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Selective infection of lower respiratory tract by respiratory viruses in children with recurrent respiratory tract infections

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Abstract

Thirty preschool children presenting with recurrent respiratory infections and their unaffected siblings were observed prospectively for a year. The index children experienced more episodes of acute respiratory infection than their siblings. Respiratory viruses were the major cause of respiratory infections. The index children had lower respiratory tract disease, predominantly wheeze, during 34% of proved respiratory virus infections compared with 11% of such infections experienced by the control children ($p < 0.02$). Atopic children had an increased tendency to wheeze that did not reach significance, but atopy was not associated with increased susceptibility to respiratory infections.

Introduction

There is a large group of children with recurrent respiratory tract infections who are seen by their general practitioners and by paediatricians and for whom conventional immunological tests show no cause for their increased susceptibility to infections.¹ It is not known whether such children are experiencing mainly viral or bacterial infections. The association between wheezy bronchitis and respiratory virus infections is, however,

well documented. Horn and colleagues isolated respiratory viruses from tissue culture in 146 (24%) of 554 episodes of acute wheezy bronchitis in children aged 0 to 12 years, and half of the viruses isolated were rhinoviruses.² The same workers isolated rhinoviruses in large numbers from the sputum of children with wheezy bronchitis, suggesting lower respiratory tract multiplication of the virus.³

Some, but not all, children who wheeze during virus infections are atopic.²⁻⁴ Atopy and increased bronchial lability are thought to be determined independently, since children with a persistent increase in bronchial lability after bronchiolitis are not atopic.⁵ It is not known whether atopy is associated with an increased susceptibility to respiratory infections; Minor *et al* suggested that asthmatic children are more susceptible to respiratory virus infections than their non-asthmatic siblings,⁶ but the total number of respiratory infections experienced by asthmatic and non-asthmatic children in their study was identical and atopic status was not specified.

We undertook a prospective study of 30 preschool children with recurrent respiratory infections and their unaffected siblings.

Patients and methods

Thirty children aged 6 months to 6 years presenting consecutively to the paediatric department with recurrent upper or lower respiratory tract infections (or both) were admitted to a prospective study. The index children were reported by their parents to have had at least 10 infections in the previous year and all had an unaffected sibling in the same age range who acted as control. Sibling pairs were observed prospectively for a year from admission to the study. The sibling control group was 1.4 years older on average than the index group ($p < 0.05$ by the Student's paired *t* test). The mean age of the index group at presentation was 2.2 years. Only one index child and one control sibling were under one year of age at presentation.

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Index and control children were visited at home by one of us (DI) during each respiratory episode, a clinical diagnosis was made according to the criteria of Court⁷ and recorded, and specimens of respiratory secretions were obtained for viral and bacterial cultures. Nose and throat swabs were taken with sterile serum-coated wool swabs and broken into viral transport medium containing penicillin, streptomycin, and amphotericin for viral culture and plated on to blood and chocolate agar plates for bacterial culture. A neonatal mucus extractor and mucus trap (Chilton Surgical ME/30) was used to take a nasopharyngeal aspirate, to which 2 ml of viral transport medium was added. Specimens for virus isolation were transported to the laboratory frozen on solid carbon dioxide and stored at -70°C until cell cultures were available. Specimens were put up in roller-tube cultures on monolayers of MRC-5 fibroblasts, Ohio HeLa cells, LLC-MK2 monkey kidney cells, and fetal tonsil cells.⁸ Viruses were serotyped by virus neutralisation tests where possible.⁹ Rhinoviruses were identified by acid lability test—namely, a 100-fold reduction in titre after treatment at pH 4 for two hours.⁹

Venous blood was taken from index and control children at presentation, and total serum IgE concentration was measured by a double antibody inhibition radioimmunoassay technique.¹⁰ Children underwent prick tests at presentation with eight common inhalant allergen extracts: *Dermaphagoides pteronyssinus*, house dust, cat fur, dog fur, grass pollen, tree pollen, mixed feathers, mixed moulds, and a control solution (Bencard). Skin tests were read at 15 minutes and were positive if a weal was present with a diameter 2 mm or more greater than that of any control weal.^{11,12} Children with one or more positive skin reactions were defined as atopic.^{11,12}

The study was undertaken with the prior approval of the Northwick Park Hospital ethical committee.

Results

The 30 index children each experienced from three to 16 clinical episodes of acute respiratory infection in a year with a mean of $9.3 \pm \text{SD } 3.3$ episodes/child/year, while the control siblings experienced from one to 11 episodes, mean 5.4 ± 2.7 episodes/child/year. Even after adjustment for age, which was related to the incidence of infections, the difference in the means was highly significant when analysed by paired *t* test ($p < 0.001$).

The index children had lower respiratory tract infection in 92 (33%) of their 279 episodes compared with 16 (10%) of 162 episodes

experienced by the control siblings (see fig 1). This difference was highly significant ($p < 0.01$) when the results were compared by weighted two-way analysis of variance of the logits of the proportions (this analysis is equivalent to a paired *t* test but allows for a variable number of episodes experienced by each child). The index children had upper respiratory tract infection in 180 (64%) of the 279 episodes compared with 143 (88%) of the 162 episodes experienced by control siblings. Middle respiratory tract infections accounted for seven (2%) episodes in index children and three (2%) in controls. These differences were not significant.

VIRUS ISOLATION AND ILLNESS

Viruses were isolated from tissue culture in 38% of acute infectious episodes, the virus isolation rates from index and control groups being 40% and 36% respectively (see table I). Rhinoviruses accounted for over half of all viruses isolated from each group. We did not attempt to isolate coronaviruses, and we did not succeed in isolating any influenza or parainfluenza viruses. There was no difference in the proportions of different viruses isolated from index and control groups.

The incidence of lower respiratory tract infection during proved virus infections was virtually identical to that during all episodes. The index children had lower respiratory tract infection during 34% of proved virus infections, compared with 11% of infections experienced

Total serum IgE concentration of study children related to normal range of Kjellman *et al.*⁶ ● = Index children; △ = control children; ● or △ = four or more episodes of wheeze/year.

TABLE I—Viruses isolated from specimens from nasopharynx during acute respiratory infections

	Index (n = 250)	Control (n = 127)
Viruses:		
Rhinovirus	59	24
Echovirus	12	7
Adenovirus	10	6
Respiratory syncytial virus	7	3
Coxsackievirus	6	3
Varicella	3	2
Mumps	1	1
Rubella	1	
Total	99	46

TABLE II—Clinical diagnosis in association with positive virus isolations

	Upper respiratory tract				Middle respiratory tract		Lower respiratory tract
	Common cold	Upper respiratory tract infection	Tonsillitis	Otitis media	Croup	Wheezy bronchitis	Pneumonia
<i>Index children</i>							
Rhinovirus	11	18	9	2	2	17	1
Echovirus	1	7	3	0	0	1	0
Respiratory syncytial virus	0	1	0	1	0	4	1
Coxsackievirus	2	1	1	0	0	2	0
Adenovirus	2	1	1	0	0	5	1
<i>Control children</i>							
Rhinovirus	11	3	3	1	3	3	0
Echovirus	2	2	2	0	0	1	0
Respiratory syncytial virus	0	1	1	0	0	1	0
Coxsackievirus	2	1	0	0	0	0	0
Adenovirus	1	1	3	1	0	0	0

by the control children ($p < 0.02$). Since viruses were isolated in the same proportions from index and control children, the index children had selective infection of the lower respiratory tract by respiratory viruses. Table II shows the clinical diagnosis made in association with illnesses from which viruses were isolated,^{13 14} and clearly shows that all viruses tended to cause wheezing in the index children.

ATOPY

On the strict diagnostic criteria of Pepys⁴—namely, one or more positive reactions to skin tests to common inhalant allergens—eight index children and seven control children were atopic. When total serum IgE concentrations were compared with the normal range documented by Kjellman *et al*¹⁵ 13 of the index children and five control children had concentrations more than 2 SD above the geometric mean for age (see figure). All eight index children with positive reactions to skin tests but only three of the seven control children with positive skin test results had raised total serum IgE concentrations.

Positive skin reactions and raised total serum IgE concentrations were both associated with an increased incidence of recurrent wheezing, though this increase did not reach significance. Six (40%) of the 15 children with positive skin reactions had four or more episodes of wheezing per year compared with eight (19%) of the remaining 45 children with negative reactions ($\chi^2 = 1.9$, $p > 0.1$). Seven (39%) of the 18 children with raised total serum IgE concentrations, and seven (17%) of the 42 children with normal serum IgE concentrations wheezed on four or more occasions ($\chi^2 = 2.7$, $p = 0.1$).

We examined the relation between positive skin reactions, raised total serum IgE concentrations, and the number of infections experienced to determine whether the atopic children in the study were more susceptible to infection. Children with positive skin reactions did not have an increased incidence of respiratory infections compared to those with negative reactions ($6.9 \pm \text{SD } 2.9$ v 7.5 ± 3.8 ; $t = 0.3$, $p > 0.5$). Similarly, children with raised total serum IgE concentrations had the same incidence of infections as children with normal serum IgE concentrations ($7.4 \pm \text{SD } 2.9$ v 7.3 ± 3.6 ; $t = 0.1$, $p > 0.5$).

Discussion

We studied a group of 30 children, whose parents' impression that they were having more infections than their siblings was confirmed. The index children were younger and this contributed to their increased susceptibility, but even allowing for age they were significantly more susceptible to infections than their siblings.

Most infections were caused by respiratory viruses. Our bacteriological data, presented elsewhere,¹⁶ showed that bacteria caused less than 10% of all infections and bacterial superinfection was not an appreciable problem in these children. We have good evidence that their infections were caused primarily by respiratory viruses. A virus isolation rate of 38% compares favourably with other ambulatory studies of respiratory illnesses thought to be caused by viruses.^{2 17-20} Interferon was present in the children's nasopharyngeal secretions during 45 of 103 episodes from which viruses could not be cultured.²¹ We did not attempt to isolate coronaviruses, which have been estimated to cause 15% of naturally occurring colds,²² and we could not avoid freezing specimens, which considerably reduces the yield of myxoviruses such as influenza, parainfluenza, and respiratory syncytial viruses.²³ Our study design precluded taking paired sera, which would have boosted our rate of positive virus identification.²⁴

Our index children not only had increased susceptibility to respiratory virus infections, but they also had an increased incidence of lower respiratory tract infection with wheeze during infections. This tendency to wheeze was only partially explicable in terms of atopy, since not all children with recurrent wheeze were atopic. Wheezing in young children may be partially mechanical owing to the small calibre of the airways.²⁵ We have also shown that defective production of interferon- α may contribute to recurrent wheezing²¹; four of our index children had defective production of interferon- α associated with recurrent infections and wheeze. These children's relative inability to eliminate locally acting viruses such as rhinoviruses from the

nasopharynx might lead to spread of the virus to the lower respiratory tract.³

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