Relationship between asthma severity and progression of Alzheimer’s disease

Severity of asthma is occasionally modulated by neuropsychiatric conditions. However, little is known about the impact of cognitive decline on asthma severity. Cognitive decline is a core symptom in patients with Alzheimer’s disease (AD). AD is a disease characterised by progressive cholinergic failure that could possibly reduce airway hyperresponsiveness to cholinergic stimulation and thus symptoms of asthma. Furthermore, the functions of T lymphocytes—which play a crucial role in the development of chronic asthma—are partially impaired in patients with AD related diseases. We hypothesised that declining cognitive function might result in an improvement in asthma, and prospectively studied the contribution of the progression of AD to the clinical course of asthma.

Eight patients with asthma of mean (SE) duration 15.3 (0.9) years with concomitant AD were identified and prospectively followed for 5 years from 1997 to 2000. All subjects were treated with oral theophylline (200 mg twice daily) and a 200 μg dose of fenoterol given by a flow driven inhaler as needed. Family members of the patients completed a diary card that recorded asthma symptoms, use of daily medication, and the number of hospital admissions for asthma during the 5 years prior to study entry and the 5 year observation period. Cognitive function was assessed by Mini-Mental State Examination (MMSE) and sputum eosinophil counts and methacholine challenge tests were performed both at enrolment in the study and at the end. Informed consent was obtained from each patient, his or her family, and an attending physician.

MMSE scores were significantly decreased during the 5 year observation period in all subjects (table 1). Overall attack frequency and severity of asthma symptoms significantly decreased during the progression of cognitive impairment in all but one asthmatic subject with AD (table 1). Induced sputum obtained at the end of the study from seven subjects with improved asthma had a significantly lower percentage of eosinophils than at the start of the study (2.2 (0.4)% at end point v 10.7 (2.8)% at baseline, n=7, p=0.008), but there were no significant differences in the mean percentages of macrophages, neutrophils, or lymphocytes. By contrast, in all subjects the minimum cumulative dose of methacholine that induced an increase in respiratory resistance at the end of the study was not significantly different from that obtained at study enrolment (0.426 (0.252) U at end point v 0.368 (0.144) U at enrolment in the study, n=8, p=0.26). No other precipitating factors for asthma were identified during the study period in any subject.

Both overall attack frequency and severity of asthma symptoms decreased significantly during the progression of cognitive impairment in asthma patients with AD. However, peripheral cholinergic function might not be impaired in the airway in patients with AD despite an extensive loss of central cholinergic neurons. It has been reported that the nervous system may modulate immunological and inflammatory responses. Our results suggest that progression of AD might provide an ameliorating effect on the clinical course of asthma, probably due to alterations in the immunological responses including eosinophilic inflammation in the airway.

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References

IL-1 haplotypes and lung function decline

We read with interest the paper by Joos et al on the association of IL-1 gene haplotypes with decline in lung function in smokers and share their view on a possible role of IL-1 genetics in inflammatory respiratory diseases. We have analysed the same polymorphism by

### Table 1: Assessment of asthma severity and change in cognitive function at study entry (baseline) and 5 years follow up (end point) in asthma patients with Alzheimer’s disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Sex</th>
<th>MMSE score</th>
<th>Asthma symptom score</th>
<th>Daily inhaler puffs</th>
<th>Number of hospital admissions for asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>End point</td>
<td>Baseline</td>
<td>End point</td>
</tr>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>23</td>
<td>18</td>
<td>6.4</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>21</td>
<td>16</td>
<td>8.6</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>F</td>
<td>23</td>
<td>17</td>
<td>10.2</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>22</td>
<td>15</td>
<td>7.8</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>M</td>
<td>21</td>
<td>16</td>
<td>7.5</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>23</td>
<td>17</td>
<td>9.4</td>
<td>3.6</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>22</td>
<td>16</td>
<td>9.2</td>
<td>2.4</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>M</td>
<td>23</td>
<td>21</td>
<td>7.6</td>
<td>7.4</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>67.0 (0.7)</td>
<td></td>
<td>22.3 (0.3)</td>
<td>17.0 (0.7)*</td>
<td>8.4 (0.5)</td>
<td>1.8 (0.4)</td>
</tr>
</tbody>
</table>

* p<0.0001 (Wilcoxon rank test) compared with baseline data in all asthma patients with Alzheimer’s disease; † p<0.0001; ‡ p=0.0001; § p=0.0001

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Table 1 Decline in FEV1 (ml/year) in non-smoking asthmatics and controls in different putative IL-1 haplotypes

<table>
<thead>
<tr>
<th>IL-1 haplotype</th>
<th>(1) IL1RN A2/IL1B –511T</th>
<th>(2) IL1RN A2/IL1B –511C</th>
<th>(3) IL1RN A1/IL1B –511T</th>
<th>(4) IL1RN A1/IL1B –511C</th>
<th>p value*</th>
<th>Post hoc tests between allele groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoking controls</td>
<td>41.8 (13.8)</td>
<td>44.8 (12.3)</td>
<td>50.7 (11.2)</td>
<td>45.5 (19.4)</td>
<td>0.27</td>
<td>Not tested</td>
</tr>
<tr>
<td>cases</td>
<td>(n=124)</td>
<td>(n=32)</td>
<td>(n=7)</td>
<td>(n=31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoking new asthma</td>
<td>63.2 (24.6)</td>
<td>37.7 (20.7)</td>
<td>30.9 (16.9)</td>
<td>51.0 (24.8)</td>
<td>0.0443</td>
<td>3-1, p=0.02</td>
</tr>
<tr>
<td>cases</td>
<td>(n=40)</td>
<td>(n=4)</td>
<td>(n=4)</td>
<td>(n=14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*pTwo way analysis of variance; TSD test of means.

Molecular analysis of drug resistant TB

Since the mid 1980s the number of notified cases of TB in the UK has continued to rise with the largest increases noted in London and inner city areas. King George Hospital in Goodmayes, Essex provides clinical services to a population of approximately 230 000; 17% are non-white subjects including immigrants from countries with high rates of M tuberculosis infection and drug resistance. From September 1996 to July 1997 47 adult cases of culture proven TB were identified including seven with drug resistant isolates. None was identified by contact tracing. A previous TB audit of African born patients revealed a high rate of drug resistance (6/24 (25%)) and delays in obtaining drug sensitivities which could have been detrimental to patient management.

Under these circumstances the rapid identification of drug resistance in M tuberculosis isolates would have been helpful. The aim of this study was to determine retrospectively the usefulness of PCR-reverse hybridisation methods for screening for mutations within or adjacent to M tuberculosis genes associated with rifampicin (rpoB) and isoniazid (inhA, katG, and abyC) resistance. We also determined whether resistance genotyping combined with IS6110 typing could help to identify clusters of drug resistant cases not previously identified by contact tracing.

Seven consecutive drug resistant M tuberculosis culture isolates were analysed for rifampicin and isoniazid resistance and the results were compared with conventional susceptibility testing. The commercially available

Table 1 Demographic data, site, phenotypic and genotypic resistance of the seven resistant study isolates

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Age</th>
<th>Country of birth</th>
<th>Site of TB</th>
<th>Drug resistance</th>
<th>Resistance genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>Nigeria</td>
<td>Pulmonary</td>
<td>INH/RIF</td>
<td>Wild type</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>Somalia</td>
<td>Pulmonary</td>
<td>INH</td>
<td>katG mutation</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>Zaire</td>
<td>Pulmonary</td>
<td>INH</td>
<td>inhA mutation</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>Zaire</td>
<td>Pulmonary</td>
<td>INH</td>
<td>Wild type</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>Zaire</td>
<td>Pulmonary</td>
<td>INH</td>
<td>inhA mutation</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>UK</td>
<td>Pulmonary</td>
<td>INH</td>
<td>inhA mutation</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>Somalia</td>
<td>Sternum</td>
<td>PZ</td>
<td>Wild type</td>
</tr>
</tbody>
</table>

INH=isoniazid; RIF=rifampicin; PZ=prazinamide. Isolates 3 and 5 had indistinguishable IS6110 types. Isolates 1 and 4 were not typable due to insufficient culture and the banding pattern of isolate 6 was uninterpretable.
assay INNO-LIPA Rif.TB" was used to detect rpoB mutations and an in-house PCR-reverse hybridisation line probe was used to detect mutations in or adjacent to the katG, inhA, and abpC genes. The isolates were also 16S rDNA typed.

The single rifampicin and isoniazid resistant isolate had an rpoB gene mutation associated with rifampicin resistance (table 1). Four of the five isoniazid resistant isolates had the same single point mutation upstream of the inhA gene and the other a single katG point mutation. Isolates 3 and 5 had indistinguishable 16S rDNA types that could represent isolates where recent transmission had occurred. No mutations were detected in the 40 fully susceptible isolates.

PCR-reverse hybridisation methods were highly sensitive and specific at detecting mutations that predict for isoniazid and rifampicin resistance. We also demonstrated that different point mutations can be used to discriminate between isoniazid resistant isolates. We believe that with automation and the addition of oligonucleotide probes designed to detect mutations associated with pyrazinamide (pncA) and ethambutol (embB) resistance, a system capable of detecting resistance to four front line antituberculous drugs will soon be commercially available. Rapid resistance detection by PCR-reverse hybridisation is likely to have a major impact on patient management and our understanding of the epidemiology of drug resistant TB.

Acknowledgements

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References


Lung bullae and marijuana

A previous paper from this hospital described apical lung bullae in four young male marijua smokers, three West Indian and one Caucasian. Further cases were recently reported, both in Caucasian men. We describe three further cases (one woman) with large upper lobe bullae. All are Caucasian and had a prolonged history of heavy marijuana smoking with an alpha-antitrypsin level within the normal range (table 1). These further cases support the view that marijuana may have a causal role in the development of lung bullae. We suggest that a detailed marijuana smoking history is taken from patients of all ethnic origins with upper lobe bullae.

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Pathophysiology of COPD

The paper by Dentener et al is interesting and contributes to the understanding of the pathophysiology of chronic obstructive pulmonary disease (COPD). It is becoming clear that COPD is a systemic syndrome, and this paper suggests some potential mechanisms. However, a number of issues merit further comment.

It is noted that, in healthy controls, there is a wide range of C reactive protein (CRP) values extending well beyond what would be considered to be the normal range. The reason for this is unclear, but it does suggest that these individuals are not as healthy as described. In addition, patients with stable COPD have a range of CRP values that also extend beyond this normal range. This is not consistent with previous studies, which suggest that, in patients with stable COPD, the range of CRP values lies within the normal range. Although patients with bronchiectasis were excluded, it is possible that undiagnosed bronchiectasis may have been present. Previous work has shown that 29% of patients presenting with what appeared to be stable COPD had CT evidence of at least mild bronchiectasis. This could conceivably explain a wider range of CRP levels. In addition, it is interesting that after just 5 days of treatment for an acute exacerbation the CRP had returned to a level below that of the stable cohort in the study. Since standard treatment for an exacerbation is able to achieve this in just a few days, it suggests that the stable group may have contained individuals that were in fact not so stable.

The authors allude to the potential confounding effect of systemic corticosteroids in the study. The changes in total leucocyte count during the exacerbation are likely to be due to the effect of prednisolone, making it difficult to interpret the changes in leucocyte count. In stable patients the action of corticosteroids may also confound the results. It is possible that in patients using inhaled corticosteroids, leucocyte numbers could be affected since there may be significant bioavailability at higher doses. Leucocyte count should therefore not be used as a marker for systemic inflammation in these patients.

Finally, it would appear that the exacerbations of COPD might have been mild, despite the presence of severe COPD on lung function criteria. Although PaCO2 was slightly higher and PaO2 slightly lower than in the stable group, these differences were small in magnitude. The pH was not significantly different and, in fact, the stable group contained individuals with a lower pH range (7.30–7.50) than in the exacerbated group (pH 7.34–7.49). Although the mean CRP level appears higher than in stable patients, the range does not differ significantly. This may therefore have led to a less profound change in inflammatory markers than might have been expected, and a study looking at more severe exacerbations may be more revealing.

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Table Characteristics at presentation of three cases of apical lung bullae in marijuana smokers

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age on presentation (years)</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Tobacco smoking history</td>
<td>9 pack years</td>
<td>10 pack years</td>
</tr>
<tr>
<td>Marijuana smoking history</td>
<td>2–3 joints/day</td>
<td>“heavy”</td>
</tr>
<tr>
<td>“heavy” 10 years</td>
<td>0.25 oz marijuana/week</td>
<td></td>
</tr>
<tr>
<td>Alpha-antitrypsin (g/l)</td>
<td>1.4</td>
<td>2.3</td>
</tr>
<tr>
<td>(normal range 1.1–2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (%) predicted</td>
<td>2.7 (64)</td>
<td>2.4 (96)</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>4.3 (85)</td>
<td>3.3 (112)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>63</td>
<td>73</td>
</tr>
<tr>
<td>Tico (%) predicted</td>
<td>9.44 (81)</td>
<td>4.99 (62)</td>
</tr>
<tr>
<td>Kco (%) predicted</td>
<td>1.44 (88)</td>
<td>1.10 (64)</td>
</tr>
</tbody>
</table>

FEV1 forced expiratory volume in 1 second, FVC forced vital capacity, Tico carbon monoxide transfer factor, Kco carbon monoxide transfer coefficient.
References

Authors’ reply
Dr Kelly has some concerns about the levels of C reactive protein (CRP) in the healthy controls and patients with clinically stable COPD in our study. The control group used consisted of randomly selected subjects over 50 years of age and living in the same area as the patients. These subjects had no evidence of COPD based on questionnaires and lung function testing, did not exhibit any acute or chronic disease, and were not taking medication. Based on these selection criteria, this group was considered a healthy population control group. Although two of the 23 control subjects had enhanced CRP levels, the reason for this was unknown, they were not excluded in order to prevent bias. Non-parametric tests were used to compare the CRP levels between controls and COPD patients, and therefore the results are not affected by these two outliers. Concerning the diagnosis of COPD, all patients in our study underwent high resolution computed tomographic scanning to exclude the presence of bronchiectasis.

There is increasing evidence that COPD is characterised by systemic effects which, among other factors, are reflected by enhanced circulating levels of inflammatory mediators in the circulation.1 In line with the observations of increased levels of the acute phase proteins CRP and lipopolysaccharide binding protein (LBP) in patients in a clinically stable condition in this study and in previous studies by our group,2 an association between increased plasma levels of the acute phase protein fibrinogen with reduced lung function and increased risk of COPD has recently been reported.3 Yasuda et al also reported enhanced CRP levels in patients with stable COPD.4 It should be noted from these studies5 that only part of the patient population exhibited enhanced acute phase protein levels, as was also the case in our study. This indicates that, although all patients were in a clinically stable condition, subgroups can be discriminated based upon inflammatory characteristics. This could be a factor contributing to the discrepancy between the studies by Gompertz et al2 and ours. No relationship was observed between CRP level and severity of disease,6 whereas separation of patients into normometabolic and hypermetabolic subgroups revealed enhanced levels of CRP in the latter group.7 Further research is needed to elucidate the cause for the production of these acute phase proteins in subgroups of clinically stable COPD patients and its involvement in the pathogenesis of the disease. It is of interest to note that, although only some of the clinically stable patients had enhanced CRP levels, almost all patients who had an exacerbation of disease had increased CRP levels on day 1 of the exacerbation which declined during treatment.

We agree with Dr Kelly that treatment with corticosteroids could affect the leucocyte count in patients with clinically stable COPD. As reported in our paper, increased circulating levels of leucocytes were observed in the subgroup of clinically stable COPD patients treated with oral corticosteroids compared with those who did not receive oral corticosteroids. However, comparison of subgroups of patients without corticosteroid treatment (oral or inhaled or both) with control subjects still revealed significantly increased leucocyte counts (data not shown). This indicates that the enhanced levels of circulating leucocytes are not solely due to corticosteroid use, and could be a marker of the systemic inflammatory process in COPD. In line with this hypothesis, Noguera et al reported enhanced circulating levels of polymorphonuclear cells in patients with stable COPD, none of whom had received steroids before the start of the study (oral or inhaled).8

As discussed in our paper, administration of prednisolone during treatment of an exacerbation is most probably the cause for the observed rise in leucocyte counts. In order to determine the effect of an exacerbation on leucocyte counts, studies are currently being performed in our hospital in which blood from patients with an exacerbation is collected before the start of treatment.

COPD comprises a heterogeneous group of conditions characterised by chronic airflow limitation and destruction of lung parenchyma with clinical manifestations of dyspnoea, cough, sputum production, and impaired exercise tolerance. The definition of an acute exacerbation of COPD is still imprecise, and is generally based on varying combinations of symptoms. Rodriguez-Roisin et al suggested staging COPD exacerbations based on use of health care.9 They defined three levels of severity: mild, moderate and severe. During a mild exacerbation the patient has an increased need for medication which he/she can manage in their own environment; patients with a moderate exacerbation have an increased need for medication and need to seek additional medical assistance; the patient with a severe exacerbation recognises obvious and/or rapid deterioration in his/her condition requiring admission to hospital. Based on this definition, the patients included in our study were suffering from severe exacerbations of disease. Only limited information is so far available concerning (changes of) inflammatory markers during exacerbations.

In our study the kinetics of pro- and anti-inflammatory markers have been analysed in patients with COPD during the first 7 days in hospital for an exacerbation of the disease. The results showed a significant decline in systemic levels of both CRP (at day 3) and LBP (at day 7) compared with day 1, whereas levels of the anti-inflammatory mediator soluble IL-1 receptor II dramatically increased (until day 5). This change in levels of inflammatory mediators may contribute to the clinical improvement of the patients. Additional studies are required to obtain more insight into the role of the inflammatory processes in the pathogenesis of exacerbations which could contribute to measurable parameters, in order to define the severity or outcome of disease more accurately.

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IL-1 haplotypes and lung function decline

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