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Reduced estimated glomerular filtration rate in Alzheimer's disease

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SUMMARY

Objectives Renal disease is increasingly regarded as an independent risk factor for vascular disease which in itself is believed to influence risk of AD. Alterations in amyloid homeostasis via reduced renal clearance of peripheral beta-amyloid (A|*beta*|) may represent another potential role for variation in renal function leading to increased risk of AD. We sought to examine estimates of glomerular filtration rate in AD and control groups.

Methods AD patients were randomly recruited from the Memory Clinic of the Belfast City Hospital ($n = 83$). Genomic DNA was extracted from peripheral leucocytes and was genotyped for Apolipoprotein E using standard methods. Using creatinine values, age and gender, estimated Glomerular Filtration Rates (eGFR) were calculated using the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) Study equation (using the United Kingdom National External Quality Assessment Scheme (UKNEQAS) correction factor). IDMS eGFR values were then compared between AD and control groups.

Results Significant baseline differences in age, diastolic blood pressure, education level attained and APOE |*epsilon*|4 carriage were noted between cases and controls. The AD group had a significantly lower eGFR versus controls (69 *vs* 77 ml/min) which persisted after adjustment for possible confounders ($p = 0.045$).

Conclusions This case-control analysis suggests that using a relatively accurate estimate of renal function, patients with AD have greater renal impairment than cognitively normal controls. This may reflect impaired renal clearance of peripheral A|*beta*| or be a marker of shared vascular processes altering cerebral and renal functioning. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; amyloid; dementia; renal disease; glomerular filtration rate

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia with a prevalence of 24–33% in those aged over 85 (Ferri *et al*., 2005). It is a progressive neurodegenerative condition leading to enormous personal and health economic burden.

Development of AD is associated with several different genetic and environmental factors. Genetic mutations in amyloid precursor protein (APP) on chromosomes 21, presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) cause autosomal dominant familial AD (Goate *et al*., 1991; Levy-Lahad *et al*., 1995; Sherrington *et al*., 1995). The ε4 allele of the APOE gene is a genetic risk factor for sporadic late onset AD (Corder *et al*., 1993; Farrer *et al*., 1997). Age, along with female gender, lower educational attainment and a history of head injury are additional risk factors for sporadic AD (Andersen *et al*., 1999; Ferri *et al*., 2005; McDowell *et al*., 2007).

A number of epidemiological studies have acknowledged a role for vascular risk factors in AD (Mayeux, 2003). Prospective cohort studies have identified smoking, hypertension, atrial fibrillation, diabetes,

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hypercholesterolaemia, APOE ε4 polymorphism, elevated CRP, low folate levels, hyperhomocysteinaemia, obesity, and arterial stiffness as potential risk factors for the development of AD (Farrer *et al*., 1997; Kivipelto *et al*., 2001; Seshadri *et al*., 2002; Gustafson *et al*., 2003; Hofman *et al*., 2007). The Rotterdam Study (Hofman *et al*., 1997) evaluated 284 patients with dementia, 207 of whom had AD, and 1698 non-demented controls. The study found that indicators of atherosclerosis (vessel wall thickness, plaques of the carotid arteries and ratio of ankle-to-brachial systolic blood pressure) were associated with dementia and its major subtypes: AD (Odds Ratio (OR) 1.3–1.8) and Vascular Dementia (VaD) (OR 1.9–3.2). The frequencies of all dementia, AD and VaD increased with the degree of atherosclerosis. The OR for AD in those with severe atherosclerosis compared to those without atherosclerosis was 3.0 (95% Confidence Intervals (CI) 1.5–6.0; $p = 0.001$). However, there has been limited and at times conflicting evidence when interventional studies targeted at key cardiovascular risk factors such as cholesterol or hypertension are examined in established and at-risk populations (Bifulco *et al*., 2008; McGuinness *et al*., 2008).

Acknowledging the established link between impaired renal function and vascular disease in general (as well as stroke and carotid atherosclerosis in particular) (Lass *et al*., 1999; Savazzi *et al*., 2001; Seliger *et al*., 2004), previous studies have focused predominantly on the increased risk of VaD associated with reduction in GFR or overt renal failure. Longitudinal and cross-sectional studies have shown that chronic kidney disease with moderate reductions in GFR is associated with an increased risk of dementia among older adults (Seliger *et al*., 2004). The Cardiovascular Health Cognition Study followed 3349 subjects and found 477 cases of incident dementia over a median 6 years (211 VaD and 244 AD). They found an elevated baseline serum creatinine (SCr) (expressed as 1/SCr) to be associated with a 58% increased risk of VaD but found no significant association with AD. Few case-control studies have previously examined differences in renal function between dementia groups and controls although we have reported a prior difference in serum creatinine levels between vascular, AD and normal subjects (McIlroy *et al*., 2002). To the best of our knowledge, no clinical trial evidence is available to show that therapeutic intervention in renal disease lessens the risk of subsequent cognitive impairment.

The chief component of senile plaques, Aβ peptides, likely play a central role in the pathological processes underlying AD (Hardy and Selkoe, 2002). Evidence suggests that Aβ deposition and plaque formation is a dynamic process involving a fine balance of Aβ production and clearance from the brain (Zlokovic *et al*., 2000; Selkoe 2001; Ghiso *et al*., 2004; Bates *et al*., 2008). Normal cerebral Aβ concentrations are maintained by numerous pathways including receptor for advanced end glycation products (RAGE) mediated influx and low-density lipoprotein receptor related protein 1 (LRP) mediated clearance across the blood brain barrier (BBB) (Deane *et al*., 2004). Increasingly, it has been recognised that peripheral production of Aβ outside the brain may play a part in this process (DeMattos *et al*., 2001; Tang *et al*., 2006; Johnston *et al*., 2008). Increased peripheral production could reduce the capacity for clearance of cerebral Aβ across the BBB triggering the sequence of events culminating in cognitive deficits.

Regulation of Aβ levels is also dependent on cerebral and systemic Aβ catabolism and elimination. Multiple proteases which degrade Aβ have been identified (Iwata *et al*., 2001; Selkoe, 2001; Zlokovic *et al*., 2005; Nalivaeva *et al*., 2008). The liver is a known contributor to plasma clearance of Aβ (>60%) (Ghiso *et al*., 2004). Renal clearance has also been identified as another elimination pathway with rat studies showing high urinary levels of radioactive tracer after infusion of radio labelled Aβ into the lateral ventricles (Ghersi-Egea *et al*., 1996). In human subjects, a positive correlation has been identified between serum creatinine and plasma Aβ concentrations (Arvanitakis *et al*., 2002). In addition, a recent study showed that haemodialysis effectively reduced plasma Aβ by 30% from baseline in patients with chronic renal failure (Rubio *et al*., 2006). Aβ immunotherapy promotes clearance of Aβ from the brain, resulting in increased plasma Aβ and reduced cortical amyloid load (Lemere *et al*., 2004). If peripheral clearance of Aβ is reduced, this 'peripheral sink' capacity would be compromised and cortical amyloid levels would be predicted to increase.

The role of impaired renal function in AD remains a relatively unexplored area. Renal disease is increasingly regarded as an independent risk factor for cerebrovascular and cardiovascular disease via proposed mechanisms involving inflammatory mediation, activation of the renin-angiotensin system, enhanced production of reactive oxygen species and endothelial dysfunction, promotion of vascular calcification, hypertension and dyslipidaemia (Schiffrin *et al*., 2007). This process, perhaps in conjunction with the alterations in amyloid homeostasis outlined above, may indicate a potential role for changes in renal function to increase risk of AD. We have therefore

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studied the relationship between an accurate measure of renal function, namely eGFR (as measured by the IDMS-MDRD eGFR equation), and AD, using a case control design in the context of examining measures of known vascular risk.

METHODS

Ethical approval for this study was obtained from the Research Ethics Committee, Queen's University Belfast. Written informed consent was obtained from patients, caregivers and controls. All subjects with a strong family history of dementia ($\geq$1 first degree relative) were excluded. All patients and controls were Caucasian.

Patients were randomly recruited from the Memory Clinic of the Belfast City Hospital ($n = 83$). Controls were recruited from non-demented healthy spouses and volunteers from the local podiatry clinic or retirement clubs throughout Northern Ireland ($n = 71$).

The diagnosis of probable AD was determined by two experienced clinicians using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al*., 1984). A computerised tomography scan was performed to aid diagnosis in the majority of cases. Cognitive function was assessed using Mini Mental State Examination (MMSE) (Folstein *et al*., 1975). Controls subjects with a MMSE $\geq$ 28 were included.

All subjects and controls had age, gender, blood pressure, smoking status and level of educational attainment recorded. Fasting blood samples were reserved for measurement of serum cholesterol and serum creatinine. Genomic DNA was extracted from peripheral leucocytes by the salting out method and was genotyped for APOE using standard methods (Hixson and Vernier, 1990). Using creatinine values, age and gender, eGFRs were calculated using the IDMS traceable MDRD equation (Levey *et al*., 1999; Vickery *et al*., 2006) (employing the UKNEQAS correction factor) as shown:

IDM traceable equation

$$\begin{aligned}\text{GFR} = 175 &\times [(\{\text{serum creatinine} - \text{intercept}\}/\text{slope}) \\ &\times 0.011312]^{-1.154} \times \text{age}^{-0.203} \\ &\times (0.742 \text{ if female})\end{aligned}$$

$$\begin{aligned}\therefore \text{GFR} = 175 &\times [(\{\text{serum creatinine} - 7.71\}/0.988) \\ &\times 0.011312]^{-1.154} \times \text{age}^{-0.203} \\ &\times (0.742 \text{ if female})\end{aligned}$$

A factor for race is excluded as all subjects were Caucasian.

IDMS eGFR values were then compared between AD and control groups (C).

STATISTICAL ANALYSIS

Student's *t*-test was used to compare normally distributed eGFR values in AD and control groups. Multiple regression analysis was used to adjust for potential confounding factors. Normally distributed confounding variables were analysed using Student's *t*-test. The level of statistical significance was set at $p = 0.05$. All analyses were performed using the SPSS statistical software package (version 14.0 Chicago, IL).

RESULTS

Comparison of the control and patient groups is presented along with demographic and baseline data in Table 1. Control subjects were younger and more commonly female. Although there were no differences in systolic blood pressure, controls had a higher diastolic blood pressure. There was no difference in cholesterol levels. There were no significant differences in smoking status between AD and control subjects. The proportion of subjects attending secondary level education or higher was significantly lower in the AD group. As expected, APOE ε4 allele carriage was more prevalent in the AD group. The AD group had significantly higher creatinine levels.

Differences in IDMSeGFR between groups was significantly lower in AD subjects ($p = 0.002$; 69.0 *vs* 76.9 ml/min).

After adjustment for the potential confounders (age, diastolic, APOE e4 and education level) identified during baseline comparison, (Table 2) a significantly lower eGFR remained in the AD group compared to controls ($p = 0.045$).

DISCUSSION

Our cross-sectional study shows an association between impaired renal function as measured by IDMSeGFR and AD. Our report is the first to use

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Table 1. Subject characteristics

	AD	Control	
N	83	71	
Age mean{SD}/yr	77.2 {8.1}	74.3 {7.6}	$p = 0.023$
Gender			
% male	30.1%	19.7%	NS
% female	69.9%	80.3%	($p = 0.097$)
Positive carriage of APOE ε4	43.8%	18.3%	$p = 0.001$
Systolic BP mean{SD}/mmHg	144 {23}	148 {14}	NS
Diastolic BP mean{SD}/mmHg	79 {12}	83 {9}	$p = 0.017$
Smoking Status			
Never	64.2%	69.6%	
Ex-smoker	21.0%	17.4%	NS
Current	14.8%	13.0%	
Cholesterol mean{SD}/mmol/l	5.5 {1.8}	5.5 {1.9}	NS
MMSE median {IQR}	18.4 {14–22}	≥28	N/A
Education level			$p = 0.001$
% secondary + above	26.3%	52.9%	
Creatinine mean{SD}/μmol/l	87.4 {18.0}	77.9 {12.1}	$p < 0.001$
IDMSeGFR Mean{SD}/ ml/min	69.0 {14.6}	76.9 {16.3}	$p = 0.002$

corrected glomerular filtration rate equations as a measure of renal function and thus has the advantage of greater accuracy over previous measures dependent on serum creatinine (Swedko *et al*., 2003). The MDRD and the IDMS equations are now accepted as the gold standard measurements of eGFR (Levey *et al*., 1999; Vickery *et al*., 2006). There are no known studies using these techniques in AD and the increased sensitivity of these measures of renal impairment may explain our findings and which require confirmation.

After vascular influences were examined, statistical significance was retained. One weakness of our report is that not all key cardiovascular risk factors were available for analysis; additional vascular factors may account for the observed differences. Another is the lack of drug-use data in our dataset.

Alterations in amyloid homeostasis and in the peripheral sink capacity may represent an independent pathogenic mechanism. Ghiso and co-workers, examining the excretion and catabolism of circulating peripheral Aβ in mice, found labelled substrate mostly cleared by liver (>60%), followed by the kidney (Ghiso *et al*., 2004). We note the recent report by Arvanitakis *et al*. (2002) showing a positive correlation between serum creatinine and plasma Aβ levels in both normal individuals and subjects with AD. The implications are therefore two-fold: that renal impairment slows or prevents the passage of amyloid from brain to periphery where it is subject to excretion, or alternatively, that amyloid excess is somehow limiting to normal renal function in a subclinical context and is thus the upstream event.

The result should be seen in the context of issues relating to apparently overlapping pathogenic mechanisms involving cerebrovascular and Aβ plaque pathology in AD as well as the clinical and neuropathological distinction between VaD and AD. The neurovascular hypothesis of AD suggests that dysfunctional blood vessels could contribute to cognitive dysfunction by impairing delivery of nutrients to neurons and by reducing Aβ clearance from the brain (Iadecola, 2004). Other researchers argue that vascular pathology in AD occurs independently and synergistically acts to expose cognitive

Table 2. The Difference in estimated glomerular filtration rate in Alzheimer's dementia compared to control

	Difference in eGFR	95% CI	*p*-value	*N*
Unadjusted	−7.95	−12.9 to −3.0	0.002	151
Adjusted for Age			0.006	
Adjusted for APOE			0.001	
Adjusted for Diastolic BP			0.005	
Adjusted for Education level			0.012	
Adjusted for Age, APOE, Diastolic BP, + Education level			0.045	

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impairment where there is otherwise low grade burden of pathology (Riekse *et al*., 2004; Blennow *et al*., 2006). It is believed that VaD and AD represent opposite ends of an overlapping continuum and this can lead to difficulties in definitively classifying patients with dementia into distinct groups and will necessarily produce uncertainties in interpreting studies involving vascular risk factors.

Cognitive decline, cardiovascular ill-health and renal impairment may arise from shared vascular and/or inflammatory mechanisms. Candidate genes such as apolipoprotein E (*APOE*) exist as an established susceptibility factor for AD and have been linked to cardiovascular disease: knockout of the *APOE* gene in mice causes hypercholesterolemia and early atherosclerosis (Plump *et al*., 1992). Similarly, angiotensin-converting enzyme (ACE) which is expressed in vascular endothelial tissue and renal epithelial cells is of possible relevance to end organ damage in brain and kidneys as evidenced by some, but not all, genetic susceptibility studies (Betram *et al*., 2007; Jeunemaitre, 2008). Shared putative genetic correlates involving inflammatory pathways are in the same way advocated in AD and CKD (Rao *et al*., 2007; Skaper, 2007). In these areas, the possibility exists that preventative or slowing strategies developed in the context of one disorder may have crossover benefit in another.

This cross-sectional study is consistent with the hypothesis that lowered eGFR acts as risk factor for AD. As these associations are not necessarily causative they do highlight the need for confirmatory work as well as prospective studies and intervention trials.

CONFLICT OF INTEREST

None known.

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