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 1995 to 2000. All subjects were treated with oral theophylline (200 mg twice daily) and a 200 µg dose of fenoterol given by a nebulizer daily). The severity of asthma was occasionally modulated by neuropsychiatric conditions. 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 year 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>F</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>22.3 (0.3)</td>
<td>17.0 (0.7)*</td>
<td>8.4 (0.5)</td>
<td>1.8 (0.4)*</td>
<td>2.2 (0.3)</td>
</tr>
</tbody>
</table>

MMSE=Mini-Mental State Examination; SE=standard error.

*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 compared with baseline data in seven asthma patients with Alzheimer’s disease (cases 1–7).
 previously been found to be associated with more rapid decline.

New adult asthma cases and controls were selected from a cohort of the Mini-Finland Health Survey (MFHS) and later re- evaluated. A more detailed description of the methods used in MFHS has been published elsewhere. The accuracy of the method of asthma case ascertainment has also recently been described.1–1 Haplotypes were found to be significantly associated with the rate of decline of lung function in non-smoking incident cases of asthma (new asthma during follow-up) but not in controls (table 1). Of the individual haplotypes, Joos et al found that IL1RN A2/IL1B –511T was associated with a rapid decline of lung function in smokers and IL1RN A2/IL1B –511C with a slow decline. In our control group the observed differences were not significant. Surprisingly, in the asthma group the haplotypes had the opposite effects from those in smokers: IL1RN A1/IL1B –511C was associated with a slower decline in lung function and IL1RN A1/IL1B –511T with a more rapid decline. IL1RN A2/IL1B –511T has previously been found to be associated with many inflammatory diseases. The function of these haplotypes would therefore appear to be disease specific.

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References

Authors’ reply
Karjalainen and colleagues present interesting data on the relationship of IL-1β and IL-1 receptor antagonist haplotypes and the rate of decline of lung function in incident asthmatic subjects in a Finnish cohort. We reported that the IL1RN A1/IL1B –511T haplotype was associated with a more rapid decline in lung function in smokers in the Lung Health Study; in contrast, they found that this same haplotype was associated with a slower rate of decline in lung function in patients with asthma. The authors suggest that this apparent contradiction may be because the function of these haplotypes is disease specific. We agree that a different effect of the same haplotype could occur because of fundamental differences in the pathophysiological processes which cause airflow obstruction in asthma and chronic obstructive pulmonary disease (COPD). In asthma, CD4+ Th2 cells underlie persistent eosinophilic inflammation and remodelling in medium sized and larger airways. In COPD, neutrophils and CD8+ cells appear to play an important role in the airflow limitation by causing proteolytic destruction of peripheral lung parenchyma and fibrous scarring of the small membranous and respiratory bronchioles. Although inflammation appears to be central to both processes, the roles of IL-1β and IL-1 receptor antagonist in these conditions is unknown and it is possible that the polymorphisms that are responsible for this haplotype could have opposite effects.

Alternatively, these apparently contradictory results could be due to different genetic histories of the two study groups. Our study group was taken from the white population in the United States whereas Karjalainen et al studied Finnish individuals. It may be that the polymorphisms which are typed to establish these haplotypes do not, by themselves, change the function or level of expression of the IL proteins but are in linkage disequilibrium with a causal polymorphism(s). In this case, the IL1 allelic associations could be confounded by different populations. The bottleneck effect in the genetic history of the Finnish people could have established a founder effect and resulted in the function altering allele being found on a different genetic background from that in the white population of the United States.

Whatever the correct explanation, these results support the growing evidence that genetic variation at the IL-1 locus is important in modulating the severity and/or functional consequences of a number of inflammatory conditions.

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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.1 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.2 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 (rpsD) and isoniazid (inhA, katG, and abpC) 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>
<thead>
<tr>
<th>Isolate</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>Pulmonary</td>
<td>INH/RIF</td>
<td>Wild type</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>Pulmonary</td>
<td>INH</td>
<td>katG mutation</td>
</tr>
<tr>
<td>3</td>
<td>Zaire</td>
<td>Pulmonary</td>
<td>INH</td>
<td>inhA mutation</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>Pulmonary</td>
<td>INH</td>
<td>Wild type</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>Pulmonary</td>
<td>INH</td>
<td>inhA mutation</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>Pulmonary</td>
<td>INH</td>
<td>Wild type</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>Sternal</td>
<td>PZ</td>
<td>Wild type</td>
</tr>
</tbody>
</table>

INH=isoniazid; RIF=rifampicin; PZ=pyrazinamide. Isolates 3 and 5 had indistinguishable IS6110 types. Isolates 1 and 4 were not typeable due to insufficient culture and the banding pattern of isolate 6 was uninterpretable.

Table 1

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

The function of these haplotypes would therefore appear to be disease specific.
assay INNO-LIPA Rif.TB was used to detect rifampicin resistance and an in-house PCR-reverse hybridisation line probe was used to detect mutations in or adjacent to the katG, inhA, and rpoB genes. The isolates were also IS6110 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 IS6110 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 mari-juana smokers, three West Indian and one Caucasian. Two 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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References


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 suggests that, in patients with stable COPD, the range of CRP values falls within the normal range. Although patients with bronchitis were excluded, it is possible that undiagnosed bronchitis 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 conceivably explains a wider range of CRP levels. In addition, it is interesting that after just 5 days of treatment for an acute exacerbation of COPD, 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, even 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>Characteristic</th>
<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>
<td>38</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Tobacco smoking history</td>
<td>9 pack years</td>
<td>10 pack years</td>
<td>20 pack years</td>
</tr>
<tr>
<td>Marijuana smoking history</td>
<td>2–3 joints/day</td>
<td>-</td>
<td>0.25 oz</td>
</tr>
<tr>
<td>“Heavy” years</td>
<td>“Moderate” years</td>
<td></td>
<td>“Heavy”</td>
</tr>
<tr>
<td>Alpha-antitrypsin (g/l)</td>
<td>1.4</td>
<td>2.3</td>
<td>1.6</td>
</tr>
<tr>
<td>(normal range 1.1–2.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (%) predicted</td>
<td>2.7 (64)</td>
<td>2.4 (96)</td>
<td>3.7 (90)</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>4.3 (85)</td>
<td>3.3 (112)</td>
<td>4.7 (94)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>53</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>Tico (%) predicted</td>
<td>9.44 (81)</td>
<td>4.99 (62)</td>
<td>–</td>
</tr>
<tr>
<td>KCO (%) predicted</td>
<td>1.44 (88)</td>
<td>1.10 (64)</td>
<td>–</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.

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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 which is 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. 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, 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. Yasuda et al also reported enhanced CRP levels in patients with stable COPD. It should be noted from these studies 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 al and ours. No relationship was observed between CRP level and severity of disease, whereas separation of patients into normometabolic and hypermetabolic subgroups revealed enhanced levels of CRP in the latter group. 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).

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 exacerbation on leucocyte counts, studies are currently being performed in our hospital in which blood is collected before the start of the study (oral or inhaled).


References