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Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years

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In a prospective study 101 children aged less than 2 years (median age 10 months), were examined the first time they were admitted to a paediatric ward for asthmatic symptoms. Two-thirds were boys and 58 had parents or siblings with allergic symptoms. During winter–spring, respiratory syncytial (RS) virus was verified in 50% of children. Other viral agents were adenovirus, parainfluenza 3, coxsackie B 2, ECHO 6 and rotavirus. At the acute stage, 54% of the children displayed changes on pulmonary X-ray. The total IgE value was $\geq +2$ SD score units in 14 children. At reinvestigation after 3–4.5 years, when the children were aged 3.3–6.3 years, 53% were free from asthmatic symptoms; the median age for the last episode was 2 years. A total of 33% had mild asthma, 8% moderate and 6% severe asthma. The factors which correlated significantly with persistent asthma were: (1) The need for daily medication for at least 6 months. (2) A young age in conjunction with the first wheezing episode and on the first admission to a paediatric ward because of asthmatic symptoms. (3) Other past or present atopic symptoms. Heredity, tobacco smoking at home, having a furry pet, RS virus infection, or high total IgE at the time of the first admission did not correlate significantly with the persistence of asthma 3–4.5 years later. The results emphasize the good overall prognosis of wheezing in early childhood, even when the wheezing is severe enough to lead to inpatient treatment. □ *Allergy, bronchial asthma, infant, obstructive bronchitis, prognosis, respiratory syncytial virus*

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Obstructive airway symptoms with wheezing, rhonchi, tachypnoea and subcostal retractions are a common acute problem in early childhood. The trigger factor is often a viral infection (1), producing mucosal oedema and varying degrees of bronchial smooth muscle contraction and mucus secretion, thereby narrowing the small-dimensioned bronchial lumen. This group of infants with clinically similar symptoms include children with wheezing of different etiology and prognosis, some of whom have infantile asthma which will continue throughout childhood and others who only have occasional and transient obstructive symptoms (2, 3). When the obstructive airway symptoms with dyspnoea occur repeatedly, the child often has hyperreactive airways and a diagnosis of bronchial asthma is therefore used (2). The aim of the present study was to analyse the prognostic value of different characteristics of obstructive bronchitis in the very young child with symptoms severe enough to warrant inpatient hospital treatment, and to identify current infectious agents and their possible impact on the long-time course.

Patients and methods

Admission

One hundred and one children aged less than 2 years, who were admitted with a first wheezy episode severe enough to require inhospital treatment from March 1984 to November 1985 were included in the study. The children were moderately to severely affected by wheezing, retractions, rhonchi and an increased respiratory rate. In 73 of the children, the symptoms were rated as 3 or more on a six-grade scale for asthmatic symptoms in infants, and as 4 or more in 22 children (4). Grade 3 denotes symptoms of constant wheezing, retractions and rhonchi and an increased respiratory rate of 40–50 breaths/min but without apparent fatigue. Grade 4 denotes very marked wheezing, retractions and rhonchi, a respiratory rate above 50 breaths/min and obvious fatigue. Many of the children thus fulfilled the criteria for the diagnosis of acute bronchiolitis as used by some authors (5).

The protocol included a detailed case history with emphasis on allergy and infections, chest X-ray, nasopharyngeal culture for bacteria, viral isolation from the nasopharynx and faeces, and the demonstration of virus antigen in nasopharyngeal secretion, blood samples for the determination of C-reactive protein (CRP), eosinophilic count and total serum IgE. Virus antigen in nasopharyngeal secretion was identified using radioimmunoassay for detection of respiratory syncytial (RS), adenovirus, influenza A and B, and parainfluenza 1, 2 and 3 viruses. The total IgE values were expressed as standard deviation (SD) score units relating each measurement to the normal values for Swedish children (6).

Sera for the determination of viral antibodies were obtained on admission and 3 weeks later, and stored at −20°C until analysis. Paired sera were obtained from 95 patients. An ELISA method was used for RS virus serology (7) and the antibody concentration was expressed as a percentage of a positive reference serum. A significant rise in RS IgG antibodies was defined as a 25% increase in arbitrary units of paired sera. The complement fixation test was used (7) to analyse antibodies against adenovirus, enterovirus, influenza A and B, parainfluenza 1 and 3, rotavirus, and mycoplasma; a four-fold increase or more was considered significant. Diagnostic techniques for rhino- or coronavirus detection were not available when this study was conducted.

Treatment was based on oral and inhaled β_2-agonists, and oral or rectal theophylline. Approximately 30% of the children were given extra fluid, theophylline and hydrocortisone iv. At the end of the study, all the chest films were re-interpreted by one radiologist (IB) in a standardized manner.

Reinvestigation

The follow-up investigation was performed between 1988–1989, i.e. 3–4.5 years later, when the children were aged 3.3–6.3 years. The study was approved by the local Ethics Committee. A case history was obtained using a questionnaire which the parents completed, supplemented by an interview and matched with the records available at the Children's Hospital. Blood was obtained for analysis of total serum IgE and RAST for egg, animal dander, birch pollen, grass pollen (timothy), house dust mite (*Dermatophagoides pteronyssinus*) and mould (*Cladosporium*). Ninety-four children were included in the follow-up study and the questionnaire was completed for all of them. Blood samples were obtained from 68 children (72%).

Asthma was ranked according to a system used in the department (8), i.e. grade 1 asthma = 1–5 obstructive periods of less than 2 weeks' duration during the last year; grade 2 = 6–10 obstructive periods of less than 2 weeks' duration during the last year, and occasional symptoms during the intervening intervals; and grades 3–4 = > 10 obstructive periods of less than 2 weeks' duration, or repeated lengthy periods during the last year, requiring constant bronchodilator and anti-inflammatory treatment.

Conventional statistical methods including the chi-square test were used. Factors predicting the presence of asthma at reinvestigation were analysed using Fisher's permutation test and Fisher's exact test for dichotomous variables.

Results

Admission

Table 1 summarizes the history and laboratory findings for the 101 children. The median age for the first wheezing episode was 7 months, and 10 months for the first admission. Six children had their first wheezing episode aged only 1 month and 76 before the age of 12 months (Fig. 1). Two-thirds of the children were boys, with the same proportion over the studied age range. In 67 of the families, one or both of the parents smoked and in 32 families cats, dogs or other furry animals were kept. These figures did not differ between families in which parents or siblings had symptoms of asthma or allergy and families without such symptoms. The mean total IgE value for the total group was +0.4 SD score units (ns) (6).

Table 1. Condensed clinical data from 101 children.

	Number of children
History	
Atopic symptoms in the child (other than wheezing)	25
Eczema	18
Atopy in parent or sibling	58
Either other atopic symptoms in the child or atopy in parent or sibling	64
Earlier upper respiratory tract infection	86
Earlier episodes of acute otitis media	31
Earlier pneumonia	18
Earlier wheezing episodes	
n = 0	57
1–5	35
6–10	7
11–15	1
Current respiratory infection in the family or in the day care centre	66
Laboratory findings in blood or serum	
Leucocyte count/mm^3 × 10^{-3} (≥ 10)	61
Eosinophil count/mm^3	
≥ 300	28
≥ 400	21
C-reactive protein (CRP) mg/l (≥ 20)	15
Sedimentation rate (MSR) mm/h (≥ 25)	23
IgE-level (SD score)	
≥ +1	28
≥ +2	14

Ninety-four children had clinical signs consistent with a current respiratory infection. A virus infection was verified by serology in 32 children and by viral isolation and/or virus antigen detection in nasopharyngeal secretion in a further eight children. The RS virus was predominant and demonstrated in 28 children, the majority of whom were identified during the period December 1984 to May 1985, when they constituted 50% of the patient population (Fig. 2). Other viral agents included adenovirus (n = 9), parainfluenza 3 (n = 2), coxsackie B2 (n = 1), ECHO 6 (n = 1) and rotavirus (n = 5). Mixed adenovirus and RS virus infections were verified in four children, and mixed rotavirus and RS virus infections in two. None of the children had a positive serology for mycoplasma. A CRP increase in the range of 20–30 mg l^{-1} was seen in six children with

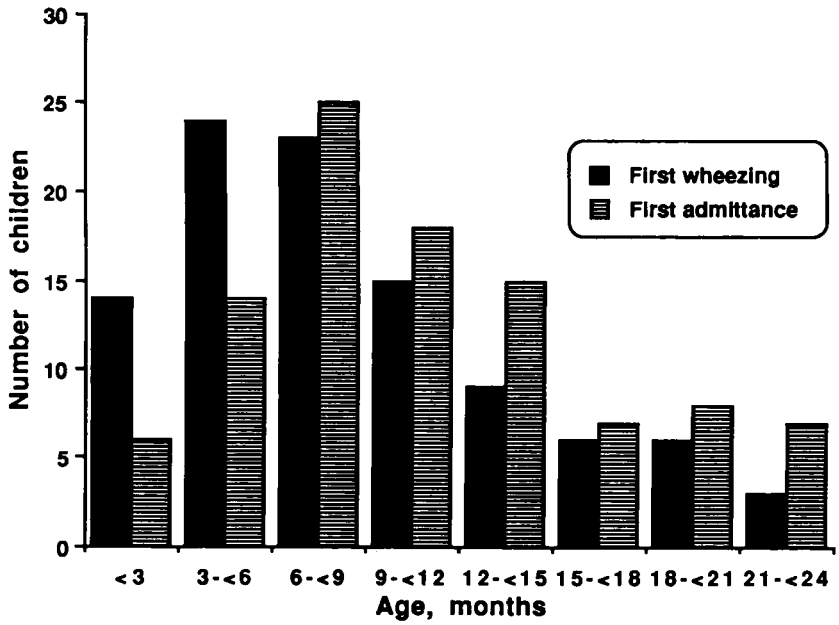

Fig. 1. Age at the first episode of wheezing and on the first admission to a paediatric ward due to asthmatic symptoms.

RS virus infection and three with adenovirus infection. Two additional children with the RS virus had higher CRP increases, 50 and 79 mg/l.

A positive bacterial culture from the nasopharynx was obtained in 78 children. *Haemophilus influenzae* was isolated in 26 children, *Branhamella catarrhalis* in 46, *Streptococcus pneumoniae* in 27, and haemolytic streptococci in two. A mixed growth of two or three different species was seen in 23 children. Only 12 positive cultures were accompanied by an increase in CRP; *Haemophilus influenzae* in two, *Branhamella catarrhalis* in six, and *haemophilus influenzae* with pneumococci and/or *Branhamella catarrhalis* in four.

A chest X-ray showed perihilar infiltrates in 19% of the 95 children examined, peripheral infiltrates in 32% and peripheral infiltrates with atelectasis in 3%. In the group of infants with a CRP value ≥ 20 mg/l 73% had changes of this type on chest X-ray (46.5% peripheral infiltrates, 26.5% perihilar) while in the group with a CRP value < 20 mg/l only 50% showed such changes. A hyperinflation of the lungs was present to a greater or lesser degree in almost all of the children.

In the children with an RS virus infection, 34% had peripheral infiltrates and 8% perihilar infiltrates, whereas the chest film was normal in 58%. In the children with the RS virus without an increase in CRP, these figures were 32%, 5% and 63%, respectively, while there were peripheral infiltrates in 34% and perihilar infiltrates in 21% of the other children with a CRP value of < 20 mg/l.

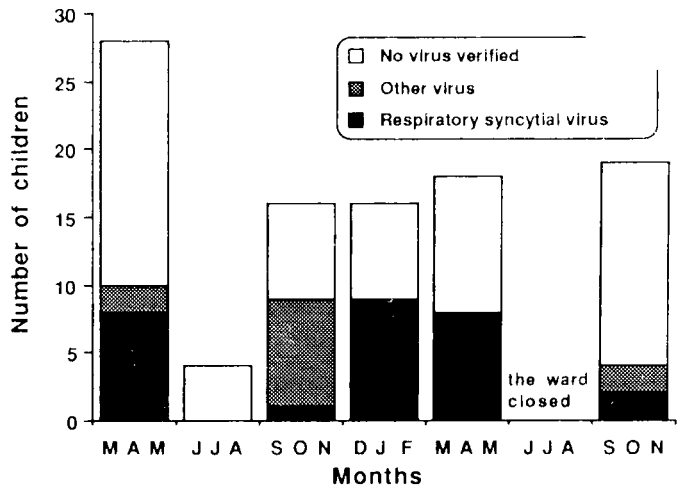

Fig. 2. Respiratory virus findings in the children.

Reinvestigation

Eighty-one per cent of the children had additional periods of wheezing since the initial study and 71% had visited a physician as a result of wheezing during the follow-up period. During the last 12 months, 53% had been free from wheezing episodes (Fig. 3). The median age at the last episode of wheezing in the symptom-free group was 2 years. Symptoms of mild asthma (grade 1) remained in 33% of children, 8% had moderate asthma (grade 2), and 6% severe asthma (grades 3–4). The trigger factors were respiratory infections (93%), cold weather (53%), physical exertion (47%), pollen grains (16%) and furry animals (12%).

Past or present atopic symptoms other than asthma were noted in 33% of the total group of children. In two-thirds the symptom was eczema. In the children with ≥ 400 eosinophils/mm^3 blood at admission, 52% were in the group with other atopic symptoms, most of them having eczema. In the total group, the mean total serum IgE was now 0.8 SD score units above the mean value for the population ($p < 0.01$). Twenty-five per cent had a total IgE value of $\geq +2$ SD score units, compared with 14% on admission. There was no significant difference between the total IgE values (expressed in SD score units) and those obtained in the same children on the first admission either in the children with asthma or those who were free from symptoms. Positive RAST tests were obtained in 15% (10/68) of the patients (grass = 5, eggs = 4, cat = 3, horse = 2, birch = 2 and *D. pteronyssinus* = 1).

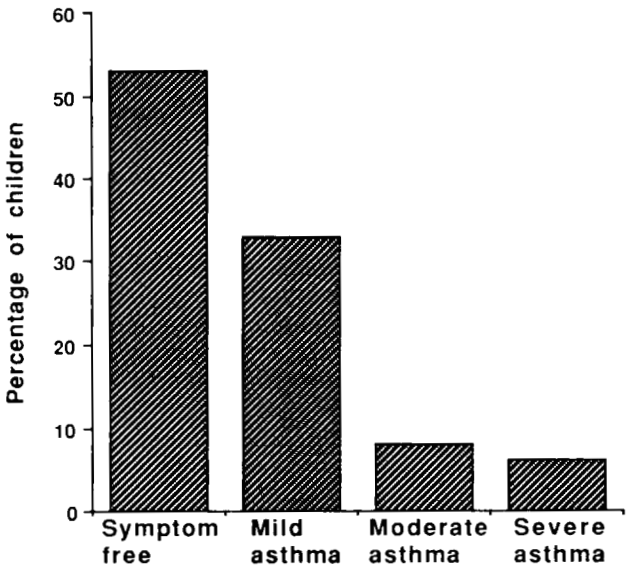

Fig. 3. Persistence of asthma at follow-up, 3–4.5 years after the first admission to a paediatric ward due to wheezing.

Tobacco smoking at home took place in 73% of the cases with persistent asthma and in 58% of the cases of healthy children (ns). There was no difference between the families regarding animals or horse riding, 32 vs 28%. The factors which were shown to be significantly related to asthma at follow-up were: (1) The need for daily medication for at least 6 months. (2) A young age for the first symptoms of wheezing and the first admission to a paediatric ward. (3) Other past or present atopic symptoms (eczema in most cases) (Table 2). Heredity, tobacco smoking at home, having furry pets or horse riding, a verified RS virus infection, a high total IgE level on the first admission and gender, were not found to be significant discriminatory factors between symptom-free children and those with persistent asthma at reinvestigation, nor were atopic symptoms present on admission. The outcome was not significantly different between children admitted outside the RS virus season (46% asthma at follow-up), and those who had been admitted during the RS virus season proper (39% asthma). Separate analysis of children with an established RS infection and those without (during RS virus season) did not alter these results. The results in terms of freedom from symptoms or asthma were not correlated to age at the time of reinvestigation (Fisher's permutation test). To elucidate how retrospective application of current Swedish criteria for the diagnosis of asthma would fit with the follow-up results, we analysed the outcome of children who at admission had either at least three wheezing episodes, other atopy, or parents or siblings with asthma or allergy (separate information on

Table 2. Correlation of various factors to presence of asthma at follow-up. Values are percentage, or mean ± SD, for the factors in the symptom-free and asthma group, and significance levels for correlation to asthma at reinvestigation (Fisher's permutation test). ns = non-significant.

Factor	Symptom-free	Asthma	Level of significance (p)
Need for lengthy anti-asthmatic medication	8%	34%	<0.001
Age at first symptoms of wheezing (months)	9.4 ± 5.7	6.7 ± 4.8	<0.001
Other atopic disease (past or present)	20%	45%	<0.01
Age at first admission to ward (months)	11.8 ± 6.2	9.3 ± 5.3	<0.05
Smoking at home*	58%	73%	ns
Parent or sibling with atopic disease	54%	66%	ns
Eosinophil count/mm^3*	279 ± 300	267 ± 344	ns
Furry animals*	28%	35%	ns
RS virus infection*	28%	30%	ns
Acute symptom score*	3·0 ± 0.7	3.0 ± 0.8	ns
Total IgE (SD score)*	+0.65 ± 1.3	+0.25 ± 1.1	ns

* = at admission.

asthma was lacking) vs those not fulfilling the criteria. However, this did not give a significant prognosis of the outcome at follow-up.

Discussion

Wheezing, usually in connection with a respiratory tract infection, is a common problem in infants and young children. It has been calculated that during the first years of life more than 10% of children have episodes of wheezing in association with respiratory infection (9). In this study, the upper age cut-off limit was set as low as 2 years. This was done to focus the study on subjects with anatomically narrow airways in whom mucosal swelling and smooth muscular constriction triggered by respiratory infection results in symptomatic obstruction. Later on in childhood these conditions change and other pathogenetic mechanisms increase in importance.

The importance of respiratory tract infections as precipitators of asthmatic symptoms in this age group is underlined by signs of current infection preceding the wheezing in 94% of the children. Although this figure was largely based on the clinical history obtained from the parents at the time of admission, it is still very high.

In early childhood, RS virus infection is often a trigger factor for airway obstruction and can also cause pneumonia (7). In our study, signs of an ongoing RS virus infection were demonstrated in as many as 50% of the children during the winter–spring period, a season in which RS virus infections are to be expected (10). Viral infections are usually demonstrated in 40–50% of wheezing episodes in infected children (11, 12) but are also suspected of being involved in the majority of the remaining cases (2, 3). Rhino- and coronavirus infections are also known to be able to trigger wheezing in children (13), but techniques for diagnosing rhinovirus infection were, unfortunately, not available in the present study. It is interesting to note that rotavirus was detected in five children. However, the pathogenetic importance of these findings *vis-à-vis* airway obstruction is uncertain.

Bacteria were isolated from the nasopharynx in the majority of patients. Only rarely was there a concomitant rise in the level of CRP indicating parenchymal involvement. In the majority of cases, the presence of bacteria merely reflected a colonization or a superficial mucosal infection. Similarly, in a study of children aged between 1–2 years in a day care centre, 72% had bacterial growth of potential pathogens in the nasopharynx without signs of clinical infection (14). The use of antibiotics is unnecessary in most of these cases.

Changes on pulmonary X-ray, including peripheral infiltrates, were common in the acute phase of obstructive bronchitis, and also in the absence of signs of bacterial infection in terms of increase in CRP. This demonstrates that an infiltrate on the chest film is not synonymous with a bacterial infection and suggests that chest X-ray alone is not sufficient to determine whether antibacterial treatment is indicated or not. An increase in CRP is not, however, exclusive to bacterial infection. A moderate CRP increase accompanying adenovirus and RS virus infections was not uncommon. In the group with no increase in CRP, chest film infiltrates, peripheral as well as perihilar, were just as common in the children in whom the RS virus was not found as it was in those with the RS virus. This lends support to the view that no pattern of radiographic change is specific to RS virus infection (15).

Smoking occurred in two-thirds of the families of these young children, a figure which is even higher than the one found by Åberg et al. (16) of 55% in Swedish families with children aged 7–14 years. Surprisingly, there was a tendency towards an even higher figure at reinvestigation in the families of children with persistent asthma. The figure for furry pets remained at the same level, one-third of the families, at reinvestigation and at admission. The high proportion of children with an elevated total IgE, other atopic symptoms, as well as atopic heredity (Table 1) clearly demonstrated that children with an atopic disposition are overrepresented in obstructive bronchitis in early childhood compared with a normal population (17).

At follow-up, more than half of the children were healthy, one-third had mild asthma, and 15% moderate to severe asthma. This agrees with other studies which reveal that the majority of children with obstructive bronchitis in early childhood are free from wheezing when they reach school age (2, 18, 19). It is known, however, that future asthmatic children are overrepresented in the wheezy group (18, 19). In studies of such children, a prevalence value of asthma of 11%–28% has been found later in childhood (18–20). The overall prevalence of asthma in Swedish school children, for example, has been reported to be 2.4% (16), whereas the corresponding figure for British school children is 9.3% (21).

The mean total IgE level in the group was significantly above the mean for the age, +0.8 SD score units. This tendency was seen also in the first investigation (+0.4 SD score units). The proportion of children with elevated levels was the same as that in a previous study by Foucard & Sjöberg (19). However, as in our study, the level of total IgE was a poor predictor of asthma at follow-up.

Only four factors correlated significantly with persistent asthma at follow-up. The need for continuous antiasthmatic medication for at least 6 months reflects a disease of greater intensity and duration. The predictive value of other atopic symptoms in the child has also been pointed out by other authors (19, 22). A knowledge of all these factors is, however, often lacking the first time the child is admitted to hospital. In our study, the atopic symptoms already present at that time, did not significantly predict asthma at follow-up, presumably because other atopic symptoms had not appeared to a sufficiently large degree at such a young age. It was only

when the atopic symptoms which appeared subsequently were included that the correlation became statistically significant. The factors of young age in conjunction with the first symptoms and the first admission to a paediatric ward are naturally strongly correlated. At first sight, the finding of a correlation between young age in conjunction with the first episode and persistent asthma at follow-up contrasts with what has earlier been claimed (19). However, entry to our study was restricted to children below the age of 2 years with obstructive symptoms severe enough to lead to inpatient hospital treatment. By using these inclusion criteria, we have probably defined a risk group with hyperreactive airways resulting in pronounced wheezing already at an early stage. It has been found previously that young age at first symptoms predisposes to severe asthma later on (23). This does not contradict the finding that wheezing which begins after the age of 2 years is often a sign of asthma that will persist for several years (19).

The influence of RS virus infection on the development of asthmatic disease can theoretically be seen from two different points of view. On the one hand it could be hypothesized that the RS virus is associated with a high risk of future asthma through the induction of IgE production and atopic disease. On the other hand, the RS virus might be associated with a low risk of acquiring asthma because of its considerable tendency to elicit wheezing symptoms in any individual. However, we were unable to find any statistically significant relationship between RS virus infection and asthma, and we found no significant difference between children from different seasons with regard to asthma at follow-up. Similarly, in a prospective 12-year follow-up study of children with wheezy bronchitis, the outcome was no different in terms of asthma or allergy for those who wheezed initially in association with an infection caused by the RS virus, parainfluenza or the ECHO virus (2). In a recent study, Rylander et al. found that RS virus infection in early infancy was more frequently related to only occasional subsequent wheezing than to subsequent recurrent wheezing (24).

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