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Histocompatibility antigens, aspirin use and cognitive performance in non-demented elderly subjects

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Abstract

HLA genotype and anti-inflammatory drug use have independently been associated with a lower risk of Alzheimer's disease (AD). We recently reported a negative association between aspirin use and AD. To investigate this further, we performed a cross-sectional study to investigate cognitive performance in 151 non-demented individuals in relation to HLA-DRB1 genotype and aspirin use. Aspirin and HLA-DRB1*01 were positive predictors of performance on logical memory (aspirin, $p=0.04$) and verbal fluency tests (HLA-DRB1*01, $p=0.018$), respectively. HLA-DRB1*05 had a negative impact on the Boston naming test ($p=0.002$). Our results suggest that aspirin use and inflammatory genotype may influence cognition in non-demented subjects.

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1. Introduction

The concept that anti-inflammatory drugs may be protective against the development of Alzheimer's disease (AD) is based on a number of studies suggesting a reduced risk of dementia in subjects who consume anti-inflammatory medications (for review see Henderson et al., 1997; McGeer et al., 1996; Prince et al., 1998; Stewart et al., 1997). An additional benefit appears to be better cognitive performance in patients with AD (Rogers et al., 1993; Rich et al., 1995; Scharf et al., 1999). The basis for this theory initially came from studies showing a reduced incidence of dementia amongst rheumatoid arthritis sufferers, a disease in which anti-inflammatory drugs are commonly prescribed. The mechanism behind this apparent protective effect is uncertain, but the observation of a significantly upregulated inflammatory response within the AD brain (Shepherd et al., 2000) has led to the hypothesis that immune events con-

tribute to the neurodegenerative events underlying cognitive decline (McGeer and McGeer, 1997). This 'inflammatory hypothesis' is also supported by the more recent observation of an association between AD and certain human leukocyte antigens (HLA-DR, Curran et al., 1997; Neill et al., 1999). An individual's HLA-DR genotype has also been shown to affect cognitive performance (Cohen et al., 1981). These studies have led to the hypothesis that HLA-DR genotype and anti-inflammatory drug use in combination may influence cognitive performance (Curran et al., 1997).

Our own studies in this area have examined the cross-sectional association between various medications and the presence of AD in the Sydney Older Persons Study (SOPS), a randomly selected sample of community-living elderly people in inner suburban Sydney. As well as a negative association between taking anti-inflammatory drugs and the presence of dementia, we found a similar association with low-dose aspirin which was specific for AD rather than vascular or other types of dementia (Broe et al., 2000).

In the present study, we examined the association between HLA-DR genotype, aspirin use and performance on cognitive testing in the non-demented subjects from SOPS.

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2. Methods

2.1. Study sample

The Sydney Older Persons Study, including details of subjects and medical assessments, have been described elsewhere (Waite et al., 1996, 1997). In brief, 630 randomly selected, community-dwelling people aged 75 years and over were recruited to investigate aspects of successful ageing. The baseline assessment (SOPS-1) involved the collection of detailed medical and social histories as well as neurological and cognitive evaluation and was performed by a physician experienced in geriatric medicine. Additional information was collected from a nominated informant.

A progress assessment at 3 years (SOPS-2) provided the data for the current study. The neuropsychological test battery consisted of the Mini Mental State Examination (MMSE; (Folstein et al., 1975)) and tests designed to examine the specific cognitive domains of memory, language, perceptual/spatial and executive/frontal. Memory was assessed using Logical Memory from the Wechsler Memory Scale-Revised (Wechsler, 1987). Per cent [two words] forgetting between immediate and delayed recall of the prose passages was computed as it has been shown to be sensitive in the detection of AD (Troester et al., 1993). Expressive language integrity was measured with the Boston Naming Test (Kaplan et al., 1983), which has been shown to be very sensitive to mild AD (Zec et al., 1992). Visuo-perceptual abilities were measured with a subset from the Judgment of Line Orientation test (Benton et al., 1983). In this task, participants have to determine the angles of sets of two lines against a template. Two tasks of executive functions were administered. The first task was the Similarities subtest from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), which is a task of concept formation and abstraction. The second task was the Controlled Oral Word Association Test (Benton and Hamsher, 1983). This is a phonemic fluency task where the instructions are to provide as many words as possible starting with a specific letter in one min, with some restrictions applying to the accepted words. The score is the total number of correct words for three letters (F, A and S). Dementia diagnosis made based on the physician's assessment at the time of SOPS-2 was used in the analysis of this study.

In addition, 341 of the 420 participants at SOPS-2 consented to blood donation. At that time, an audit of all medications at the subjects' home was conducted in addition to self/informant reported medication use as described (Broe et al., 2000). Complete data were available for 321 participants at SOPS-2. Of these, 170 participants met DSM-III-R diagnostic criteria for dementia and were not included in the present study. Thus, the final sample comprised 151 individuals (82 males and 69 females) with a mean age of 79 ± 3 years, who remained without dementia at 3-year follow-up.

2.2. Genotyping

Molecular DNA typing of the HLA-DRB1 locus was carried using polymerase chain reaction sequence specific oligonucleotide probes according to standard protocol (Kimura and Sasazuki, 1992). Each sample was assigned to broad DRB1 alleles (i.e. DR1, DR2, DR3, DR4, etc.). The allelic specificities DRB1*13 and DRB1*14 were detected using a number of oligonucleotide probes and were grouped together as DRB1*06. ApoE genotyping was carried out according to standard protocol (Hixson and Vernier, 1990).

2.3. Statistics

We analysed the frequency of HLA-DRB1 alleles in relation to performance on cognitive tests and MMSE scores collected at the time of the 3-year review as described above. All data were assessed in subjects receiving aspirin compared to their non-treated counterparts. Chi-squared statistics were used for direct comparisons between groups (two-tailed) and the effect of selected variables on cognitive status was investigated using multiple regression methods.

3. Results

Participants included 69 aspirin users and 82 non-users. The mean age difference in the two groups was not significant. The frequencies of HLA-DRB1*1–7 in aspirin users and non-users are given in Table 1. Statistical analysis of alleles 8–10 was not performed due to their low frequency. Statistical analysis of the allelic frequencies of HLA-DR 1–7 was performed in both aspirin users and non-users and in relation to performance on the cognitive tests. We looked at cognitive measures as outcome variables using multiple regression analysis. Consistent with previous studies (O'Hara et al., 1998; Dik et al., 2001), both increased age and ApoE ϵ 4 status were associated with poorer performance on the MMSE. Combined, these variables explained 11% of the variance seen on test scores ($p=0.002$). Cognitive test scores for aspirin users and non-users are shown in Table 2. Aspirin use was a significant and positive predictor of performance on the Logical

Table 1
Frequencies of HLA-DRB1*1–7 alleles in aspirin users and non-users

	Allele frequency %	
	Non-users	Users
DR1	12.5	7.5
DR2	15.4	13.3
DR3	14	15
DR4	26.5	26.7
DR5	3.7	8.3
DR6	6.6	11.7
DR7	15.4	15

Table 2
Cognitive test scores for aspirin users and non-users

Variable	Total sample		Non users (n = 82)		Asp users (n = 69)	
	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	Range
MMSE score (max. 30)	27.2 (2.4)	11–30	27.0 (3.0)	11–30	27.5 (1.6)	23–30
WMS-R logical memory % forgetting*	32 (21.2)	0–100	36 (23.6)	5–100	29 (17.5)	0–70
Boston naming test (max. 24)	19.8 (3.0)	12–24	19.4 (3.1)	12–24	20.2 (3.0)	12–24
Judgment of line orientation (max. 20)	17.4 (2.1)	11–20	17.4 (2.2)	11–20	17.5 (1.9)	13–20
Phonemic fluency	30.6 (11.2)	5–56	29.7 (12.0)	5–56	31.8 (10.2)	11–55
WAIS-R similarities (max. 20)	10.2 (4.3)	0–20	9.9 (4.4)	0–19	10.4 (4.3)	3–20

MMSE = Mini mental state examination; WAIS-R = Wechsler Adult Intelligence Scale Revised; WMS-R = Wechsler Memory Scale Revised.

* Significant difference $p < 0.05$ between Aspirin users and non-users.

memory test, contributing to 3% of the explained variance ($p = 0.04$). Similarly, the presence of HLA-DRB1*01 allele had a significant positive contribution to the Controlled Oral Word Association Test, explaining 4% of the variance ($p = 0.018$). In contrast, the presence of HLA-DRB1*05 allele was associated with a poorer performance on the Boston naming test. This allele explained 6% of the score variation ($p = 0.002$). No interaction between aspirin use and HLA-DR genotype on cognitive performance was found using multi-variate analysis statistics (data not shown).

4. Discussion

In agreement with previous studies (Bruce-Jones et al., 1994; Doraiswamy et al., 1997; Rozzini et al., 1996), the present data demonstrate a significant difference in some aspects of cognitive performance in a well-characterised elderly sample receiving aspirin. This effect was also observed in individuals with the HLA-DRB1*01 allele. In contrast, the presence of the DRB1*05 allele was associated with impaired performance on the Boston naming test, highlighting possible new genetic modifiers of cognition. This study supports a beneficial effect of aspirin on cognitive performance in both ageing and AD, and highlights potential, genetic modifiers of cognition.

Two general mechanisms concerning the beneficial effects of aspirin on cognitive performance have been suggested. The first hypothesis focuses on reducing the central inflammatory response, which is thought to contribute to the disease process (McGeer and McGeer, 1998). Indeed, a reduction in AD brain pathology and improved cognitive performance has been demonstrated in animal models receiving anti-inflammatory medication (Lim et al., 2000). However, two recent studies investigating the effect of anti-inflammatory drugs on human brain pathology have yielded conflicting data. Whilst a reduction in inflammatory microglia was seen in elderly non-demented individuals receiving anti-inflammatory medications by MacKenzie and Munoz (1998), no reduction in either inflammatory or AD-related pathology was observed in a group of AD patients (Halliday et al., 2000). Furthermore,

recent studies have demonstrated a decrease in AD-pathology, but an increase in inflammation in the brains of mice receiving anti-inflammatory medication (Jantzen et al., 2002), highlighting the need for further research in this area. As over 80% of aspirin users in SOPS were taking a dose of less than 175 mg/day, this anti-inflammatory mechanism is less likely to be important here.

An alternative hypothesis concerns cerebral perfusion rates and the prevention of cerebral vascular damage. The anti-platelet aggregation properties of aspirin have been studied extensively and are known to reduce the incidence of cerebrovascular accidents in high-risk patients. Indeed, in a controlled clinical trial, Meyer et al. (1989) demonstrated that daily aspirin use improved cognitive performance and cerebral perfusion in patients with mild to moderate vascular dementia. This hypothesis is consistent with our own findings (Broe et al., 2000), which demonstrated that the use of aspirin at anti-platelet levels provided equivalent protection against AD to the higher anti-inflammatory doses. Whilst inflammatory processes do increase with age (Vogelgesang et al., 2002) the effect is modest compared to inflammation in AD (Shepherd et al., 2000). Therefore, an effect on cerebral perfusion is more likely to account for the better cognitive performance seen in our elderly non-demented population.

Genetic polymorphisms in drug receptors, metabolising agents, and transporters are known to modify disease processes. For example, the ApoE $\epsilon 4$ is not only associated with an increased risk of AD, but the presence of the ApoE $\epsilon 4$ (Cruz-Sanchez et al., 2000) and an absence of the HLA-DRB1*04 allele (Aisen et al., 1998) are associated with greater AD-related pathology. HLA-DR antigens have also been shown to influence multiple sclerosis-like diseases in primates by enhancing the pathogenic effect and reducing the protective effect of immune mechanisms (t Hart et al., 2001), thus providing one mechanism whereby inflammatory genotype may significantly alter the pathogenesis of neurodegenerative diseases. Only one study to date has investigated the effect of HLA alleles on cognition. Cohen et al. (1981) demonstrated that AD patients with HLA-B7 antigens had significantly lower selective attention scores than AD patients without the antigen. Whilst associations between HLA and cognitive decline have only been inves-

tigated amongst AD patients, a more recent study by Bartres-Faz et al. (2000) has demonstrated that polymorphisms in the inflammatory angiotensin 1 converting enzyme influence cognitive performance in a population with age-associated memory impairment. These data, along with the present study, provide support for an immunological basis not only for AD, but also for age-related cognitive impairment. Such aberrant immunological phenomena may alter development of neural structures, thereby altering an individual's susceptibility to age-related pathologies and/or neurological disorders in later life. Indeed, HLA cell surface protein structures are known to influence embryonic development (Marinova et al., 2001). Similarly, the presenilin-1 protein plays an important role in determining cell fate during neurogenesis (Handler et al., 2000), and mutations in this gene are responsible for causing an early-onset form of AD (Sherrington et al., 1995).

Collectively, these data provide support for a trend towards a modifying effect of inflammatory drug use and genotype on pathological processes related to cognition in non-demented elderly individuals. Longitudinal studies are now required in larger, elderly populations to determine the protective (aspirin use and HLA-DRB*01) and detrimental (HLA-DRB*05) effect of these variables on the development of AD.

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