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ORIGINAL ARTICLE

Recurrent wheezing and asthma after bocavirus bronchiolitis☆

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Abstract
Background: Human bocavirus (HBoV) was recently discovered and identified as an important cause of respiratory infection in young children. However, the relationship between HBoV-bronchiolitis and the development of recurrent wheezing has not yet been established.
Objective: We designed this study in order to describe the mid-term outcome, regarding the development of recurrent wheezing and asthma of HBoV-bronchiolitis patients and to compare it with RSV-bronchiolitis infants.
Methods: We studied 80 children (10 with HBoV and 70 with RSV infection), currently aged ≥4 years and previously hospitalised during the seasons 2004–2009 due to acute bronchiolitis. Epidemiological and clinical data were collected through structured clinical interviews at the follow-up visit. Spirometry and skin prick tests to common food and inhaled allergens were performed.
Results: All HBoV-patients developed recurrent wheezing and half of them had asthma at age 5–7 years. Almost 30% required hospital admission for recurrent wheezing. Asthma (odds ratio (OR) = 1.28) and current asthma (OR = 2.18) were significantly more frequent in children with HBoV-bronchiolitis than in RSV-bronchiolitis. FEV_1 values were 99.2 ± 4.8 in HBoV-group vs. 103 ± 11 in RSV-group, *p*: 0.09. No differences were found with respect to allergic rhinitis, atopic dermatitis, food allergy, proportion of positive prick tests, and family history of atopy or asthma.
Conclusions: Severe HBoV-bronchiolitis in infancy was strongly associated with asthma at 5–7 years.

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Background and objective

Bronchiolitis is one of the leading causes of hospital admission for infants.[1] Long-term studies have demonstrated that infants hospitalised with bronchiolitis have a 2- to 3-fold increase in the risk of asthma. To date, most research has focused on respiratory syncytial virus (RSV) and in the last years, in rhinovirus infections.[2]

Human bocavirus (HBoV) was discovered in 2005 in nasopharyngeal specimens from children with respiratory tract infection,[3] and identified as an important causative agent of respiratory infections in young children.[4] However, the relationship between HBoV-bronchiolitis and the development of subsequent recurrent wheezing and asthma has not been investigated yet.

We designed this study in order to describe the mid-term outcome, regarding the development of recurrent wheezing and asthma, of HBoV-bronchiolitis patients and to compare it with RSV-bronchiolitis infants.

Study design

This is a sub study of an ongoing prospective investigation on respiratory tract infections in children, funded by FIS (Fondo de Investigaciones Sanitarias – Spanish Health Research Fund) grants n°: PS09/00246 and PI12/0129 and approved by The Medical Ethics Committee of Severo Ochoa Hospital.

The study population consisted of children of at least 4 years of age with a previous history of hospital admission at age 0–24 months due to HBoV or RSV bronchiolitis. To avoid the confounding role of coinfections, patients with dual or multiple infections were excluded. Nasopharyngeal aspirates were obtained and sent to the Influenza and Respiratory Viruses Laboratory at the National Microbiology Center (ISCIII, Madrid). Simple and multiplex reverse transcription-nested PCR assays previously described[5–8] were used to assess the viral aetiology of bronchiolitis, including 16 different respiratory viruses or group of viruses.

A total of 738 children less than 2 years were admitted at the secondary public hospital Severo Ochoa (Leganés, Madrid, Spain), between September 2004 and August 2009 due to bronchiolitis. Fifty-four parents refused NPA collection but accepted their children to be included in the clinical study of the 684 analysed samples, 588 (86%) were positive for at least one virus, 421 (71.6%) of which were single infections: 274 RSV, 62 rhinovirus, 31 HBoV, 18 hMPV, 14 parainfluenza, 13 adenovirus and 9 influenza. At the time of the study, 18 HBoV and 225 RSV children were older than 4 years of age. A random sample of 80 RSV-hospitalised bronchiolitis was selected using Excel data analysis function.

Parents of children with bronchiolitis due to single HBoV and single RSV infection were contacted by telephone from June to October 2012 and invited to a follow-up visit. Ten HBoV and 70 RSV patients could be contacted and were finally recruited in the study. Informed consent was obtained from parents or legal guardians.

A clinical interview based on a structured questionnaire was performed, to obtain information regarding wheezing episodes, hospital admissions, use of bronchodilators and maintenance medication for asthma. In addition, information about the presence of atopic dermatitis, allergic rhinitis and food allergy was also collected, as were demographic factors, environmental exposures and family history of respiratory and atopic disease. The researchers were not blinded to the status of the child when the interviews were performed.

Primary care paediatricians were also contacted by phone and asked to review the patients' electronic records in order to confirm the presence of wheezing episodes, their number and the use of bronchodilator and maintenance medication prescription for asthma. Only the information confirmed by the paediatrician in charge of the patient was taken into account.

Spirometry was performed according to established guidelines[9] using a Jaeger MasterScope-PC spirometer (VIASYS HealthCare GmbH, Hochberg, Germany). Forced expiratory volume in first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and forced expiratory flow at 50% of FVC (FEF_{50}) were recorded. Measurements were compared to values predicted by standard reference equations[10] and expressed as percentages of predicted values. FEV_1 and FVC $\geq$80% of predicted values were considered as normal.

For the estimation of allergic sensitisation, skin prick tests for common inhaled allergens (*Dermatophagoides pteronyssimus*, *D. farinae*, grass pollen mix, *Olea europaea*, *Platanus hispanica*, cat, dog, *Blatella germanica* and *Alternaria tenuis*) were performed using standardised extracts (ALK-Abelló SA, Madrid, Spain). Histamine (10 mg/ml) was used as a positive control and 0.9% saline solution as a negative control. Children were advised not to take antihistaminic medication for 1 week before the test. Commercially available lancets were used to prick the epidermis with the allergen extract drops. The tests were read at 15 min, and mean wheal diameters were calculated (sum of the longest diameter and its perpendicular one divided by two). A mean wheal diameter of at least 3 mm greater than the negative control was taken as positive.

Bronchiolitis was defined as the first episode of expiratory wheezing of acute onset with previous signs of viral respiratory infection in children younger than 2 years. *Asthma* was defined as at least three episodes of bronchial obstruction confirmed by a paediatrician. *Current asthma* was defined as recurrent wheezing with at least one episode occurring in the year prior to the follow-up visit.

Statistical analysis

Values were expressed as percentages for discrete variables, or as mean and standard deviation and median and interquartile range for continuous variables. Clinical characteristics and laboratory variables were compared using the Student *t* test, the Mann–Whitney *U* test, the χ^2 test, and Fisher's exact test, where appropriate. A two-sided value of $P = 0.05$ was considered to be statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (SPSS), Version 20.

Results

All children included were older than 4 years, with a mean age at the time of the study of 6.3 ± 1.3 years for HBoV