

RESPIRATORY DEVELOPMENT OF 5 TO 6 YEAR-OLD CHILDREN EXPERIENCING A FIRST BRONCHIOLITIS EPISODE BEFORE AGE ONE

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SUMMARY:

■ **Background:** The relationship between early infections due to respiratory syncytial virus (RSV), particularly bronchiolitis in infancy, and the subsequent development of asthma, bronchial hyper-responsiveness, and/or other allergic manifestations, seems increasingly certain, even if the mechanisms involved are not yet quite clear.

■ **Objectives:** The objectives of this work were to determine the prevalence of, and risk factors for, asthma and allergy in 5 to 6 year-old children who five years previously, had experienced their first episode of bronchiolitis before the age of twelve months, and to define the possible effect of the age at which the bronchiolitis occurred on the subsequent development of asthma.

■ **Method:** A retrospective cohort survey was conducted, based on the registers of two hospital paediatric emergency units (Unit A: the Ambroise Paré teaching hospital at Boulogne, France and unit B: the General Hospital of Cherbourg, France). The cohort comprised 5-6 years old children who had consulted or been admitted to emergency unit A or B between October 1993 and March 1994 for a first attack of bronchiolitis before the age of 12 months.

■ **Results:** One hundred and twenty eight children were included in the two centres (centre A: 78; centre B: 50). A familial history of allergy was found in 92 children (71.8%). Fifty-two (40.6%) were exposed to tobacco smoke. One hundred and five children (81.2%) had been hospitalised during the first episode of bronchiolitis, but none had been placed in intensive care. Their mean age at admission was 5.1 months, and 29 children were less than three months old.

Ninety seven children (75.8%) had experienced at least one episode of wheezing at some time of their life. In the twelve months before the telephone interview, 40 children (31.3%) had had at least one such episode, 47 (36.7%) an attack of asthma, 32 (25.0%) wheezing after an effort, 43 (39.4%) a dry cough at night, 52 children (40.6%) had exhibited allergic rhinitis signs, and 32 (25.0%) eczema.

Among the 47 children who had experienced at least one attack of asthma during the previous twelve months, 27 (57.4%) had a history of familial asthma ($p < 0.04$). This was the only significant relationship observed in this study with regard to risk factors for asthma. No relationship was observed between asthma or recent wheezing on the one hand, and on the others age less than three months during the first bronchiolitis episode ($p = 0.6$), initial hospital admission ($p = 0.6$) tobacco smoke exposure ($p = 0.27$), sex ($p = 0.10$) or day care management until age three ($p = 0.73$).

■ **Discussion:** This study showed a high prevalence of asthma and other allergic manifestations in children who five years previously, had experienced their first bronchiolitis episode before the age of twelve months. The only risk factor for asthma or chest wheezing identified in this study was a familial history of allergy. These data support the idea that for most children, early acute bronchiolitis, even if severe, is a transient event, with no or very few consequences in the middle or long term. Nevertheless it may be the expression of an interaction between viral infection and atopic familial predisposition leading to lasting bronchial hyper-responsiveness.

INTRODUCTION

The present prevalence of asthma and allergic manifestations in children seems considerable in most countries, as reflected by the results of the ISAAC study (International Study of Asthma and Allergies in Childhood) conducted among 460 000 children in 56 countries [1].

Among the possible factors determining this prevalence, acute respiratory infections in young children are often incriminated, although in the long term they may have a protective effect [2].

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The relationship between early infections due to respiratory syncytial virus (RSV), especially bronchiolitis in infancy, and the subsequent development of asthma, bronchial hyper-responsiveness, and/or other allergic manifestations, seems increasingly certain [3-5], even if the mechanisms involved are not yet quite clear [6-8].

METHODS

A retrospective cohort survey was conducted on the basis of two hospital paediatric emergency unit registers (Unit A: the Ambroise Paré teaching hospital at Boulogne, France and unit B: the General Hospital of Cherbourg, France). The cohort comprised 5-6 years old children who had consulted or been admitted to

emergency unit A or B between October 1993 and March 1994 for a first attack of bronchiolitis before the age of 12 months. Children with a history of prematurity, mechanical ventilation during the neonatal period, chronic pulmonary disease or a congenital heart defect were excluded.

After at least one parent of each child included had given written consent to the study design, the families concerned were called by phone and asked to answer a questionnaire which had been validated for the ISAAC study (Table 1).

Hospital admission: Yes/no

If yes:

- General paediatrics ward
- Intensive care unit

■ Evolution:

Has your child ever experienced wheezing or whistling in the chest at any time in the past: yes/no/do not know. During the last twelve months (answers: yes/no/do not know):

- Has your child ever had wheezing or whistling in the chest?
- How many attacks of wheezing has your child had?
- How often, on an average, has your child's sleep been disturbed due to wheezing?: never/less than one night per week / one or more nights per week
- Has wheezing ever been severe enough to limit your child's speech to one or two words at a time between breaths?
- Has your child ever had asthma?
- Has your child's chest sounded wheezy during or after exercise?
- Has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?
- Has your child sneezed, or had a blocked nose, although he/she had neither a cold, nor influenza?
- Has your child at any time had an eruption on the skin (red patches or spots) that itches (desire to scratch) which appeared and/or disappeared intermittently over a period from of least 6 months?
- Did such an eruption occur during the last 12 months?

■ Family history:

- total number of children in the family
- Eczema (siblings, father, mother)?
- allergic rhinitis ?
- asthma ?

■ Personal history:

- Rank in the family/.....
- Eczema or equivalent
- allergic rhinitis or equivalent
- passive nicotine at home

Preferential day care organisation from the age of 3 months to 3 years:

- collective day nursery,
- family day nursery,
- wet nurse,
- intermittent day nursery,
- parental day care.

Table 1: Phase 1 of the ISAAC Questionnaire (6-7 year old children). Initial episode of bronchiolitis

ANALYSIS

The data obtained from the answers to the questionnaire were processed with Excel software and analyzed with SPSS software version 8.0. Qualitative data were compared by the chi-squared test, or by Fischer's exact test for small samples. Quantitative data were compared by the Student t test. The significance level was set at less than 0.05.

RESULTS

During the winter of 1993-1994, 253 children less than twelve months old were seen for bronchiolitis in the paediatric emergency units of the two investigating centres. A letter of information was sent to the 138 families involved that could be traced in 2000. One hundred and thirty five agreements to participation in the study were obtained. Six children were excluded: two for prematurity, two for a congenital heart defect and trisomy 21, and two for neonatal respiratory disease. One child died of purpura fulminans. A hundred and twenty eight children were finally included in the two centres (centre A: 78; centre B: 50). The sex ratio was 1.28. Atopic signs (allergic rhinitis, eczema and/or asthma) were found in first degree relatives of 92 children (71.8%). Fifty two children (40.6%) were exposed to tobacco smoke, with a large difference between centres: 26.6% in Boulogne but 64.0% in Cherbourg ($p < 0.001$). In this sample, more of the Boulogne children (mostly urban) had day care management by a non parental organisation than Cherbourg children who were mostly from semi-rural areas (74.3% versus 20.0, $p < 0.001$) (Figure 1).

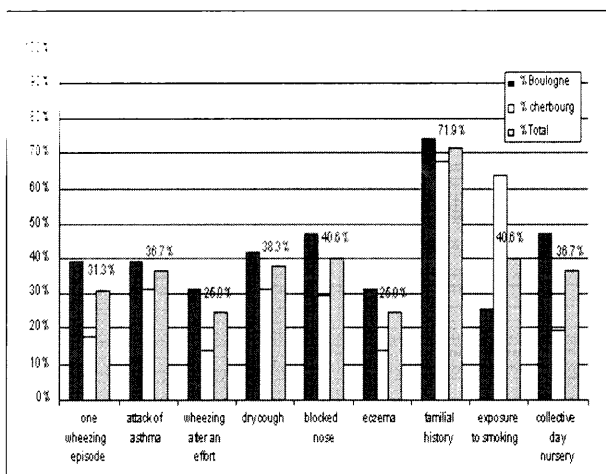


Figure 1: Respiratory signs recorded in 5-6 year-old children in Boulogne (n=78) and Cherbourg (n=50) between October 1993 and March 1994.

HOSPITALISATION AT THE FIRST BRONCHIOLITIS EPISODE

One hundred and five children (81.2%) were admitted during their first bronchiolitis episode. None of them was admitted to an intensive care unit. The mean age of the children admitted was 5.1 months, and 29 were less than three months old.

CLINICAL SIGNS IN THE 5-6 YEAR- OLD CHILDREN

Of the 128 children studied, 97 (75.8%) had experienced at least one episode of wheezing at some time in their life, and 29 (26.6%) at least one episode of eczema. During the twelve months before the telephone interview, 40 children (31.3%) had had at least one episode of wheezing, 47 (36.7%) an attack of asthma, 32 (25.0%) wheezing after an effort, and 43 (39.4%) a dry cough at night. Fifty two children (40.6%) had allergic rhinitis signs, and 32 (25.0%) eczema. Three children had experienced at least four episodes of wheezing during the previous year. Five children had been woken at night by asthma, from once (two cases) to ten times (one case) during the previous twelve months.

RELATIONSHIP BETWEEN THE DIFFERENT CLINICAL SIGNS AT 5-6 YEARS

A significant relationship was observed between the occurrence of at least one attack of asthma during the year preceding the interview, and one episode of wheezing at rest, wheezing at effort or a dry cough at night ($p<0.001$). There seemed to be a link between asthma and allergic rhinitis, and between wheezing and allergic rhinitis ($p<0.001$). The relationship between asthma and eczema seemed weaker in our study ($p=0.11$).

RISK FACTORS FOR ASTHMA AND WHEEZING AT 5-6 YEARS (UNIVARIATE ANALYSIS)

Among the 47 children who had had at least one attack of asthma in the previous twelve months, 27 (57.4%) had a familial history of asthma ($p<0.04$). This was the only significant risk factor for asthma observed in this study. No relationship was found between asthma or recent wheezing on the one hand, and on the other, age less than three months during the first bronchiolitis episode ($p=0.6$), initial

admission ($p=0.6$) tobacco smoke exposure ($p=0.27$), sex ($p=0.10$) or day care management until age three ($p=0.73$).

DISCUSSION

This study showed a high prevalence of asthmatic and other allergic signs in a sample of children who had experienced a first episode of bronchiolitis before the age of twelve months. We compared these results with those previously obtained with the same questionnaire in phase 1 of the ISAAC study of 6-7 year-old children in various regions of France (data delivered by self questionnaire and not by phone) [9]. In our study 36.7% of the children included had had at least one recent attack of asthma versus 9.3% in Bordeaux (the main town in the Gironde administrative area), and 6.7% in Strasbourg (the main town in the Lower-Rhine area); 31.3% of our children had experienced wheezing in the previous twelve months versus 8.0 % in the Bordeaux sample and 6.1% in the Strasbourg sample (Table 2). In another survey conducted in the Pyrenean region of south-west France a cumulative prevalence of asthma of 8.6% was found in 5-6 year-old children [10].

The question of defining asthma as a typical crisis, wheezing or night cough did not seem to have much effect on the results of this study, for all these factors appeared to be closely connected at the statistical level. The frequency of wheezing reported in the questionnaires, which was lower than that of asthma proper, may be surprising, but it probably reflected a recall bias, because an attack of asthma is an event which makes a greater impression on parental minds than "simple" wheezing, whose therapeutic consequences are not as burdensome.

Transient bronchial hyper-responsiveness, as reflected by isolated episodes of wheezing, may have an especially strong link with tobacco smoke exposure, independently of allergic history [5], but no significant relationship between wheezing and tobacco smoke exposure appeared in our study, probably because it lacked statistical power.

	Our study (%)	ISAAC survey (%)	
		Bordeaux	Strasbourg
At least one episode of wheezing at any time	75.8	18.3	14.8
Wheezing in the last 12 months	33.0	8.0	6.1
Asthma in the last 12 months	33.0	9.3	6.7
Wheezing after an effort	26.0	3.3	2.7
Dry cough at night	39.0	16.4	17.9

Table 2: Comparison of our results with those of the ISAAC survey for France including children of an age (6-7 years) close to that of our cohort (5-6 years).

The recent updating of the definition of "atopic background" allowed us to reduce the risk of confusion in our questionnaire (Table 1). It is now defined as follows: "Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis" [11]. Therefore it would be preferable, on the basis of simple interview data, to talk about "allergic background" or "atopy suggestive signs".

The relationship between bronchiolitis in infancy and school age asthma has often been studied. Thus in a case-control study performed in France [3], with an opposite design to our's, it was observed that 54% of asthmatic children aged between four and twelve had a history of bronchiolitis in their first year of life, versus 17% in the control group ($p < 0.001$).

In a Scandinavian prospective survey [12] which included 47 children without any underlying chronic condition, who were hospitalised for RSV-related bronchiolitis before the age of twelve months and followed up until they were 7 and half years old (with 93 controls), the experimental group showed a high cumulative prevalence of wheezing, close to our results: 68% versus 34 in the control group. In the previous year the prevalence of asthma was 23% (versus 2%) at 6-7 years old, and of allergic sensitization, 41% (versus 22). In a multivariate analysis, RSV clearly appeared to be the main risk factor for asthma (OR: 12.7; 3.4-7.1) and allergy (OR: 2.4; 1.1-5.5). With regard to the role of the family background, the risk of asthma in this study was only increased if both parents exhibited allergic manifestations (OR: 3.0; 1.2-7.8).

On the other hand in the study by Kotaniemi-Syrjanen *et al.* [13], the presence of RSV during episodes of wheezing leading to hospital admission before the age of two was a weak predictor of asthma at seven, contrarily to the criteria for atopy (hypereosinophilia, atopic dermatitis, and high blood IgE).

In our study, the prevalence of wheezing occurring at any time up to age 6 was clearly higher than the prevalence reported for the previous twelve months, probably reflecting a decrease in frequency with time. Many other studies have confirmed the idea that, although wheezing is frequent in the years following an initial viral episode, its frequency decreases with time. The Tucson cohort study (Arizona, USA) included 1246 children on long-term follow-up since birth for their clinical, allergologic and functional evolution (970 children are still being followed) [14]. In this study a correlation between lower RSV tract infection and an increased risk of frequent wheezing at age 6

was noted. Although this relationship decreased, it remained significant at 11, but was no longer so at 13. At the age of ten, only 6.2% of children were asthmatic after a RSV bronchiolitis in the Pullan study [15], 22% in the Milner study [16], and 21% in the Noble study [17].

The absence of a relationship between RSV and subsequent atopic status is generally emphasized, indicating that a virus alone is rarely able to initiate lasting allergenic sensitization. On the other hand an aggravating role in the persistence of clinical signs is frequently attributed to a history of familial allergy [4, 18]. Moreover, this was the only risk factor for asthma or chest wheezing identified in our study.

Despite the harmful role attributed to RSV in the genesis of asthma, some authors argue in favour of the a protective long-term impact of early infections. In the Tucson cohort study, the presence of at least one sibling at home and /or collective day care attendance during the first semester of life (involving high early microbial exposure), indeed led to more wheezing at 2 (OR: 1.4 ; 1.1-1.8), but less asthma at 6 (OR : 0.8 ; 0.7-1) and at 13 (OR : 0.3 ; 0.2-0.5). Accordingly, when a young child is not affected by infection with, at the theoretical level, a delay in the maturation of the Th1 pathway which is usually predominant, the Th2 pathway becomes predominant, with increased risk of sensitization to respiratory allergens, and of wheezing bronchitis [2, 20].

Although this "hygienist" theory* remains highly debatable, the importance, from the physiopathological point of view, of the reaction of IgE and /or hyper-eosinophilia during the acute period of an RSV infection seems to be strongly correlated with both a familial history of asthma and the persistence of wheezing at an older age [6,8, 14].

Among the other potential risk factors for allergy, maternal smoking implies an increased risk of early respiratory infections, bronchial hyper-responsiveness and transient wheezing, but does not seem predictive of subsequent persistent asthma [12, 19, 21].

Masculine gender, which is over expressed in early infections, does not appear in our study to be a risk factor for asthma, wheezing or subsequent isolated cough ; in fact we found, at age 5-6, more wheezing boys in Boulogne, and more wheezing girls in Cherbourg ! In the first phase of the ISAAC study, more boys than girls exhibited atopic signs at this age [22]. This male predominance in early childhood is reversed as from puberty. It was recently suggested that testosterone may have an immunodepressive

and protective effect on allergic risk, whereas female sexual steroids may have the opposite effect [23].

The risk of short-term wheezing recurrence after an early RSV lower tract infection seems to have been firmly established [11,24]. However, as in the study by Ploin *et al.* [3], the occurrence of wheezing at a very early age, before three months, does not emerge here as a risk factor for further asthma.

Combining the data for Boulogne and Cherbourg allowed us to obtain a larger cohort, although the power of the present study was probably still insufficient. The sample populations differed in two respects: the method of day care management before age three, and exposure to smoking. These differences probably reflect gaps relating to the urban or semi-rural nature of the two towns, as well as their different economic levels, but they had no apparent effects on our results. Another possible selection bias related to the fact that all the children included in Cherbourg had been hospitalized for a first episode of bronchiolitis should also be stressed (the records of the children treated in the Cherbourg emergency unit but not hospitalized were not available at the time of our study). However any such bias does not seem to have affected our results, because the criteria for hospital admission were not found here to be a factor of additional risk.

In conclusion these data highlight the fact that, although acute, even severe, RSV-related bronchiolitis is a transient event for most children with few or no long term consequences, it may nevertheless, given a predisposing terrain, be the expression of an interaction between virus and atopy, leading to persistent bronchial hyper-responsiveness.

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* According to the Th1/Th 2 immune system paradigm, Th1-related reactions, as characterized by interferon γ and interleukin-2 (IL-2) secretion, are involved in infection mechanisms, whereas Th2-related reactions are responsible for the inflammatory reactions observed in allergic diseases, especially the secretion of IL4 and IL5.

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