

Wheezing bronchitis in children. Incidence, viral infections, and other risk factors in a defined population

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Risk factors for severe wheezing bronchitis were studied in children aged 4 months to 4 years in need of hospitalization. The children included in the study consisted of all cases generated from a geographically defined population, the catchment area of St Göran's hospital in Stockholm. The incidence was 3/1000 children and year, during the two years of observation, with the highest rate in boys under the age of 18 months (4.7/1000). Symptoms of a preceding upper respiratory tract infection were reported in 90% of the cases, but a viral etiology could only be demonstrated with virus isolation in 26%. Respiratory syncytial virus was the most common finding in younger children. Rhinovirus was primarily seen in older children with a history of previous wheezing. Regardless of whether the cases had a positive or negative virus isolation they showed the same seasonal distribution. Furthermore, there was no difference in risk factors between children with a positive and negative virus isolation. Children older than 18 months with negative virus isolation had higher IgE levels than those with positive isolation, suggesting that atopy is of greater importance in this group.

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Wheezing bronchitis is an increasing problem in children (1, 2). Risk factors for wheezing bronchitis have usually been investigated with cohort-study designs, often focusing on selected risk groups (3–6). In the few published population-based cohort or cross-sectional studies, incidence or prevalence of asthma and persistent wheezing has been estimated, but the limited size of the populations studied has only rarely permitted an assessment of more severe manifestations, such as the need of hospitalization (9).

It is well known that viral infections may cause wheezing, and in most of young children with wheezing bronchitis a history is given of a preceding upper respiratory tract infection (7, 8). However, a viral etiology can be established only in 20–40% of wheezing children at the time of hospitalization (10–14). It is not known to what extent risk factors differ between wheezing children with and without a proven viral infection.

One aim of this study has been to determine the incidence of wheezing, requiring hospitalization,

during 2 years of observation of a well defined population. Another aim was to study risk factors in children with and without proven viral infection.

Material and methods

Study subjects

A population-based, case-control study of wheezing bronchitis in early childhood was conducted in the northwestern part of greater Stockholm constituting the catchment area of St. Göran's Children's Hospital (15). In 1986 the population was approximately 540 000 with 16 282 boys and 15 634 girls aged from 4 months to 4 years.

Cases were defined as 4–48-month-old children, born in Sweden and living in the catchment area of St Göran's Children's Hospital, who were admitted to hospital for the first time because of breathing difficulties with wheezing. This is the only hospital in the area to which children with these symptoms would be admitted. Children below 4 months of age

were excluded to avoid breathing difficulties of neonatal origin. At inclusion the children were examined by one of the three pediatricians participating in the study. Further criteria for inclusion were a clinical evaluation showing an obvious airway obstruction with wheezing and a respiratory rate exceeding 60/min in children below 12 months of age and above 40/min in older children. The Stockholm County Council register of hospital admissions was also checked in order to exclude children who had previously been hospitalized for wheezing.

A total of 204 cases were diagnosed from September 1986 through September 1988 and the parents of 199 children (97.5%) agreed to participate in the study. On admission, a case history about triggering factors of importance was taken. Virus isolation from nasopharyngeal samples were obtained in 88% of the children. Following discharge, a structured home interview with one of the parents was performed by a paediatric nurse trained in allergy. Data were obtained on heredity of atopic disease, pregnancy, exposure to allergens, breast-feeding, previous history of infection, day-care arrangements, housing conditions and socioeconomic factors. Atopic heredity was defined as allergic disease in a first-degree relative and parental atopy as allergic disease in one or both parents. A suspected allergic reaction to milk, egg or fish was classified as "food allergy".

Controls were selected to provide information on the distribution of risk factors in the population from which the cases originated. The population register of Stockholm County was used to recruit the controls. An age-stratified random sample of children from the same area as the patients was selected twice a year during the recruitment period of the cases. A total of 409 controls were contacted and 351 (85.8%) agreed to participate. Home interviews were performed in the same way as for the cases within 6 months after sampling.

Virus isolation and IgE determination

A nasopharyngeal swab was applied to a virus isolation transport medium containing antibiotics and cycloheximide. At the laboratory 2.2 ml of Parker medium, penicillin, streptomycin and mycostatin were added. After homogenization, 0.2 ml of the mixture was added to tubes of HeLa cells, green monkey kidney cells, rhabdomyosarcoma cells, canine kidney cells (MDck) and cells of a fetal kidney cell line (Ma104). These cell lines were chosen to allow for isolation of the respiratory syncytial virus (RSV) as well as the influenza, parainfluenza, herpes simplex viruses, and entero- and adenoviruses. The tubes were inspected under ordinary light microscopy for cytopathogenic effects twice weekly for 2

Table 1. Yearly incidence of first-time hospitalization for wheezing bronchitis or asthma 1986–8 in children from Stockholm

Age (months)	Incidence (per 1000)			
	Boys	95% confidence-interval	Girls	95% confidence-interval
4–18	4.7	3.5–6.4	2.1	1.3–3.3
18–48	3.9	2.7–5.6	1.6	0.9–2.9

weeks. Hemadsorption was carried out on days 6 and 13. Immunofluorescence was used to identify viruses. The remaining virus isolation fluid was kept at -70°C and transported to the Department of Virology in Turku, Finland, for viral culture in HeLa Ohio cells at 33°C , in order to detect rhinoviruses (14).

Serum total IgE was quantified with the Stratus IgE Fluorometric Enzyme Immunoassay and expressed as IU/ml following the instructions of the manufacturer.

Statistical methods

The associations between different risk factors and wheezing bronchitis were described with maximum likelihood estimates of relative risks (RR) and 95% confidence intervals (CI) based on logistic regression (25). The confidence intervals for cumulative incidence are based on a normal approximation of the logarithm of cumulative incidence. IgE levels in different groups were compared by using the Wilcoxon rank sum test.

Results

Incidence

A total of 204 children (145 boys and 59 girls) fulfilled the case definition criteria during the 25-month observation period. They constituted 46% of the total 446 admissions for asthma and wheezing bronchitis during this period in the age group under study. The overall incidence of first-time hospital-

Table 2. Type of virus in nasopharynx among children in Stockholm hospitalized for wheezing bronchitis or asthma in 1986–8

Age	Previous wheezing*		No previous wheezing	
	≤18 months n=53	>18 months n=65	≤18 months n=50	>18 months n=13
Type of virus				
Respiratory syncytial virus	6	1	14	0
Rhinovirus	2	9	0	0
Parainfluenza virus	4	3	4	1
Adenovirus	2	0	1	0
Enterovirus	0	1	1	0

* Information missing in 18 children.

No. of children

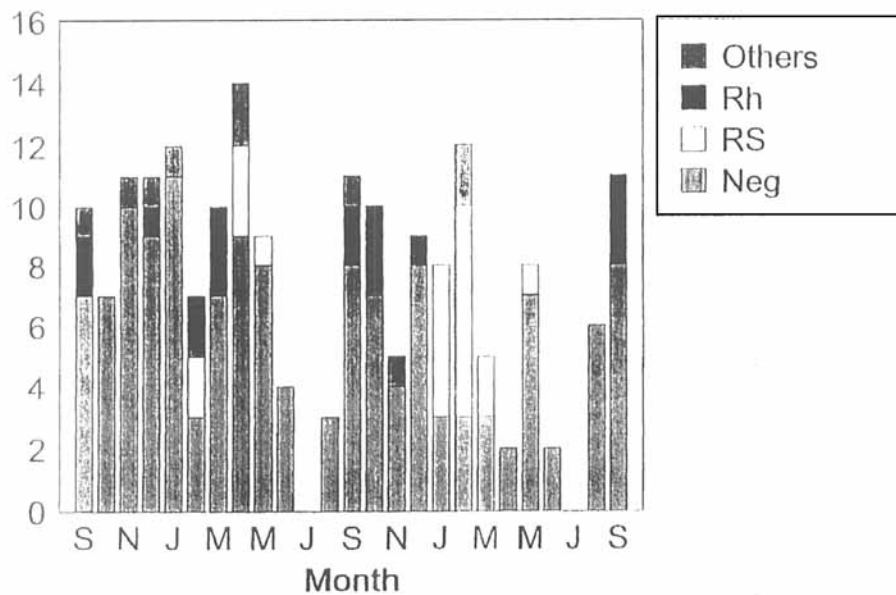


Fig. 1. Seasonal distribution of all first-time hospital admissions to St Göran's Hospital, Stockholm, for wheezing bronchitis or asthma in children during the period 1 September 1986 through 30 September 1988. Results from nasopharyngeal virus isolations: Rh – rhinovirus; RS – respiratory syncytial virus; Other – parainfluenza, adeno- or enteroviruses; Neg – no virus isolated.

ization for wheezing bronchitis was 3.0 per 1000 children and year as shown in Table 1. The incidence was higher among boys than girls, 4.3 and 1.9 cases per 1000, respectively ($P = 0.00004$).

Clinical data

Of the 204 children, 124 (61%) had experienced wheezing at least once before admission. A total of 184 (90%) gave a history of continual upper respiratory tract infection. Five of the children (3%) were admitted to the intensive care unit.

Even though children with other possible causes of wheezing had been excluded, bronchial tuberculosis was later diagnosed in one child and pulmonary vascular malformation in another. A third child had a bronchial stenosis (15).

Fifteen of the children (7%) were preterm, below 34 weeks of gestation, and among them six had experienced significant pulmonary problems in the neonatal period. Furthermore, 11 (5%) suffered from a chronic disease that could contribute to breathing difficulties such as cardiac malformation, cleft palate, or morbus down.

Viral studies

Fig. 1 shows the seasonal distribution of the admissions and results of the virus isolation. In 26% of the children, a virus was isolated from the nasopharynx. The peak of admission for children below 18 months of age coincided with the peak of the RSV epidemics, which during the first year of the study was in March–April and during the second year in

Table 3. Risk factors in children from Stockholm hospitalized for wheezing bronchitis or asthma in relation to age and proven viral infection

	40–18 months			18–48 months		
	Controls n=198	Patients		Controls n=153	Patients	
		Virusneg n=67	Viruspos n=34		Virusneg n=52	Viruspos n=14
Parental smoking	1	1.9 (1.2–3.4)	2.6 (1.2–5.4)	1	1.7 (0.9–3.1)	1.6 (0.5–4.9)
Parental atopy	1	1.1 (0.7–2.0)	1.2 (0.6–2.4)	1	1.6 (0.9–3.1)	2.5 (0.8–8.2)
Breast-feeding less than 3 months	1	2.1 (1.2–3.7)	1.9 (0.9–4.0)	1	1.0 (0.5–1.8)	1.6 (0.5–4.6)
Birth weight less than 2500 g	1	2.3 (0.9–5.9)	3.6 (1.3–10.0)	1	1.5 (0.6–4.0)	1.7 (0.3–8.0)
Pets in the household	1	2.0 (1.1–3.5)	1.7 (0.8–3.7)	1	0.9 (0.4–1.7)	0.4 (0.1–1.7)
More than five upper respiratory tract infections below 18 month of age	1	3.4 (1.8–6.3)	1.6 (0.6–3.9)	1	2.3 (1.1–4.9)	3.8 (0.9–15.9)
IgE (median) IU/ml		11	10 ^{a)}		48.5	18.5 ^{b)}

+ Relative risk and 95% confidence interval (in parenthesis).

a) Wilcoxon test for IgE levels in patients 4–18 months of age $P = 0.3$.

b) Wilcoxon test for IgE levels in patients 18–48 months of age $P = 0.02$.

Table 4. Risk factors in children from Stockholm hospitalized for wheezing bronchitis or asthma in relation to atopic heredity and previous wheezing

Risk factors	Atopic heredity ^a			No atopic heredity		
	Controls <i>n</i> = 73	Patients		Controls <i>n</i> = 178	Patients	
		No previous wheezing <i>n</i> = 36	Previous wheezing <i>n</i> = 67		No previous wheezing <i>n</i> = 27	Previous wheezing <i>n</i> = 51
Parental smoking	1	1.9 (0.9–4.0)	1.0 (0.6–1.8)	1	3.9 (1.5–9.8)	2.7 (1.4–5.2)
Pets in the household	1	1.8 (0.8–4.0)	0.5 (0.2–1.1)	1	2.1 (0.9–4.9)	1.5 (0.8–3.0)
Breast-feeding less than 3 months	1	1.0 (0.4–2.4)	1.0 (0.5–1.8)	1	1.4 (0.6–3.4)	2.2 (1.2–4.3)
Virus isolation positive	-	38%	27%	-	30%	24%
IgE (median) IU/ml	-	18.5	30.0 ^{b1}	-	7.0	11.5 ^{b1}

^aAllergic disease in first-degree relative.

^aThe estimates of relative risks are adjusted for age.

^aRelative risk and 95% confidence interval (in parenthesis) adjusted for age.

^{a1} Wilcoxon test for IgE levels in group with atopic heredity *P* = 0.09

^{b1} Wilcoxon test for IgE levels in group without atopic heredity *P* = 0.11

January–February. The older children had peaks of admissions in September coinciding with the occurrence of rhinovirus infection.

Table 2 shows the different isolates in relation to age and previous wheezing. RSV was primarily seen in the youngest children, while rhinovirus was mostly found in older children with a history of previous wheezing.

Risk factors

A higher proportion of the children above 18 months of age had a history of previous wheezing than the younger children (83 and 51%, respectively), and the older children also exhibited more of the other symptoms of atopic disease (48 and 25%, respectively). These symptoms mostly included atopic dermatitis and food allergies. The occurrence of risk factors did not differ between the age groups and was independent of virus isolation results except that children that had had repeated respiratory infections before 18 months of age more often had negative cultures (Table 3). In children above 18 months of age, the serum IgE level was increased when the virus isolation was negative (*P* = 0.02). No difference in IgE levels occurred in the younger age group in relation to virus isolation.

Table 4 shows three risk factors for wheezing bronchitis and asthma in relation to atopic heredity and history of previous wheezing. In the group of children with both atopic heredity and reported wheezing before admission, the number of pets in the household was surprisingly low, indicating that some preventive measures had been undertaken. A short breast-feeding period can be seen as a more important risk factor in children with previous wheezing without atopic heredity than in the other groups.

Discussion

There are several studies on the incidence of asthma and wheezing bronchitis in children below 4 years of age (1–3). However, the size of the populations studied has generally not permitted estimation of severe manifestations, such as the need for hospitalization. In this study we included only children who were hospitalized for the first time and had severe breathing difficulties. With these criteria, the incidence was 3/1000, which is close to what is reported from the USA over a 30-year period (9, 16). In hospital-based studies approximately 50% of the hospital admissions are first-time admissions (10, 11). From Canada a rate of 7.2/1000 was reported for hospital admissions for asthma among 3-year-old children (24). Since about half of hospital admissions with wheezing are first-time admissions, the Canadian data are in good agreement with the Swedish and the US statistics.

In a Finnish study of mainly younger children, a higher rate of 14/1000 can be calculated from the presented data (10). The probable reasons for the higher incidence in the Finnish study were that children under the age of 4 months were also included and that there was a large RSV epidemic during the study period. The incidence of hospitalization in infants below 1 year of age for verified RSV infection in our area is 6–20/1000 during an RSV epidemic (personal communication, Eriksson 1993).

In families with a history of atopic disease and children with previous wheezing, a changed behaviour in relation to risk factors can be suspected. This was illustrated by the fact that there were fewer pets in the households of the children in this group of cases than among the controls and the occurrence of parental smoking and breast feeding did not differ. One interpretation of these data is that exposure to

important environmental risk factors, such as fur-coated pets and ETS is actively avoided by high-risk parents, particularly if their child already has symptoms suggestive of asthma.

High IgE levels have been found in children with hyperreactive airways and a family history of atopic disease (17, 18). This concurs with our findings of the highest IgE levels in children of the older age group with negative viral isolation but atopic heredity.

Rhinovirus peaks in the autumn were most common in the older children. These autumn peaks have also been reported by others (13, 21, 22). The importance of rhinovirus in exacerbation of asthma has received increasing attention recently (23). In this study rhinoviruses were found in the older children with both symptoms of atopic disease and a history of previous wheezing. Other viruses such as RSV and parainfluenza were more evenly distributed among all the children studied. This confirms that RSV and parainfluenza are common causes of respiratory infections both in children with and without wheezing, while the rhinovirus infections are uncommon causes of hospitalization except when wheezing is triggered in predisposed children (21). The prevalence of wheezing and RSV infections show a similar pattern over time, as demonstrated in our study.

In spite of the fact that the majority of children had a history of a preceding upper respiratory tract infection, viral etiology could only be found in 26% of the children. This discrepancy between the clinical history and the outcome of the virus isolation probably has several causes. First, all cases with virus infection are not identified; for example, the sensitivity of virus isolation for RSV is known to be about 70% in relation to cases detected by immunofluorescence diagnosis. Second, the time lag between the start of infection and wheezing leading to admission is sometimes a few days. This would further reduce the chance to obtain a positive virus isolation. No serological analyzes were performed. The slightly lower rate of positive virus isolation in the children with previous wheezing, who were also somewhat older, may indicate that they were reinfected, e.g., by RSV, and then harboured the virus in the nasopharynx during a shorter period of time. The fact that children who had had more than five upper respiratory tract infections before 18 months of age also had more negative virus isolations could be interpreted in the same way; i.e., repeated viral infections result in a shorter time period during which virus can be recovered in nasopharynx.

The patients of the population studied could probably be divided into two different groups of children, one with a virus infection and the other with an atopic disease aggravated perhaps by a virus in-

fection. In this latter group, symptoms interpreted by the parents as caused by infection could in fact have been those of atopic pathogenesis. This could be another reason for the low rate of positive virus isolations. In a recent study of wheezing and asthma during the first 6 years of life, it was shown that children with wheezing probably belong to separate groups with different underlying pathogenic mechanisms (26). It was also demonstrated, as in our study, that smoking is a risk factor for early and often transient wheezing. This emphasizes the necessity of considering several pathogenic mechanisms of wheezing in early childhood.

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