogeneous group of syndromes with different pathophysiology. However, subsequent attempts to distinguish different clinical phenotypes have had little success, partly due to a lack of reliable data (3). In 2008, an ERS task force recommended the use of two pragmatic clinical phenotypes based on symptom patterns: *episodic viral wheeze* (EVW) and *multiple trigger wheeze* (MTW), although the task force acknowledged that this recommendation was based on little evidence and that it was likely to change when new evidence became available (4). EVW was defined as wheeze in discrete episodes, associated with a viral upper respiratory tract infection, whilst children were classified as MTW when they also wheezed in response to other triggers. Although this phenotype distinction appears straightforward, a Canadian study showed considerable variation between physicians in the phenotype assessment of the same patient vignettes (5). In addition, considerable within-patient phenotype switching has been reported in two prospective cohort studies in primary and hospital-based paediatric care, with up to 80% of phenotype changing in children with recurrent wheeze over a period of 1 to 2 years (6, 7).
Conversely, in two large population-based birth cohort studies, Spycher et al. recently reported a tendency of wheeze phenotypes to track in children who continued to wheeze between the ages of 2 and 7 years (8).
These conflicting findings underscore the limited evidence base for the concept of EVW and MTW (9).

Several predictive models have been developed in order to identify children that are most at risk of having persistent symptoms later in life, such as the Asthma Predictive Index (API) and Prevention and Incidence of Asthma and Mite Allergy (PIAMA)(10, 11). Studies investigating the probability of developing childhood asthma in the case of a MTW or EVW phenotype are rare. Van Wonderen found that if stable, MTW in 1-3-year-olds was associated with an increased risk of childhood asthma (7). Kappelle et al. showed a majority of children < 4 years referred with severe EVW to be diagnosed with asthma at the age of 5-10 years (12).
Viral infections appear to play an important role not only in exacerbations of preschool wheezing, yet also in the development of childhood asthma. Rhinovirus and respiratory syncytial virus (RSV) infections are associated with an increased prevalence of asthma persisting into early adulthood (13, 14).
Colonizing commensal bacteria play an important role in immunity and resistance against pathogens. Recently, it has been hypothesized that the susceptibility to and severity of respiratory disease is influenced by the respiratory

microbiome early in life, and that microbiome composition is associated with wheeze and asthma (15, 16). So far, little is known about the causal mechanisms underlying the observed associations. Acquiring more insight in microbial colonization patterns in children in relation to asthma might eventually have diagnostic and therapeutic potential.

In the original WHEEP study, we evaluated whether EVW and MTW are clinically distinguishable and stable phenotypes, by the use of symptom diaries, clinical assessments and nasal samples. We performed an observational 12-month prospective cohort study of 1- to 4-year old children with recurrent wheezing, treated by hospital-based paediatricians. Parents were instructed to record respiratory symptoms (cough, wheeze and dyspnoea) and symptoms of viral upper respiratory infections (rhinorrhoea, ear- and/or throat pain and fever > 38 *C) on a weekly basis during 12 months. At the beginning of the study period and after 3, 6, 9 and 12 months, a scheduled clinical assessment by the patient*s own paediatrician took place. The paediatrician was asked to classify the child*s wheezing phenotype based on the clinical history taken during the visit. At the last visit, paediatricians were asked to predict whether or not a child would develop childhood asthma.
For each 3-month period ending at the date of the clinical assessment, the diary-based phenotype was re-assessed by the researchers by evaluating the prospectively reported symptoms, using the following definitions. A respiratory episode was defined as reported cough, wheeze or dyspnoea (at least 2 of these) for at least 2 consecutive days. A viral upper respiratory tract infection (URTI) episode was defined as rhinorrhoea and/or ear-/ throat pain and/or fever > 38 *C (at least 2 of these) during at least 2 consecutive days (17).
Symptom patterns were classified as EVW if respiratory episodes exclusively coincided with URTI episodes; the respiratory episode had to begin at or until 2 days after the start of the URTI episode. MTW was assigned when respiratory episodes also occurred outside URTI episodes. We compared prospectively reported symptoms to clinical assessments by the patient*s own physician.
Also, parents were instructed by the electronic diary to take nasal swab samples in prespecified random periods. During the study period, 503 nasal samples were taken from 154 children: 290 samples were taken during URTI episodes, 108 during only respiratory symptoms, and 105 in complete absence of symptoms. semi-quantitative real-time PCR was used to detect human rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), influenzavirus A and B, parainfluenzaviruses and Mycoplasma pneumoniae (18).

A total of 189 children were included. Our study showed a very weak agreement between phenotypes derived from prospectively recorded symptoms by parents at home, and phenotype classification by paediatricians based on parental history taking over the same 3-month periods. Prospective symptom diaries showed phenotype switching between periods in 32% of the study subjects. Presence of viral DNA or RNA was found in 71% of episodes with symptoms of viral infection and in 66% of episodes with only respiratory symptoms, compared to 38% in completely symptom-free episodes. The poor agreement between symptom patterns

proving from symptom diaries and the pattern that the paediatrician apparently deduces from the clinical history, the phenotype instability and the limited relation of symptoms of viral infection to PCR positivity challenge current paradigms on the phenotype classification of preschool wheeze.

The aim of this follow-up study is to evaluate the predictive value of the initial phenotype (clinical as well as diary-based), the presence of stable EVW or stable MTW (clinical as well as diary-based), the prognosis according to the paediatrician and the occurrence of viral upper airway infections in the development of childhood asthma.

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Study objective

We aim to investigate the predictive value of the wheezing phenotypes EVW and MTW at preschool age (based on prospectively reported symptoms of wheezing, dyspnoea and cough or based on clinical assessments) and the predictive value of viral upper respiratory infections in the development of childhood asthma. Our hypothesis is that children with a stable MTW phenotype have an increased risk of asthma at the age of 6-8 years compared to children with EVW. We also expect children in whom a rhinovirus or RSV was detected to have an increased risk of asthma.
Secondly, we wish to evaluate differences in microbiome at preschool age between children who develop childhood asthma and children who do not. The sensitivity and specificity of the Asthma Predictive Index (API) and the Prevention and Incidence of Asthma and Mite Allergy risk score (PIAMA) in our cohort will be analysed.

Study design

In the previous study, respiratory symptoms and symptoms of viral infections were reported by parents on a weekly basis during 12 months, by the use of an electronic diary. For each 3 month-period, the diary-based phenotype was reassessed by evaluating the prospectively reported symptoms. Besides the registration of symptoms of viral infections, the occurrence of viral upper respiratory infections was investigated by the collection of nasal samples.

Semi-quantitative real-time PCR was used to detect human rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), influenzavirus A and B, parainfluenzaviruses and Mycoplasma pneumoniae.
Symptom patterns were classified as EVW if respiratory episodes exclusively coincided with viral episodes and as MTW when respiratory episodes happened also outside viral episodes. A third category was used for 3 month-periods in which no respiratory episodes occurred. At the beginning of the study period and after 3, 6, 9 and 12 months, a clinical assessment by the patient*s own pediatrician took place. The pediatrician was blinded for the content of the electronic registration of symptoms.
The clinically assessed phenotype was compared to the diary-based *prospectively assessed phenotype* for every 3 month-period.

Meanwhile, the children in this cohort are 6- to 8- years old. For the follow up study, a follow-up visit will be planned for each patient. During this visit, a pulmonary function test (FEV1, FVC, FEF75) will be performed before and after administration of Salbutamol aerosol. as well as exhaled NO (FeNO) will be measured. Blood testing for eosinophilia, total IgE and RAST test for inhaled allergens will take place. A throat swab will be collected to evaluate the microbiome. The ISAAC (International Study of Asthma and Allergies in Childhood) standardized questionnaire on asthma will be completed. Moreover, information on medication use, hospital admissions, courses of prednisone, number of wheezing episodes in the past 2 years, wheezing in relation to viral infections, other triggers and symptom-free intervals will be collected.

Study burden and risks

The burden for the patients participating in this study is judged to be minimal. Patients and parents will have to visit the outpatient clinic only once. The blood drawing, throat swab and pulmonary function test may cause slight transient discomfort but do not expose the patient to relevant health risks.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

The study population consists of 6- to 9-year-old children who were known for recurrent wheezing at the age of 1- to 4- years, treated by hospital-based paediatricians and included in the previous (WHEEP)study. Recurrent wheezing was defined as a minimum of 3 reported episodes in the year before inclusion, of which at least one must have been confirmed by a pediatrician. Children were then recruited from pediatric departments of ten general and academic hospitals in the Netherlands. During the 1-year (WHEEP)study period wheeze patterns were classified from patient diaries and compared to pediatrician assigned phenotypes.

Exclusion criteria

No new exclusion criteria. All children who participated in the former study are eligible. As in the former study children of whom their parents do not understand the Dutch language are not eligible.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-08-2019
Enrollment:	171
Type:	Actual

Ethics review

Approved WMO

Date:	25-04-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL64758.100.18