PostScript

Relationship between asthma severity and progression of Alzheimer's disease

Severity of asthma is occasionally modulated by neuropsychiatric conditions.[1] 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).[2] AD is a disease characterised by progressive cholinergic failure[3] 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.[4] 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 flow driven inhaler as needed. Family members of the patients completed a diary card that recorded asthma symptoms,[5] 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)[6] and sputum eosinophil counts[7] and methacholine challenge tests[8] 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.[3] It has been reported that the nervous system may modulate immunological and inflammatory responses.[9] 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

1 **Campbell DA**, Yellowlees PM, McLennan G, *et al.* Psychiatric and medical features of near fatal asthma. *Thorax* 1995;**50**:254–9.
2 **McKhaan G**, Drachman D, Folstein M, *et al.* Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;**34**:939–44.
3 **Davis KL**, Mohs RC, Martin D, *et al.* Cholinergic markers in elderly patients with early signs of Alzheimer's disease. *JAMA* 1999;**281**:1401–6.
4 **Park E**, Alberti J, Mehta P, *et al.* Partial impairment of immune functions in peripheral blood leukocytes from aged men with Down's syndrome. *Clin Immunol* 2000;**95**:62–9.
5 **Nakasato H**, Ohrui T, Sekizawa K, *et al.* Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist. *J Allergy Clin Immunol* 1999;**104**:585–8.
6 **Folstein MF**, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for clinicians. *J Psychiatr Res* 1975;**12**:189–98.
7 **Fahy JV**, Liu J, Wong H, *et al.* Cellular and biochemical analysis of induced sputum from asthmatic and from healthy subjects. *Am Rev Respir Dis* 1993;**147**:1126–31.
8 **Takishima T**, Hida W, Sasaki H, *et al.* Direct-writing recorder of the dose-response curves of the airway to methacholine. *Chest* 1981;**80**:600–6.
9 **Shalit F**, Sredni B, Brodie C, *et al.* T lymphocyte subpopulations and activation markers correlate with severity of Alzheimer's disease. *Clin Immunol Immunopathol* 1995;**75**:246–50.

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IL-1 haplotypes and lung function decline

We read with interest the paper by Joos *et al*[1] 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

			MMSE score		Asthma symptom score		Daily inhaler puffs		Number of hospital admissions for asthma	
Case	Age (y)	Sex	Baseline	End point	Baseline	End point	Baseline	End point	Baseline	End point
1	67	M	23	18	6.4	1.2	1.3	0	2	0
2	66	M	21	16	8.6	2.2	1.4	0	2	0
3	70	F	23	17	10.2	1.6	2.4	0	3	1
4	65	M	22	15	7.8	1.2	2.6	1.4	3	0
5	65	F	21	16	7.5	0.4	3.3	1	2	0
6	69	F	23	17	9.4	3.6	1.9	0.4	3	0
7	66	F	22	16	9.2	2.4	2.2	0	2	0
8	68	M	23	21	7.6	7.4	2.8	2.6	3	2
Mean (SE)	67.0 (0.7)		22.3 (0.3)	17.0 (0.7)*	8.4 (0.5)	1.8 (0.4)†	2.2 (0.3)	0.4 (0.2)‡	2.4 (0.2)	0.1 (0.1)§

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).

Table 1 Decline in FEV_1 (ml/year) in non-smoking asthmatics and controls in different putative IL-1 haplotypes

IL-1 haplotype	(1) IL1RN A2/ IL1B –511T	(2) IL1RN A2/ IL1B –511C	(3) IL1RN A1/ IL1B –511T	(4) IL1RN A1/ IL1B –511C	p value*	Post hoc tests between allele groups†
Non-smoking controls (n=124)	41.8 (13.8) (n=54)	44.8 (12.3) (n=32)	50.7 (11.2) (n=7)	45.5 (19.4) (n=31)	0.27	Not tested
Non-smoking new asthma cases (n=40)	63.2 (24.6) (n=18)	37.7 (20.7) (n=4)	30.9 (16.9) (n=4)	51.0 (24.8) (n=14)	0.0443	3<1, p=0.02 2<1, p=0.06

*Two way analysis of variance; †LSD test of means.

the same methods in adult incident non-smoking asthmatic patients and non-smoking controls. Our results indicate that the association of IL-1 genetics with rate of decline in lung function is not limited to smokers.

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.[2] The accuracy of the method of asthma case ascertainment has also recently been described.[3] IL-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 A1/IL1B –511T* was associated with a rapid decline of lung function in smokers and *IL1RN A2/IL1B –511T* 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 –511T* was associated with a slower decline in lung function and *IL1RN A2/IL1B –511T* with a more rapid decline. *IL1RN A2/IL1B –511T* has previously been found to be associated with many inflammatory diseases.[4] The function of these haplotypes would therefore appear to be disease specific.

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References

1 **Joos L**, McIntyre L, Ruan J, *et al*. Association of IL-1beta and IL-1 receptor antagonist haplotypes with rate of decline in lung function in smokers. *Thorax* 2001;**56**:863–6.
2 **Von Hertzen L**, Reunanen A, Impivaara O, *et al*. Airway obstruction in relation to symptoms in chronic respiratory disease: a nationally representative population study. *Respir Med* 2000;**94**:356–63.
3 **Karjalainen A**, Kurppa K, Martikainen R, *et al*. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. *Am J Respir Crit Care Med* 2001;**164**:565–8.
4 **Hurme M**, Lahdenpohja N, Santtila S. Gene polymorphisms of interleukins 1 and 10 in infectious and autoimmune diseases. *Ann Med* 1998;**30**:469–73.

Authors' reply

Karajalainen 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 of 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 different in different populations. The bottleneck 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 (*rpoB*) and isoniazid (*inhA, katG*, and *ahpC*) 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

Isolate	Age	Country of birth	Site of TB	Drug resistance	Resistance genotype	
					Isoniazid	Rifampicin
1	24	Nigeria	Pulmonary	INH/RIF	Wild type	*rpoB* mutation
2	21	Somalia	Pulmonary	INH	*katG* mutation	Wild type
3	40	Zaire	Pulmonary	INH	*inhA* mutation	Wild type
4	17	Zaire	Pulmonary	INH	*inhA* mutation	Wild type
5	20	Zaire	Pulmonary	INH	*inhA* mutation	Wild type
6	42	UK	Pulmonary	INH	*inhA* mutation	Wild type
7	44	Somalia	Sternum	PZ	Wild type	Wild type

INH=isoniazid; RIF=rifampicin; PZ=pyrazinamide. 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.