Acute severe deterioration in cystic fibrosis associated with influenza A virus infection

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Abstract

Background The role of non-bacterial infection in respiratory exacerbations of cystic fibrosis has been studied less than that of bacterial infection. Some non-bacterial infections, such as influenza A, may be associated with acute respiratory deterioration and may be preventable.

Methods and results Three patients with cystic fibrosis showed severe deterioration in lung function and general wellbeing during the influenza A virus epidemic in the winter of 1989–90. Serological confirmation of influenza A virus infection was obtained in each case.

Conclusions As immunisation against influenza A virus is safe and provokes an adequate antibody response in patients with cystic fibrosis, it is concluded that patients with cystic fibrosis should be offered immunisation at the beginning of each influenza season. Rapid diagnostic tests and the use of antiviral drugs may have a prophylactic role in minimising lung damage.

Pseudomonas aeruginosa is the microorganism most commonly associated with respiratory exacerbations in cystic fibrosis.1 Haemophilus influenzae, Staphylococcus aureus, Pseudomonas cepacia, and other pseudomonads are also important pathogens. Exacerbations are generally treated with high dose and often expensive antibiotics. Therapeutic protocols now tend to specify earlier and more frequent treatment.2 The role of non-bacterial infection in chronic lung disease is recognised3 and there is evidence of its relevance to cystic fibrosis.4 Coincidental viral and bacterial infections appear to be synergistic in their capacity to damage the respiratory tract,10 11 though the contribution of non-bacterial infection to respiratory deterioration in cystic fibrosis has been incompletely studied and addressed in clinical practice.

Serological tests for respiratory viruses are routinely performed in our unit during all respiratory exacerbations. We report three patients in whom a retrospective diagnosis of influenza A virus infection was made on serological evidence. In each case the viral infection precipitated a severe and unexpected respiratory exacerbation, which was documented with clinical and objective data.

Case reports

Clinical and laboratory data on the three patients are shown in the table.

PATIENT 1

A 20 year old woman presented with a 10 day history of acute respiratory deterioration, an increase in cough with production of green sputum, coryza, fever, and muscle aching in December 1989. She had chronic colonisation with P aeruginosa but had stable lung function with only two previous admissions for intravenous treatment and no intravenous treatment during the preceding three years. On admission she was febrile (37.8°C), with crackles in the right upper and left basal zones. A chest radiograph showed new and widespread focal nodular shadowing. Sputum culture showed a profuse growth of P aeruginosa. Serological testing for viruses on blood sampled at admission and 13 days later showed a titre of antibody to influenza virus A above 512. Eleven months earlier a titre of less than 8 had been recorded. One month after admission the antibody titre had fallen to 64. The exacerbation was treated with intravenous tobramycin (180 mg thrice daily) and azlocillin (5 g thrice daily) with oral flucloxacillin (500 mg four times a day). She recovered slowly over 13 days of inpatient care.

CASE 2

A 22 year old woman with chronic P aeruginosa colonisation who had shown a gradual deterioration in lung function over the preceding two years presented in December 1989 with cough and fever, coryza, increased production of green and tenacious sputum, anorexia, and muscle aches. On admission she had a temperature of 38.2°C and generalised crackles on auscultation. A chest radiograph showed widespread moderate to severe changes of cystic fibrosis with new diffuse nodular (<0.5 cm) areas of bilateral consolidation. Sputum culture grew profuse P aeruginosa. She received intravenous cefazidime (6 g daily) and aztreonam (2 g four times daily) with oral flucloxacillin (500 mg four times daily). Serological testing for viruses showed a fourfold rise in the titre of antibody to influenza A virus from below 16 (November 1989) to 256 at admission. She was in hospital for 15 days.

CASE 3

A 14 year old girl, with chronic P aeruginosa colonisation but stable lung function,
presented with a two week illness with increased cough and production of green sputum, haemoptysis, fever, coryza, aching limbs, and headache. She had improved a little at home with oral ciprofloxacin during the preceding week. On examination she was afebrile but had bilateral scattered crackles. Her chest radiograph showed no acute change. Sputum culture yielded a moderate growth of \textit{P. aeruginosa} and \textit{Staphylococcus aureus}. Four months previously the titre of antibody to influenza A virus was below 8, but at admission and 10 days later it was at least 512. Repeat serological testing seven months later showed a titre of less than 32. She recovered in the course of 10 days' inpatient treatment with intravenous tobramycin (150 mg thrice daily), azlocillin (5 g thrice daily for five days), and aztreonam (2.5 g four times daily for five days) and oral fluvoxacinil (500 mg four times daily).

**Discussion**

An epidemic of influenza A virus infection occurred in the United Kingdom in the winter of 1989–90, starting in November and with a peak incidence in the first half of December.\(^{12}\) All our three patients showed serological evidence of influenza A virus infection. Patients 1 and 3 had antibody titres on admission that were significantly higher than previous values, confirming acute infection (personal communication, M H Hambling, Regional Viral Laboratory, Public Health Laboratory Service, Leeds) and the second showed a fourfold rise in antibody titre. The Department of Health recommends vaccination before the start of the influenza season for people at special risk,\(^{13}\) including those with cystic fibrosis. Non-bacterial infection in cystic fibrosis is well documented. Although respiratory viral infection may occur without an acute exacerbation of respiratory symptoms,\(^{1,4}\) at least 20% of acute respiratory exacerbations are associated with viral, mycoplasma, or chlamydial infection.\(^{14,9}\)

Viral infections may be more evident in patients with deteriorating lung function,\(^{6}\) in whom they appear to accelerate progression of disease.\(^{8}\) Pulmonary deterioration in cystic fibrosis following non-bacterial infection may be more frequent when chronic bacterial infection is present.\(^{1}\) It may also lead to the development of chronic \textit{P. aeruginosa} infection in lungs hitherto uncolonised, or only intermittently colonised,\(^{1}\) and it may initiate signs of chronic respiratory disease in children with cystic fibrosis.\(^{4}\)

The influenza virus infects the nasopharynx, tracheobronchial tree, and alveolar spaces, causing destruction and desquamation of the mucous membrane and impeding clearance of inhaled microorganisms.\(^{15,16}\) Influenza A virus and respiratory syncytial infection in cystic fibrosis are associated with an increase in precipitins to \textit{P. aeruginosa} (especially when chronic infection is present), suggesting an increased capacity for bacterial invasion coincidental with the viral infection.

The inactivated influenza virus vaccine is safe and 70–80% effective in decreasing influenza infection and its associated mortality. It is underused, however, reaching less than 30% of the target population, including patients with cystic fibrosis.\(^{17}\) Although the ability of patients with cystic fibrosis to mount an effective antibody response (determined by complement fixation test) to influenza vaccine has been questioned,\(^{18}\) further studies by the same group using a single radial haemolysis test have shown that such patients do produce protective levels of antibody. The vaccine is well tolerated. Titres of antibody to influenza virus were low in the study before vaccination, but intermediate to high antibody titres were well maintained one year after vaccination.\(^{18}\) Other forms of antiviral treatment may be underused. Amantadine is active against influenza A virus and well tolerated.\(^{9}\) Its use has been suggested as an adjunct to the vaccine in a regular prophylactic daily dose during the influenza season and during an epidemic.\(^{17}\) Amantadine can also be administered as a two week course after vaccination to confer protection against influenza while antibody formation is taking place. Once influenza has been contracted, amantadine given within the first 18 hours of illness will decrease the severity and duration of illness.\(^{10,17}\) Vaccination followed by a course of amantadine should be considered for non-vaccinated patients who have been in contact with influenza and during epidemics.

Ribavirin is a broad spectrum virostatic agent to which influenza A and B viruses are

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**Clinical and laboratory data at admission for acute influenza A virus infection and at discharge compared with values at the previous most recent hospital assessment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>6 weeks before admission</th>
<th>7 weeks before admission</th>
<th>Patient</th>
<th>7 weeks before admission</th>
<th>Patient</th>
<th>7 weeks before admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission</td>
<td>Discharge</td>
<td>Admission</td>
<td>Discharge</td>
<td>Admission</td>
<td>Discharge</td>
</tr>
<tr>
<td>FEV(_1)</td>
<td>2.36</td>
<td>1.53</td>
<td>2.18</td>
<td>1.72</td>
<td>1.52</td>
<td>1.65</td>
</tr>
<tr>
<td>FVC</td>
<td>3.91</td>
<td>3.21</td>
<td>3.2</td>
<td>2.94</td>
<td>2.93</td>
<td>2.59</td>
</tr>
<tr>
<td>PEF(_{50})</td>
<td>2.92</td>
<td>1.3</td>
<td>2.92</td>
<td>1.06</td>
<td>0.96</td>
<td>0.85</td>
</tr>
<tr>
<td>% weight for</td>
<td>102</td>
<td>96</td>
<td>96</td>
<td>80</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td>height</td>
<td>Total blood white cell count</td>
<td>(× 10(^9)/l)</td>
<td>C reactive protein</td>
<td>(mg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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\(^{1}\) Acute severe deterioration in cystic fibrosis associated with influenza A virus infection.
very sensitive. In animals it is effective if given within 72 hours of virus inoculation.20
Treatment for 18–20 hours a day is necessary to ensure an adequate inhibitory concentration in the lung; it might be considered in cases not responding to other treatment. The combination of ribavirin and amantadine is more effective than either drug given alone.20

The consequences of viral infection are more severe in cystic fibrosis than in healthy individuals.2,5 Our patients showed acute and serious deterioration in respiratory function and general wellbeing and needed intensive inpatient treatment. Two of our patients had had stable respiratory function previously and had required only occasional inpatient treatment and minimal maintenance treatment at home. Acute infection with influenza virus is associated with more severe respiratory deterioration than with other non-bacterial agents, or infections where no agent is identified.21

We believe that patients with cystic fibrosis should receive a yearly vaccination against influenza virus, and that during influenza epidemics immunofluorescence of nasopharyngeal secretions should be used for rapid diagnosis. Temporary prophylaxis with amantadine, and the treatment of acute influenza like illnesses with amantadine and ribavirin, should be considered. Rapid diagnostic tests for other viral infections in cystic fibrosis are needed.