Lung function tests and risk factors for pneumonia in adults with chickenpox

A H Mohsen, R J Peck, Z Mason, L Mattock, M W McKendrick

Abstract

Background—Varicella is 25 times more likely to be complicated by pneumonia in adults than in children. Data on changes in lung function following pneumonia are limited. This study was undertaken to describe the epidemiological factors associated with pneumonia and to investigate lung function up to 1 year following chickenpox.

Methods—Thirty eight consecutive suitable patients admitted to a university hospital were enrolled in the study; 19 had pneumonia and 19 did not. Epidemiological data and density of rash were recorded, spirometric tests were performed, and carbon monoxide transfer factor was measured.

Results—Varicella pneumonia was associated with the presence of respiratory symptoms (p=0.006), current smoking (p=0.003), and history of close contact (p=0.009). There was a trend towards patients with pneumonia having a more severe rash. No association was observed between pneumonia and age or sex. Current smokers had a higher mean number of spots than non-smokers (p=0.005). Carbon monoxide transfer factor at hospital discharge was reduced in 27 patients (71%), more markedly in the group with pneumonia (p=0.009). Nine patients (seven with pneumonia) still had a reduced carbon monoxide transfer factor (mean reduction 36%) at 12 months. Conclusion—Chickenpox may result in a defect in carbon monoxide transfer factor for at least a year after acute illness.

Keywords: varicella pneumonia; chickenpox; lung function; carbon monoxide transfer factor

The incidence of chickenpox in adults has more than doubled in England and Wales over the last two decades and has been paralleled by an increase in admissions to hospital and mortality. A similar trend has also been observed in the USA. Varicella pneumonia is the most common serious complication of chickenpox infection in adults with a reported incidence of 16–33% and mortality of up to 20%, although the incidence and mortality figures are probably high due to selective reporting. Early diagnosis and appropriate treatment is likely to reduce morbidity and mortality related to these complications. Chickenpox can lead to permanent radiological changes on the chest radiograph—mainly speckled calcification—which may develop up to 7 years after recovery, but there are few data on the long term effects on lung function. There is evidence to suggest that bacterial pneumonia in childhood can cause a reduction in lung function in later life, typical changes including a restrictive ventilatory defect with a reduction in static lung volumes.

The purpose of this study was to identify the clinical and epidemiological characteristics associated with pneumonitis and to investigate prospectively lung function up to 1 year following chickenpox.

Methods

Immunocompetent adults with a clinical diagnosis of chickenpox admitted to the North Trent Department of Infection and Tropical Medicine between June 1997 and November 1999 were studied prospectively (fig 1). Patients were excluded if they had a history of prior lung disease. Patients were referred to hospital for further assessment by the general practitioners or accident and emergency officers who were not aware of the study.

The characteristics collected at the time of admission included age, sex, history of contact with chickenpox (within the previous 2 months, with type of contact), smoking history (current, past, never smoked, number of cigarettes per day), and current pregnancy. The incubation period was calculated by taking the first day of contact with the source patient (after rash had occurred) to the day of developing rash. Respiratory symptoms of breathlessness, chest pain, chest tightness, and cough were recorded.

The density of the rash was recorded by a single observer who counted the number of spots within a “chest box” defined as the area between parallel vertical lines through the clavicle and nipples and horizontal lines at the levels of the clavicle and nipples. Patients were considered to have chickenpox pneumonia if the chest radiograph on admission showed changes consistent with acute infection (diffuse nodular/reticular changes). A single observer (consultant radiologist), blinded to the diagnosis,
reviewed all the chest radiographs. Duration of admission and complications were recorded.

Respiratory function tests were performed on discharge, at 2 months and, if abnormal, every 3 months until they became normal or up to 1 year from the acute infection. The tests included forced expiratory volume in 1 second (FEV$_1$), forced vital capacity (FVC), FEV$_1$/FVC ratio (Vitalograph), and single breath carbon monoxide transfer factor (TLCO) (Sensormedics Vmax 22). Smokers were asked not to smoke on the day of the tests.

The results of lung function tests in the patient group were compared with the predicted normal values for those of comparable age, sex, height, and weight. The methods used for calculating predicted TLCO and lung volumes were based on the European guideline. TLCO and FEV$_1$ measurements were considered abnormal if they were below 75% of predicted normal values. The percentage of the reference predicted normal value was used to compare the different groups of patients. All patients who had a TLCO measurement had a normal haemoglobin and TLCO values were corrected for alveolar volume to produce the transfer coefficient (KCO). The FEV$_1$/FVC ratio was considered abnormal if it was less than 70% of the predicted normal value.

**DATA ANALYSIS**

Patients with radiological pneumonia were compared with patients with a normal chest radiograph at presentation. Odds ratios (OR) were calculated for each comparison and Fisher’s exact test was used to assess significance. A non-parametric test (Mann-Whitney U test) was used to compare age and difference in TLCO between the two groups. To examine the effect of smoking on TLCO, the numbers of smokers in normal and reduced TLCO groups were counted in patients with complete follow up data. The OR of reduced TLCO in patients with pneumonia versus patients with a normal chest radiograph was calculated by logistic regression and corrected for the presence of smoking.

The study was approved by the local ethics committee and all patients gave written informed consent.

**Results**

Sixty six patients with chickenpox were admitted to the department during the period of study; 38 fulfilled the entry criteria and agreed to participate, 95% of whom were white. All those enrolled in the study had a chest radiograph. The demographic and epidemiological details of the 38 patients with and without pneumonia are shown in table 1.

The mean (SD) age of the 38 patients was 29 (7) years with a male to female ratio of 1.7:1. Twenty six patients (67%) gave a history of contact with chickenpox, the incubation period being 15 (6) days. Twenty seven patients (71%) had one or more respiratory symptoms on admission which started within a median of 1 day (range –2 to 5 days) from onset of the rash. Of the 11 patients (29%) with no respiratory symptoms on admission, only one had an abnormal chest radiograph. The presence of new respiratory symptoms in patients with chickenpox was 95% sensitive in identifying those with radiological pneumonia but only 53% specific.

Current smokers had a higher mean number of chickenpox spots in the “chest box” (138, median 150) compared with non-smokers (71, median 65), p=0.009. Two patients developed cerebellar ataxia which resolved spontaneously within a few days. Three patients required admission to ITU, all female smokers one of whom was in the third trimester of pregnancy; two had caught infection from their own child. All patients with pneumonia were treated with acyclovir, initially intravenously, for 7 days. Eighteen patients (95%) without lung involvement received acyclovir. There were no deaths. A repeat chest radiograph was available for 16 of the 19 patients with radiological pneumonia; 14 normalised, one woman developed diaphragmatic hernia which resolved spontaneously within a few months. Both patients had severe changes on their initial radiograph.

The FVC was reduced at discharge in eight patients (21%; five with pneumonia). This normalised during follow up in five patients, two were lost to follow up after the second test, and in one the FVC was 74% of the predicted value at 12 months. The FEV$_1$ was reduced at discharge in 14 patients (37%; nine with pneumonia); 11 normalised at follow up, two were lost to follow up, and one achieved an FEV$_1$, of 74% of the predicted value. The FEV$_1$/FVC ratio was reduced in seven patients (18%); three normalised, one was lost to follow up, and three continued to have abnormal results.

Carbon monoxide transfer factor was reduced at discharge in 27 patients (71%), 16 (84%) with pneumonia and 11 (57%) with a normal chest radiograph (fig 2A). Seven

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**Table 1** Demographic data of cohort and risk factors for developing pneumonia

<table>
<thead>
<tr>
<th>Pneumonia (n=19)</th>
<th>No pneumonia (n=19)</th>
<th>Odds ratio (OR), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F:M)</td>
<td>7:12</td>
<td>7:12</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Mean no of spots in chest box</td>
<td>129</td>
<td>91</td>
</tr>
<tr>
<td>Mean hospital admission (days)</td>
<td>6.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Respiratory symptoms at presentation</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>OR=18 (95% CI 2 to 165); p=0.006†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Any contact with chickenpox</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>History of contact with own child</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2 (both 3rd trimester)</td>
<td>2 (1st and 3rd trimester)</td>
</tr>
<tr>
<td>Admission to ITU</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mean no of spots in chest box</td>
<td>129</td>
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<td>0</td>
</tr>
</tbody>
</table>

* Non-parametric Mann-Whitney U test; †Fisher exact test.
greater risk of complications than in a child.16

Discussion

with persisting reduced TLCO for each of the groups (mean

Hospitalised patients are clearly a selected

tion in TLCO than those with a normal chest

Figure 2 (A) Percentage of patients remaining with reduced

carbon monoxide transfer factor (TLCO) in patients with

normalised during follow up, but nine patients

(seven with pneumonia) still had a reduced

transfer factor at 12 months (mean 36%) as

shown in fig 2B. On discharge from hospital,

patients with pneumonia had a greater reduc-

tion in TLCO than those with a normal chest

radiograph (p=0.003). Complete data on TLCO

were available on 27 patients, 10 smokers

(seven reached normal levels) and 17 non-

smokers (11 reached normal levels). The

frequency of smoking was not significantly dif-

ferent between the two group (p=0.77). The

OR for reduced TLCO in the pneumonia group

was 8.75 (95% CI 0.88 to 86.6, p=0.06) com-

pared with the group with a normal chest

radiograph. This OR did not reach significance

because of the small number of patients in the

study. Nevertheless, the OR did allow the

interaction of smoking to be examined. After

correcting for smoking, the OR was 12.99

(95% CI 0.77 to 217, p=0.07) for reduced

TLCO in the pneumonia group.

Discussion

Chickenpox in healthy adults has a 25 fold
greater risk of complications than in a child.16

Hospitalised patients are clearly a selected

population and most in the UK are referred by

general practitioners or A&E departments

because of the severity of the infection. In this

study 73% of suitable patients admitted to the

department agreed to participate in the study,

50% of whom had radiological pneumonia. It

is probable that subclinical lung involvement

in chickenpox is common but, for the purposes

of this study, patients were defined as having

pneumonia only if they had radiological

changes. The study was not designed to assess

the incidence of pneumonia in chickenpox.

We found that a history of contact with a

patient’s own child with chickenpox was a risk

factor for pneumonia (OR=7.8), an association

that has not been shown previously. There was

also an association between any recognised

contact and development of pneumonia

(OR=4.8). This could be a consequence of

these patients having a closer contact with the

index case and therefore receiving a larger

“infesting dose” with an enhanced primary

viraemia; it has previously been demonstrated

that children who get chickenpox from siblings

usually have a worse disease with more spots.17

Smoking was associated with increased inci-
dence of pneumonia in this series (OR=11.5),
as has been previously noted.14

Deciding who should be referred to hospital

can be difficult for the general practitioner. We

found a strong correlation between pneumonia

and new respiratory symptoms (breathlessness,

chest pain, chest tightness, and cough), symp-

tomatic patients having an 18 fold higher risk

of radiological pneumonia. Referral to hospital

for formal evaluation should definitely be

recommended for patients with chickenpox

who develop new respiratory symptoms. Pa-

tients with pneumonia also had a trend towards

having an increased number of skin spots

(p=0.13) but, interestingly, smokers were also

found to have more skin spots than non-

smokers (p=0.009), an association not previ-

ousl reported. It is possible that smokers have

more spots because of an enhanced primary

viraemia secondary to the effects of smoking on

the nasal mucosa, and this predisposes to

pneumonia. Unfortunately, there were insuffi-

cient patients in this study to perform a multi-

variate analysis and to determine whether the

number of spots and smoking were independ-

ent variables. A previous report has shown that

smoking renders human alveolar macrophages

more susceptible to infection by herpes vi-

ruses15 which could be relevant pathogeneti-

cally, although this requires further study. The

number of pregnant women in this series was

small but pregnancy probably increases the risk

of developing pneumonia, particularly in the

third trimester, because of changes in the

immune system.16 20 Severe disease requiring

admission to ITU was observed only in women

in this series.

Acyclovir has been shown to be of clinical

benefit to adults receiving it within 24 hours of

the onset of rash.21 However, there has been no

study with sufficient power to address whether

antiviral therapy will prevent complications

such as pneumonia. There is indirect evidence

to suggest that intravenous acyclovir may be of

benefit in treating chickenpox pneumonia and

its usage has been recommended.1 Varicella

zoster immunoglobulin is expensive and in

short supply and its use is therefore restricted.
Chickenpox pneumonia in adults

The use of acyclovir as prophylaxis/treatment during the incubation period in chickenpox has been shown to prevent or modify illness, although it is not currently licensed for this indication in the UK but this intervention may be used more in the future. Recent evidence suggests that varicella vaccine is effective in preventing or modifying severity if used within 3 days and possibly even up to 5 days of exposure; the US Advisory Committee on Immunization Practices includes a recommendation about administration of varicella vaccine after exposure. It is contraindicated in patients with chickenpox pneumonia. Neumonia as a predictor of reduced TLCO increased monia, as was also noted in the study by Ellis et al. However, the reduction in TLCO was greater in the pneumonia group (p<0.009). It is of interest that patients with pneumonia in the present study showed no evidence of further improvement beyond 5 months from discharge. Bocles et al studied four patients with possible chickenpox pneumonia retrospectively and demonstrated a defect of diffusion up to 8 years after the acute illness, which raises the possibility that the prospectively observed changes noted in our study might be permanent.

We considered the possibility that smoking had influenced our findings. There were equal numbers of smokers in the patient groups with normal and reduced TLCO. Furthermore, multivariate analysis confirmed that the OR for pneumonia as a predictor of reduced TLCO increased after correction for smoking. There was therefore no evidence to suggest that the observed decrease in TLCO was attributable to smoking.

The temporary changes in FVC and FEV, are probably the result of diffuse inflammation of lung tissue affecting patients with and without radiological evidence of pneumonia. This indicates a reduction in lung volumes as the FVC:FEV ratio was normal in 92% of patients on their initial lung function tests. These abnormalities were observed in smokers and non-smokers and indicate that chickenpox may be associated with a restrictive lung disease pattern in the acute and recovery phase, as was noted by Bocles et al but not by Ellis et al. There was no evidence to suggest that chickenpox causes small airways disease in the recovery period.

In conclusion, we have shown that predictors of pneumonia complicating chickenpox include the presence of new respiratory symptoms, smoking, and close contact with the source of infection. Chickenpox may result in a defect in the carbon monoxide transfer factor for at least 1 year after acute illness, more commonly in patients with radiological pneumonia, and may also be associated with a temporary restrictive lung defect.

The authors are grateful to Dr Stephen Gordon, honorary clinical senior lecturer in medicine, Dr Wilf Yeo, senior lecturer in medicine and Dr Robert Read, reader in infectious diseases, for helpful comments.

No financial support was obtained for this study.

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