PAPERS AND SHORT REPORTS

Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy

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Abstract

Of the 180 children admitted to hospitals in Tyneside in the first year of life with proved respiratory syncytial virus lower respiratory tract infection, 130 were seen for review 10 years later and 34 of the remaining 50 children accounted for. Skin tests, lung function tests, and histamine-challenge and exercise tests for bronchial lability were undertaken in over 100 of the index children and a similar number of control children. A total of 55 (42%) of the 130 index children had had further episodes of wheeze, while only 21 (19%) out of 111 controls had ever wheezed; but few (6.2% v 4.5%) had troublesome symptoms at the age of 10. There was a threefold increase in the incidence of bronchial lability in the index children but no excess of atopy. Maximum expiratory air flow was reduced throughout the vital capacity manoeuvre in the index children, even when those with a history of recurrent wheeze were excluded. Results of single-breath nitrogen washout tests were normal, however, suggesting that ventilation was not appreciably uneven, even though expiratory flow was restricted. These differences might have been caused by infection damaging the growing lung but might also be explained by pre-existing differences in the airway, rendering certain children more susceptible to symptomatic infection when first challenged by the virus in infancy.

Introduction

Bronchiolitis in infancy is a common, distressing problem and several studies have documented recurrent wheezing in many children after an episode of bronchiolitis in early life.^{1,2} An

association has also been noted between subsequent wheezing and other features of atopy.³

Respiratory syncytial virus is the major cause of bronchiolitis in the first year of life.⁴ It may also precipitate wheeze in susceptible older children.⁵ Simon and Jordan suggested that children with bronchiolitis due to respiratory syncytial virus were no more likely to wheeze subsequently than other children but that those who had features of bronchiolitis without respiratory syncytial virus infection were manifesting early asthma and often suffered further recurrent wheezing.⁶ Rooney and Williams, however, looked at 62 children with proved respiratory syncytial virus bronchiolitis in the first 18 months of life and found that 35 had further wheezing.⁷ They also found an increased prevalence of atopy in these children and their families. The high incidence of subsequent recurrent wheeze was confirmed by Sims *et al*,⁸ but they failed to find an increased incidence of atopy in the 26 children who were examined in detail eight years after admission in infancy for respiratory syncytial virus bronchiolitis.⁹

Kattan *et al* looked at 11-year-old children who had had up to three attacks of bronchiolitis before 18 months of age but who had *not* wheezed subsequently.¹⁰ They found widespread minor abnormalities in lung function that they suggested were due to residual parenchymal or airway damage. Only 23 of the 106 children who met their criteria were seen, however, and virological investigations were not undertaken during the initial admission.

We have extended the study of children admitted to hospital in Tyneside during the winter of 1967-8⁸ by reviewing all the children with respiratory syncytial virus lower respiratory tract infection admitted to hospital in the first year of life during the subsequent two winters. We aimed at defining the incidences of subsequent atopy, bronchial reactivity, pulmonary dysfunction, recurrent wheeze, and overt asthma in a larger cohort of children from a defined population.

Subjects and methods

During the survey period 180 children were admitted to hospital in the first year of life (mean age 14 weeks) with respiratory syncytial virus lower respiratory tract infection. Boys and girls were equally

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represented. Children aged 1-4 months at the time of the annual winter epidemic had a 2% chance of being admitted to hospital with respiratory syncytial virus infection. No child was admitted to hospital more than once with either clinical bronchiolitis or respiratory syncytial virus infection. One child died because of his infection, and a further 28 children could not be studied in detail because they had moved out of the area (though most of these were traced). We made no attempt to contact two children who had been adopted, six with a severely disturbed family background, and five with physical handicap (spina bifida, tracheo-oesophageal fistula, cyanotic congenital heart disease, myopathy, leukaemia) severe enough to interfere with assessment. Six families were reluctant to help with the survey, and two children could not be traced because the relevant hospital records were lost.

The remaining 130 children (72%) were seen and examined, and 107 of these completed a full pulmonary reassessment. Ten of the 18 children diagnosed as having bronchitis, 109 of the 144 diagnosed as having bronchiolitis, and 11 of the 18 diagnosed as having pneumonia during the original admission (definitions as suggested by Court¹¹) were seen for assessment. There was nothing to suggest that the health of the children who were not fully assessed differed significantly from that of those who were. Of the children admitted with clinical features of bronchiolitis, 25 had shown subsegmental collapse or consolidation in the chest radiograph (of whom 21 were seen for follow-up) and 23 had had segmental shadows (of whom 15 were seen for follow-up).

Control children of comparable age, sex, and social class were contacted with the consent of the family doctor. Care was taken to ensure that the control sample was not biased by excluding children with a history of respiratory problems (a possible defect in the earlier survey, where control children had been selected by school staff).⁸ One of the controls had been in hospital with bronchiolitis (no virus was isolated), and a second had been admitted with "wheezy bronchitis" in the first year of life. Only five of the 111 control

measured with a large pneumotachograph. Between four and six curves were recorded with a Hewlett-Packard Pulmonary Function System and the curve with the highest FVC + FEV₁ analysed.

Single-breath nitrogen washout tests were performed using the same system with the child seated. After a few tidal breaths through a small pneumotachograph the child breathed out to residual volume, then slowly breathed-in 100% oxygen to vital capacity and breathed out to residual volume again, keeping the flow between 0.3 and 0.5 l/min.¹³ Up to six recordings were made in an attempt to get three satisfactory traces using the criteria for acceptability suggested by the National Heart and Lung Institute. The slopes of the alveolar plateau (phase III) and closing volume were calculated automatically¹⁴ and the results checked visually.

Procedure—The tests were generally carried out the same day and the order of testing varied. There was always at least one and a half hours between the end of one challenge test and the start of the next, and at least 40 minutes between a challenge procedure and lung function testing.

Statistical analysis was by *t* test for continuous variables and by χ^2 test for grouped data. Paired *t* tests were not used: an attempt to match in pairs was not always successful and the numbers available for analysis would have been reduced.

The study was approved by the local ethical committee of the area health authority.

Results

Analysis confirmed that the index and control children were of comparable age, sex, and social class. The children who had had respiratory syncytial virus infection in infancy were a little shorter and lighter but the difference was not significant (table I). They had more siblings and their parents smoked more.

TABLE I—Children admitted to hospital for respiratory syncytial virus lower respiratory tract infection in first year of life and their families compared with control sample

	Respiratory syncytial virus infection	Control children	Significance (p)
No in group	130	111	
Mean height in cm (range)	138 (117–161)	139 (124–163)	NS
Mean weight in kg (range)	32.5 (21–60)	33.5 (23–69)	NS
Mean No of siblings	2.2	1.6	< 0.001
Mean No of older siblings	1.6	1.0	< 0.001
Percentage of mothers who smoked	68	40	< 0.001
Time of study 10 years before	68	46	< 0.001
Percentage of fathers who smoked	66	45	< 0.001
Time of study 10 years before	73	59	NS

NS = Not significant.

children contacted declined to help with the respiratory function tests.

Exercise test—The children performed peak expiratory flow (PEFR) manoeuvres on a Mini-Wright peak-flow meter and the best of three satisfactory manoeuvres was recorded. They then ran energetically on the flat for six minutes. The PEFR was repeated 1, 3, 5, 10, and 15 minutes after the end of the run. The pulse was taken at the end of the run and the test considered satisfactory if the pulse was 170 beats/min or over.

Histamine challenge—Histamine acid phosphate in buffered saline was used in doubling concentrations from 0.03 g/l to 16 g/l and delivered from a Wright nebuliser with oxygen flowing at 7 l/min. Forced expiratory volume in one second (FEV₁) was recorded on a Vitalograph. After baseline measurements five slow inspiratory capacity breaths of nebulised saline were inhaled and a further baseline recorded after three minutes. Increasing concentrations of nebulised histamine were then inhaled and FEV₁ measured three minutes after each inhalation. If there was a fall from the post-saline FEV₁ of 20% or more the test was stopped and the concentration necessary to produce a fall of 20% (PC₂₀) noted.¹²

Skin testing—Prick tests were performed with the same allergens as before⁸ (but excluding the fish and mixed moulds) and a negative control solution (Bencard reagents). A weal 3 mm or more in diameter at 15 minutes was considered positive. Only one child (in the control group) had a response to the control solution.

Flow-volume curve—Forced vital capacity (FVC) in litres (body temperature, pressure, and saturation), FEV₁, forced mid-expiratory flow (FEF_{25–75%}), and maximum expiratory flow after 50% and 75% of the vital capacity had been expired (MEF_{50%} and MEF_{75%}) were

Wheezing and asthma—Table II shows the incidence of wheezing. The difference was most pronounced in the first four years of life, and many children with recurrent wheeze during that time had stopped wheezing by the time they were 6. Ten index and four control children, however, began to have recurrent episodes of wheeze only after they were over 2 years old, and all these children were still having intermittent symptoms when seen. Eight of the index patients and five of the controls had had more than three attacks of wheezing in the past year or were taking regular treatment for asthma. One child in each group was taking an inhalational steroid, two index patients and three controls were taking cromoglycate, while three index patients and one control had used bronchodilators intermittently in the past year. One other index patient who had had a single attack of wheeze in the past year also had a reserve bronchodilator. Boys in the control group were more than four times as likely as girls to have episodes of recurrent wheeze in the first two years of life (24% v 5%) and in the two years immediately before the survey (20% v 5%), but the incidence of recurrent wheeze in index children was almost identical in the two sexes (36% v 35% at 0-2 years of age and 22% v 23% at 8-10). The excess of recurrent wheeze in index children was largely due to the increased incidence of wheeze in girls at 2 (p < 0.001) and 10 (p < 0.02). Respiratory infection was thought by the parents to be the commonest factor precipitating wheeze (43 out of 55 index patients (78%); 15 out of 21 controls (71%)). Some were said by their parents to have exercise-induced wheezing (nine index patients (16%)), seven controls (33%)), and some to have allergen-induced wheezing (three index patients (15%)), three controls (14%)). The prevalence of wheezing among first-degree relatives was the same in both groups.

TABLE II—Wheeze, airway obstruction, and bronchial lability when seen at follow-up after 10 years

		Respiratory syncytial virus infection		Control children		Significance by χ^2 test (p)
		No	%	No	%	
History of wheeze	At any age	55/130	42	21/111	19	<0.001
	In first four years	50/130	38	17/111	15	<0.001
	In last two years	29/130	22	14/111	13	<0.07
	In first-degree relatives	88/515	17	62/398	16	NS
Currently receiving medication for asthma		7/130	5	5/111	5	NS
Evidence of airway obstruction (FEV ₁ /FVC <72%)	Children currently taking medication for asthma ..	5/7	71	2/5	40	NS
	Other children with history of wheeze	4/39	10	0/15	0	NS
	Children with no history of wheeze	5/52	10	0/84	0	<0.005
Evidence of bronchial lability	Fall in FEV ₁ >15% after exercise	13/79	16	5/100	5	<0.05
	Histamine challenge positive (<16 g/l)	19/102	19	6/104	6	<0.01
	Either of the above	26/105	25	7/106	7	<0.001

NS = Not significant.

Bronchial lability—There was more bronchial lability in the children with a history of respiratory syncytial virus infection in infancy in response both to exercise and to histamine challenge (table II), but many children gave a positive response to only one test (see fig 1). In the index group six showed a positive response to both tests, six to exercise only, and eight to histamine only; in the control group four gave a positive response to both tests, one to exercise only, and one to histamine only.

Recurrent upper respiratory tract symptoms—Twelve of the index children (9%) and two of the controls (2%) were reported by their parents as having persistent troublesome cough (p < 0.05); over half of these children also had a history of recurrent wheeze and increased bronchial reactivity on histamine challenge. Twenty-nine of the 130 index children also reported “more colds than other children” (upper respiratory tract colds or “head” colds rather than “chesty” colds) compared with five of the 111 controls (p < 0.001). Twenty of these 29 children had had further episodes of wheeze but only four were being treated for asthma and only 12 had evidence of excess bronchial lability. They also had reduced flow-volume curves, even when the 16 children who had wheezed in the past two years were excluded (p < 0.05).

Atopy—Eczema and rhinitis were less commonly reported in the children with respiratory syncytial virus infection in infancy, though this did not reach statistical significance (25 (19%) of index patients, 33 (30%) of controls). There were similar findings in first-degree relatives (57 out of 515 in the index group (11%) and 56 out of 398 in the control group (14%)). The index group also had fewer children with positive skin tests to one or more of the antigens used (16 of the 107 index patients and 28 out of 102 controls; p < 0.05). Sixteen of the 39 children tested who were still having intermittent wheeze had evidence of atopy as judged by at least one positive skin test result (≥ 3 mm), including all the children receiving continuous prophylactic treatment for asthma (fig 2). Total IgE concentrations were measured in 70 of

FIG 1—Bronchial lability in response to histamine (expressed as concentration producing 20% fall in FEV₁; PC₂₀) and exercise in 130 10-year-olds originally admitted because of respiratory syncytial virus lower respiratory tract infection in first year of life. ● = Children with current intermittent episodes of wheeze. ○ = Children with past history of recurrent wheeze.

FIG 2—Correlation between bronchial reactivity (as shown by histamine challenge and expressed as concentration producing 20% fall in FEV₁; PC₂₀) and atopy (as shown by skin testing) in children still having intermittent wheeze at age 10. ● = Children with positive skin tests. S, C, B = Children receiving treatment for asthma with inhaled steroids (S), cromoglycate (C), and bronchodilators (B).

the index children; of the 43 with no subsequent history of wheeze, 12 (29%) had concentrations that might be considered diagnostic of atopy (>150 IU/ml) and a further 4 (9%) had values consistent with atopy (>75 IU/ml) but not outside the range seen in non-atopic schoolchildren. Only six of the index children without a history of subsequent wheeze gave a positive skin test result at 10. Children who had only a past history of wheeze had little atopy but half of the children with current wheeze had IgE concentrations diagnostic of atopy and over two-thirds had concentrations consistent with atopy, including all the wheezy children with bronchial reactivity on histamine challenge. IgE measurements were not attempted in control children.

Lung function tests—Mean peak flow and all variables measured on the flow-volume curves were significantly reduced in the index group (table III). The index children were slightly shorter than the controls,

TABLE III—Lung function at 10 years old (range 8.9-11.5 years)

Test	Mean $\pm$ SD		% Predicted for height		Significance (p)
	Respiratory syncytial virus infection (n = 98)	Control children (n = 104)	Respiratory syncytial virus infection	Control children	
PEFR (l/min)	301 $\pm$ 55	335 $\pm$ 43	101.2	110.8	<0.001
FVC (l)	2.26 $\pm$ 0.39	2.38 $\pm$ 0.40	96.0	100.1	<0.005
FEV ₁ (l)	1.81 $\pm$ 0.32	2.01 $\pm$ 0.30	92.8	101.5	<0.001
FEV ₁ /FVC (%)	80.5 $\pm$ 7.1	84.6 $\pm$ 6.9	—	—	<0.001
MEF ₅₀ (l/s)	2.19 $\pm$ 0.66	2.58 $\pm$ 0.56	84.9	98.1	<0.001
MEF ₇₅ (l/s)	0.94 $\pm$ 0.32	1.24 $\pm$ 0.39	84.7	109.3	<0.001
MEF ₂₅₋₇₅ (l/s)	1.90 $\pm$ 0.56	2.27 $\pm$ 0.51	86.8	102.9	<0.001

but when the results were expressed as percentage predicted for height and sex there was still a significant difference in values (fig 3); and this remained true when those index children who had not wheezed since the original infection were compared with control children with no history of wheeze (table IV). Similar differences also remained when the children of mothers with a history of smoking were excluded from analysis. Two control children who were being treated for asthma had evidence of airway obstruction at rest ($FEV_1/FVC < 72\%$) but none of the other control children had any such evidence. Of the 98 index children tested, 14 had evidence of airway obstruction (table II).

FIG 3—Values for FEV_1 and MEF_{75} expressed as percentage of expected value for child's height in 10-year-olds originally admitted because of respiratory syncytial virus lower respiratory tract infection in first year of life and in control children. ● = Children with current intermittent episodes of wheeze. ○ = Children with past history of recurrent wheeze.

The 63 index children who performed an acceptable single-breath nitrogen washout test had a mean phase III slope of $1.24 \pm SD 0.62$ $\%N_2/l$, which was closely similar to the mean of 1.35 ± 0.49 for 89 control children. Excluding those children unable to co-operate for long enough to produce replicate measurements made no difference to the means. The two children receiving inhalational steroids and two of the five receiving cromoglycate had phase III slopes exceeding 2 $\%N_2/l$. Only seven other children had an abnormally high phase III slope (three index and four control children), and none of these had evidence of airway obstruction ($FEV_1/FVC < 72\%$). No abnormalities in closing volume were seen.

TABLE IV—Lung function in children with no further wheeze after original episode of respiratory syncytial virus infection and control children with no history of wheeze

Test	Mean $\pm$ SD		% Predicted for height		Significance (p)
	Respiratory syncytial virus infection (n = 52)	Control children (n = 84)	Respiratory syncytial virus infection	Control children	
PEFR (l/min)	312 $\pm$ 48	334 $\pm$ 43	104.1	110.8	<0.05
FVC (l)	2.32 $\pm$ 0.38	2.36 $\pm$ 0.40	97.3	100.0	NS
FEV_1 (l)	1.90 $\pm$ 0.28	2.01 $\pm$ 0.30	96.2	102.3	<0.005
FEV_1/FVC (%)	82.1 $\pm$ 6.5	85.7 $\pm$ 5.8	—	—	<0.005
MEF_{50} (l/s)	2.39 $\pm$ 0.62	2.66 $\pm$ 0.52	92.3	101.3	<0.05
MEF_{75} (l/s)	1.04 $\pm$ 0.30	1.27 $\pm$ 0.36	93.0	112.3	<0.001
MEF_{25-75} (l/s)	2.07 $\pm$ 0.50	2.34 $\pm$ 0.47	94.4	106.1	<0.005

NS = Not significant.

Findings at initial illness in relation to outcome—The clinical diagnosis, radiographic appearances, age at admission, and severity of the initial illness were analysed in relation to the outcome at follow-up. Severity was also assessed by the need for tube feeding or supplementary oxygen. No relation was found between any of these criteria and increased bronchial lability, continuing wheeze, or subsequent pulmonary function, though there was some tendency for the children who had had a severe illness to have slightly lower flow-volume curves at follow-up—for example, MEF_{50} 2.10 v 2.26 l/s.

Discussion

This study attempts to assess the progress of a complete cohort of children with respiratory syncytial virus lower respiratory tract infection requiring admission to hospital in Newcastle upon Tyne in the first year of life. The six children who were traced but could not be seen may have done particularly well and their families may not have seen the need for review; there were too few of these children to influence the main conclusion, however, and we have no reason to suppose that the other children who were not seen had done particularly well or particularly badly.

We still do not know why some infants are more likely than others to develop lower respiratory tract symptoms when exposed to respiratory syncytial virus infection in the first year of life. The correlation with maternal smoking has been reported before^{8,15} and agrees with reports that, though maternal smoking is not associated with an increased incidence of respiratory illness from all causes in infancy, it is associated with an increased incidence of lower respiratory tract illness.¹⁶ The correlation with family size may reflect increased exposure to the virus, particularly when the infant sleeps in the same room as another child.¹⁵ The belief that some index children suffered more upper respiratory tract infection than other children may merely reflect differing parental expectations; nevertheless, some virological studies support the view that the defence mechanisms of the respiratory tract against virus infection are defective in some wheezy children.¹⁷

WHEEZE AND ASTHMA

Most of the excess wheeze in the index children occurred in the first four years of life, and much of the excess wheeze at 10 occurred in girls with little atopy and only marginally increased bronchial reactivity. This might suggest that a history of respiratory syncytial virus lower tract respiratory infection in infancy is associated with an excess of "wheezy bronchitis" but no increase in "asthma." It is doubtful, however, whether this diagnostic distinction has any valid theoretical basis.^{18,19} Four of the 12 children taking medicine for asthma had no evidence of increased bronchial lability on histamine challenge, and two of these had negative skin test results (fig 2). On the other hand, three of the index children with negative skin test results but labile bronchi who were not receiving treatment were still having episodes of distressing wheeze, which responded to subsequent bronchodilator treatment. Such children are hard to categorise.

The high incidence of wheeze in infancy and the increased incidence of wheeze after respiratory syncytial virus infection in infancy have been noted before, and there is good evidence that the second of these correlates with an increased incidence of bronchial reactivity to exercise⁸ and methacholine challenge²⁰ in later childhood. Gurwitz *et al*²⁰ found that a third of the first-degree relatives of index children with increased lability also had reactive bronchi but they did not test the relatives of index children without bronchial lability; in our series a history of wheeze was no commoner in the relatives of index children than in the relatives of controls (table II). Hence while it remains probable that the index children were born with increased bronchial lability (and possible that this is inherited), the increased lability at the age of 10 might have been acquired as a result of bronchial infection in infancy. Respiratory syncytial virus infection in adult life can certainly cause increased bronchial lability for many weeks,²¹ while smoking may apparently have an even more longlasting effect.²² Reports that children with cystic fibrosis²³ and children with a past history of surgery for congenital tracheo-oesophageal fistula,²⁴ broncho-pulmonary dysplasia after ventilation for hyaline membrane disease,²⁵ a past history of accidentally inhaled foreign body,²⁶ or near-drowning,²⁷ all have a high incidence of increased bronchial lability on follow-up suggest that pulmonary damage

in early infancy may sometimes modify bronchial reactivity permanently.

There was no correlation with tests of atopy in later childhood or a family history of allergy either in this study or in the smaller study reported by Sims *et al.*⁹ Reports that babies tested for atopy at the time of admission to hospital for respiratory syncytial virus bronchiolitis are more likely to have positive skin test results than control patients of the same age²⁸ are difficult to reconcile with these observations unless manifestations of atopy change with age. It is sometimes suggested that atopy and bronchial reactivity are immutable and separately inherited characteristics.^{8,19} Were this so, we should have expected to find at least a few children with severe bronchial reactivity who had no evidence of atopy, but all the children with a PC₂₀ of less than 8 g/l had positive skin test results (fig 2), and all the index children with wheeze who responded to histamine had IgE concentrations exceeding 100 IU/ml.

STRUCTURAL DAMAGE FROM VIRAL INFECTION

Flow-volume measurements were reduced in the index children, and similar differences persisted when children with a history of parental smoking were excluded from consideration, making it unlikely that this factor was responsible for much of the observed difference. Important differences also persisted when children with a history of recurrent wheeze in later infancy were excluded. Kattan *et al.*¹⁰ reported similar findings and suggested that this might be a long-term consequence of bronchiolar infection damaging the growing lung. Sequential studies certainly show that functional abnormalities often persist for many months after acute bronchiolitis in early infancy,²⁹ and permanent damage sometimes occurs after adenovirus infection.³⁰ Such infection would certainly be expected to damage the terminal airways unevenly, and it is therefore hard to reconcile this hypothesis with the lack of any evidence of uneven gas distribution in the single-breath nitrogen washout tests. In this respect our findings differ from those of Kattan *et al.*,³¹ who found a low arterial Po₂ in 18 of their 23 children and minor nitrogen washout abnormalities in the six children tested. Our findings are compatible, however, with the hypothesis that pre-existing structural differences in the pulmonary airways at birth render some children more susceptible to symptomatic lower respiratory tract infection than most when first challenged by respiratory syncytial virus in infancy.

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MEDICINES COLD IN THE SECOND AND THIRD DEGREE—Such whose stomachs are strong, and livers hot, may easily bear such medicines as are cold in the second degree, and in cases of extremity find much help by them; as also by such as are cold in the third degree, the extremity of the disease considered, for by both these the unbridled heat of choler is assuaged. Also they are outwardly applied to hot swellings, due consideration being had, that if the inflammation be not great, use those that are less; if the inflammation be vehement, make use of medicines cold in the second or third degree, always let the remedy correspond to the just proportion of the affliction. Thirdly, sometimes the spirits are moved inordinately through heat, thence follows immoderate watchings, if not deprivation of the senses, this also must be remedied with cold medicines, for cold stops the pores of the skin, makes the humours thick, represses sweat, and keeps up the spirits from fainting. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)