Viral infection as a precipitant of wheeze in children
Combined home and hospital study

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SUMMARY Sixteen children with asthma were studied for one year and viral isolation attempted during all episodes of wheezing. In 91 episodes investigated, 13 viruses were isolated (isolation rate 14%), whereas only one virus was isolated from 120 specimens taken when the children were symptom free. Rhinovirus was the commonest isolate and most were obtained during August, September, and October. Episodes of wheezing associated with virus infection were not clinically different nor more severe than those due to other precipitants.

Upper respiratory tract infection is one of the apparent precipitants of wheezing attacks in children. A relationship between viral infection of the upper respiratory tract and wheeze has been shown in several studies—hospital inpatients (McIntosh et al., 1973), hospital outpatients (Minor et al., 1974a, 1976), and general practice (Horn et al., 1975). Some have been confined to the winter months and case selection has been biased by the exclusion of children whose wheezing attacks were thought not to be precipitated by infection (Berkovich et al., 1970; McIntosh et al., 1973; Minor et al., 1974a, 1976). We recently reported a 3-year hospital based study (Mitchell et al., 1976) free from these constraints of timing and case selection and confirmed the association of viral infection and wheeze. The selection of appropriate controls presents difficulties and to overcome this viral culture has been attempted in index patients during wheeze-free periods (McIntosh et al., 1973; Minor et al., 1976).

This study was undertaken to determine the incidence, nature, and seasonal variation of viral infection in children with recurrent wheeze. The children were chosen consecutively, whatever the suspected precipitant of wheeze, and were studied for one year. Viral culture was attempted during all exacerbations of wheeze, whether or not viral infection was suspected on clinical grounds or admission to hospital occurred. The clinical features of wheezy episodes were noted. By attempting viral culture during symptom-free period control data were obtained.

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Patients and methods

Sixteen children attending the respiratory clinic at the Royal Hospital for Sick Children were enrolled in the study between 1 January and 31 March 1975 and remained in the study for one year. They were selected if they had had three or more wheezing attacks during the preceding year, if they lived within Edinburgh, and had a telephone at home. The permission of parents and general practitioners was obtained. Table 1 gives clinical details. There were 7 boys and 9 girls whose mean age at the start of the study was 4.5 years (range 2.1–6.3). The age of onset of respiratory symptoms varied from 3 months to 5 years. 10 children had previous hospital admissions, 7 gave a history of eczema, 3 hay fever, and 2 were allergic to eggs. All were within normal limits for height and weight and had a normal chest x-ray and peak expiratory flow rate between attacks. 13 gave positive skin tests to a variety of allergens, 7 had an eosinophil count in peripheral blood of >1.0×10^9/l and 4 had a raised IgE concentration in blood. They received regular treatment throughout the study. There was a history of asthma, eczema, hay fever, or urticaria in the first-degree relatives of 14 patients.

Diaries were issued every 6 weeks (Fig. 1) to facilitate analysis of the prodromata and clinical features of the attacks. New episodes of respiratory illness were reported and patients seen at home within 48 hours by one of us (I.M.). Apparent precipitants were noted and clinical signs of upper or lower respiratory tract infection sought. Nasal and throat swabs were taken for viral cultures. Acute episodes were treated by the general practitioner. Patients were reassessed clinically every 6 weeks and swabs again taken for viral culture. These were
Table 1  Clinical details

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age at start of study (yr)</th>
<th>Age at onset of respiratory symptoms (yr)</th>
<th>No. of hospital admissions before study</th>
<th>Eczema (past or present)</th>
<th>Regular treatment during study</th>
<th>First-degree relatives</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>3.6</td>
<td>1.9</td>
<td>3</td>
<td>+</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>6.2</td>
<td>3.0</td>
<td>3</td>
<td>-</td>
<td>SCG</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>4.4</td>
<td>0.3</td>
<td>2</td>
<td>+</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>4.2</td>
<td>0.8</td>
<td>0</td>
<td>-</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>6.3</td>
<td>2.0</td>
<td>0</td>
<td>-</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>2.9</td>
<td>1.0</td>
<td>2</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>4.5</td>
<td>0.3</td>
<td>0</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
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<td>0</td>
<td>-</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>2.1</td>
<td>1.5</td>
<td>3</td>
<td>-</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>5.3</td>
<td>1.5</td>
<td>3</td>
<td>-</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>3.2</td>
<td>2.0</td>
<td>3</td>
<td>+</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>4.1</td>
<td>0.8</td>
<td>1</td>
<td>+</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>5.2</td>
<td>1.0</td>
<td>2</td>
<td>-</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>5.4</td>
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<td>8</td>
<td>+</td>
<td>B</td>
<td></td>
</tr>
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<td>15</td>
<td>F</td>
<td>6.3</td>
<td>2.0</td>
<td>0</td>
<td>-</td>
<td>SCG</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>3.2</td>
<td>3.0</td>
<td>10</td>
<td>+</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

S = salbutamol (oral or inhaled); SCG = sodium cromoglicate; B = beclomethasone dipropionate aerosol.

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Results

Table 2 shows that there were 127 episodes of wheezing and virus culture was attempted in 91 (72%). Omissions were sometimes unavoidable, for example when the child was away from home or when the parent delayed more than a day or so in reporting to us. 13 viruses were isolated (isolation rate 14%). The number of viruses isolated from individual patients varied, but no more than 3 were isolated from any one patient. There were no viral isolates from 5 patients (one with 11 episodes investigated), and one patient was symptom free throughout the study. The commonest isolates were rhinovirus (5 occasions) and Coxsackie A9 (3 occasions). Only one virus, a polio virus type 1 in a child immunised a few days previously, was isolated from the 120 control specimens.

Fig. 2 shows the monthly distribution of episodes of wheezing and virus isolation. There was some variation in the number of episodes of wheezing per month, but this was not marked, being lowest in July and highest in September and October. More than half the isolates were obtained during August, September, and October, the other viruses being seen at varying times and no isolates in May, June, July, or December.

Fig. 3 shows the relationship between the initial diagnosis and the subsequent virological results. 56 episodes of wheeze were thought to be associated with upper respiratory tract infection and 7 isolates were obtained (13%); in 35 episodes, in which the precipitant was thought to be other than infection, there were 6 isolates (17%).

Preceding nasal symptoms were also unhelpful in...
the diagnosis of viral infection, being present in 5 of the
13 episodes with positive virology (38%) and in
23 of the 78 virus-negative episodes (13%). The
12 admissions were of 5 patients (Cases 1, 3, 6, 9, 11)
of whom one (Case 9) was admitted 6 times. The
duration of wheeze (mean ± SD) in the 13 episodes
precipitated by viruses was 4·1 ± 2·6 days and in the
78 other episodes 4·8 ± 2·9 days. We have no
evidence that proven viral infection increases the
severity (by these criteria) of wheezing episodes.

All specimens were taken within 5 days of the onset
of symptoms. 60 episodes were investigated within 48
hours and in 10 (17%) virus culture was positive.
31 specimens were taken 3, 4, or 5 days after onset
and 3 were positive (10%). From the 17 specimens
taken during acute wheezy episodes and stored
overnight, 4 viruses were isolated. An additional 11
episodes of respiratory illness ('colds') not associated
with wheeze were investigated but not included in
the analysis. Two viruses (parainfluenza 3 and influ-
enza A) were isolated.

Discussion

Our virus isolation rate (14%) is similar to that in a
3-year study of children with acute asthma investi-
gated on admission to hospital (Mitchell et al., 1976).
However, many of the previous studies (Table 3)
relating viral infection and wheeziness in children
are not directly comparable. Neither of the studies of
Minor et al. (1974a, 1976) continued throughout one
complete year, and viral isolation was only attempted
when respiratory tract infection appeared to be the
precipitant of the acute attack of asthma. Thus
difference in design and more frequent sampling
during episodes of wheeze may explain the higher
Table 3  Review of published reports of virus infection and wheezing in children

<table>
<thead>
<tr>
<th>Base</th>
<th>Study</th>
<th>Index cases</th>
<th>Age (yr)</th>
<th>Duration (yr)</th>
<th>No. of patients</th>
<th>Episodes of wheezing</th>
<th>No. of virus identifications* (%)</th>
<th>Main virus n (%)</th>
<th>Controls</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Disney et al. (1971)</td>
<td>‘Acute asthma’</td>
<td>1–12</td>
<td>3</td>
<td>192</td>
<td>360</td>
<td>39 (14)</td>
<td>Rhinovirus 16 (41)</td>
<td>—</td>
<td>Specimens taken on admission to hospital—no risk of cross-infection</td>
</tr>
<tr>
<td></td>
<td>Mitchell et al. (1976)</td>
<td>‘Acute wheezy attacks’</td>
<td>0–5</td>
<td>0-7</td>
<td>32</td>
<td>139</td>
<td>58 (42)</td>
<td>Respiratory syncytial virus 24 (41)</td>
<td>—</td>
<td>As above; specimens taken whatever the apparent precipitant of wheeze</td>
</tr>
<tr>
<td>Inpatients (long-term)</td>
<td>McIntosh et al. (1973)</td>
<td>‘Respiratory infection in severe asthma’</td>
<td>0–5</td>
<td>0–5</td>
<td>136</td>
<td>88</td>
<td>33 (38)</td>
<td>Influenza A2 12 (36)</td>
<td>—</td>
<td>Potential risk of hospital cross-infection; controls not necessarily symptom free</td>
</tr>
<tr>
<td>Outpatients</td>
<td>Berkovich et al. (1970)</td>
<td>‘Respiratory infection in asthma’</td>
<td>0–5–16</td>
<td>0–5</td>
<td>136</td>
<td>88</td>
<td>33 (38)</td>
<td>Influenza A2 12 (36)</td>
<td>—</td>
<td>Large default rate (38%)</td>
</tr>
<tr>
<td>Hospital &amp; community</td>
<td>Minor et al. (1974)</td>
<td>‘Respiratory infection in asthma’</td>
<td>3–11</td>
<td>0–7</td>
<td>16</td>
<td>61</td>
<td>24 (39)</td>
<td>Rhinovirus 15 (63)</td>
<td>—</td>
<td>Study of apparent respiratory infection in asthma; controls not necessarily symptom free</td>
</tr>
<tr>
<td>Outpatients &amp; domiciliary</td>
<td>Minor et al. (1976)</td>
<td>‘Respiratory infection in asthma’</td>
<td>3–60</td>
<td>0–8</td>
<td>48</td>
<td>71</td>
<td>17† (24)</td>
<td>Rhinovirus 7 (41)</td>
<td>—</td>
<td>As above; children’s data not analysed separately</td>
</tr>
<tr>
<td>Present study</td>
<td>Asthma</td>
<td></td>
<td>2–6</td>
<td>1</td>
<td>16</td>
<td>91</td>
<td>13 (14)</td>
<td>Rhinovirus 5 (39)</td>
<td>—</td>
<td>Specimens taken irrespective of apparent precipitant; controls completely symptom free</td>
</tr>
<tr>
<td>Community</td>
<td>Horn et al. (1975)</td>
<td>‘Respiratory infection ± wheeze’</td>
<td>0–12</td>
<td>5</td>
<td>—</td>
<td>554</td>
<td>152 (27)</td>
<td>Rhinovirus 68 (42)</td>
<td>—</td>
<td>Study of clinical features of viral respiratory infection</td>
</tr>
</tbody>
</table>

*Viruses identified by culture, apart from Berkovich et al. (1970) who identified 30 viruses by serology.
†14 isolates in patients aged 3–17.
Isolation rate they obtained. However, as our results showed that apparent respiratory infection, wheezing, and viral isolation do not correlate well, other factors may be involved. In studies of different populations and design, wide variations in virus isolation rates are seen, ranging from 6% obtained by Disney et al. (1971), in acute admissions to hospital, to 42% by McIntosh et al. (1973) in long-term hospital inpatients. In a 5-year general practice survey, Horn et al. (1975) found a virus isolation rate of 27.7% in children who wheezed with apparent respiratory infections.

Difficulty in selecting controls has been common to most studies. Disney et al. (1971) used as controls 47 children admitted with respiratory infection without wheeze and found a virus isolation rate of 23% compared with 4% in asthmatic children admitted during the same period. Nonasthmatic sibs have also been used (Minor et al., 1974b) but cannot be matched for age, sex, or school environment. McIntosh et al. (1973) and Minor et al. (1974a, 1976) used index cases as their own controls and isolated viruses (parainfluenzae types 1, 2, and influenza A2) in control specimens. The isolation rate in completely symptom-free children is not clear. Their conclusion that virus isolation is less likely in symptom free children accords with ours and suggests that the viruses isolated during wheezing episodes are indeed the precipitants.

Rhinoviruses are the commonest viral precipitants of wheeze, forming some 40% of the isolates in most studies (see Table 3). The primacy of respiratory syncytial virus in one study (McIntosh et al., 1973) may be due to timing—during the winter months, the age of the patients, and possible exposure to hospital cross-infection. Respiratory syncytial virus has been identified less often in wheezy children in other studies, though it is the commonest pathogen in acute bronchiolitis of infancy. There is no clear evidence that other viruses are as consistently associated with wheeziness, although some, e.g. parainfluenza and influenza A, have been isolated from wheezy children by most of the above workers.

The question arises whether our low isolation rate of viruses resulted from inadequate techniques. Our methods of collecting and transporting specimens and the laboratory techniques compare with those of other investigators. Specimens were taken immediately to the laboratory and no child was investigated more than 5 days after the onset of symptoms. Horn et al. (1975), studying the effect of storage of specimens at 4°C overnight, showed that this did not affect the viral isolation rate. However, a slightly higher isolation rate might have been obtained by more frequent sampling during episodes of wheeze. It is likely that the viral isolation rate reflects the incidence of viral infection in these children and was not spuriously depressed to a significant extent.

We suggested previously (Mitchell et al., 1976) that viral precipitants influence the severity of asthmatic attacks. However, we were unable to confirm this or to show that asthmatic children are particularly susceptible to viral infections as suggested by Minor et al. (1974b), both points being relevant to any consideration of the use of specific antiviral measures in asthmatic children. Our patients were representative of asthmatic children seen at a hospital outpatient clinic, the majority having a family history of asthma or atopic disorders, positive skin tests, and high IgE concentrations in peripheral blood. Several in whom we isolated viruses during wheezy episodes also gave a history of wheezing with other precipitants, such as exercise or exposure to pollens or dust. We would expect specific measures such as vaccination (McIntosh et al., 1974) to be disappointing in such patients, even if this therapy were available. It is unlikely that vaccines to combat rhinovirus infection—the commonest viral pathogen—will be developed in view of the large number of rhinovirus serotypes. At present the mainstays of long-term treatment for many of these children will continue to be simple environmental control measures and the use of prophylactic drugs such as sodium cromoglycate or steroid aerosols.

We thank Mrs M. Hamilton who co-ordinated the community aspects of the study, and Mrs D. Tervit and Mrs B. Abbott for secretarial assistance.

References


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