

Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease

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Abstract

Aim of the study was to explore the correlation between the progression of carotid atherosclerosis and the evolution of cognitive impairment in 66 patients with Alzheimer's disease (AD). They underwent cognitive status evaluation and ultrasonography (US) to investigate carotid arteries intima-media thickness (IMT) and plaque index (PI). After a 12-month follow-up period, neuropsychological and US examinations were repeated to assess the progression of carotid atherosclerosis and of cognitive decline [in terms of changes in Mini Mental State Examination (MMSE) scores]. MMSE score changes were related to baseline IMT ($p=0.018$), changes in IMT ($p<0.001$) and PI ($p=0.006$), and "antihypertensive drug intake" ($p<0.001$). While the first three variables correlated with increased cognitive impairment, the last one was associated with a reduced extent of MMSE score decline. Results show a link between progression of carotid wall changes and of cognitive decline, and suggest a possible protective role of antihypertensive therapy. Given the potential clinical implications, our preliminary findings could stimulate further investigations into the role of vascular impairment in patients with AD.

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1. Introduction

The relationship between cerebrovascular disease and Alzheimer dementia is the subject of ongoing debate (Iadecola and Gorelick, 2003). Defining a role for vascular factors in the presentation and evolution of dementia would have important practical implications, especially as it would offer the opportunity of influencing the progression of cognitive decline by acting on them (de la Torre, 2002). Epidemiological investigations have repeatedly highlighted

the involvement of vascular risk factors in increasing both the risk of developing Alzheimer's disease (AD) and the probability of an adverse outcome (Luchsinger et al., 2005). There is also evidence that such factors can influence the incidence of mild cognitive impairment and the rate of its progression to dementia (Solfrizzi et al., 2004). However, there is still considerable uncertainty as to whether vascular factors are simply an additive element compounding cognitive decline, or else they play a causal role by exerting direct effects on AD pathogenesis. Most epidemiological studies have encountered difficulties in gauging precisely the role of vascular risk factors severity, the effect of specific therapies and the differential impact of concomitant treatments. Another complex problem is measuring the interindividual variability of the impact of risk factors. Studies examining the relationship between antihypertensive drugs and dementia have yielded

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conflicting results. Recent reports (Khachaturian et al., 2006; Peila et al., 2006) showed a decreased incidence of cognitive decline in treated hypertensive patients, while other studies failed to evidence an association (Morris et al., 2001). The Rotterdam study found a role of antihypertensive treatment in reducing vascular dementia, but not AD (In't Veld et al., 2001), while a recent meta-analysis concluded that further studies are needed to demonstrate the actual role of antihypertensives in reducing the risk of dementia (McGuinness et al., 2006). Reports about the impact of statins on cognitive decline in hypercholesterolemic patients are similarly not conclusive (Kivipelto et al., 2005).

Different studies have investigated the possibility that carotid steno-occlusive disease may predispose to reduced cognitive function but the results have not been univocal (Cerhan et al., 1998; Rao, 2001). Moreover, the possibility that cognitive impairment in subjects with carotid atherosclerosis may be considered as a specific consequence of the stenosis or it may simply be the effect of the associated vascular risk factors and ischemic brain injury on mental function, independently from the presence of carotid disease is still a matter of debate (Bossema et al., 2005). An interesting finding suggesting a specific role of carotid atherosclerosis in sustaining mental deterioration comes from the results of the study by Johnston et al. (2004) in which, the association between cognitive impairment and carotid atherosclerosis was demonstrated in asymptomatic patients with left internal carotid artery stenosis. The lack of correlation between right internal carotid artery stenosis and cognitive dysfunction supports the hypothesis that the effect of left carotid disease was not due to underlying vascular impairment or atherosclerosis in general.

In the present study, we sought to assess the influence of vascular factors, particularly the atherothrombotic effects, on AD progression by investigating a correlation between the evolution of carotid atherosclerosis and the progression of cognitive decline, and exploring the role of concomitant medications in a group of patients with mild or moderate dementia.

2. Methods

Patients were selected from 112 consecutive subjects referred to our dementia outpatient service by general practitioners for progressive cognitive impairment. Inclusion criteria were a diagnosis of probable AD according to NINCDS–ADRDA criteria (McKhann et al., 1984) and mild or moderate cognitive impairment defined as a clinical dementia rating score ≤ 2 (Morris, 1993).

The exclusion of subjects with a history of cerebrovascular disease, stepwise progression of cognitive impairment and focal neurological signs left 76 patients diagnosed as having probable AD and mild to moderate cognitive impairment. MR scans were obtained using a 1.5 T magnet with the spin-echo technique, T1- and T2-weighted and fluid-attenuated

inversion-recovery sequences to detect possible white matter lesions that were graded according to Wahlund et al. (2001). Only patients without vascular lesions (grade 0) or those exhibiting small subcortical focal lesions, defined as areas with high signal intensity on T2 but isointense with normal brain parenchyma on T1, classified as grade I, were included. Among 76 patients with probable AD, 10 were excluded: 5 for magnetic resonance (MR) imaging evidence of cortical infarction or extensive white matter lesions, 3 were lost to follow-up, and in 2 cases the diagnosis of dementia type was changed at the end of the 12 months, as 1 patient exhibited clinical elements suggestive of dementia with Lewy bodies and the other was diagnosed as having vascular dementia. Finally, 66 patients were considered in the study. Clinical history with a structured clinical interview (with caregivers' involvement) and hematochemical data were obtained from each patient with a focus on the major vascular risk factors (hypertension, diabetes, smoking habits, hyperlipidemia). Based on the results of our investigation or previous medical records (in the patients with specific pharmacological treatment), hypertension was defined as a systolic blood pressure of 140 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher (Chobanian et al., 2003). Diabetes was a concentration of fasting plasma glucose of 7.0 mmol/L (126 mg/dL) or more (WHO, 1999), and hyperlipidemia was a total cholesterol concentration of 5.2 mmol/L (200 mg/dL) or greater and a low-density lipoprotein cholesterol concentration of 3.4 mmol/L (130 mg/dL) or less (NCEP, 2001). These values were confirmed by repeated determinations before a definitive diagnosis was made.

Each patient was studied by means of a careful neurological examination, an extensive neuropsychological assessment of cognitive status and an ultrasonographic (US) study of extracranial vessels.

Neck arteries were evaluated by means of color-coded duplex sonography (Aspen, Acuson, USA) using validated criteria (Bartels, 1999). The degree of carotid stenosis was established by means of combined criteria considering blood flow velocities as well as morphological characteristics. The best images were digitized for later scoring. Steno-occlusive lesions in the distal common carotid artery (CCA), carotid bulb and internal carotid artery were assessed and defined according to validated criteria (De Bray and Glatt, 1995).

A plaque was defined as a localized >1.2 mm thickening that did not uniformly involve the whole artery (Nicolaidis et al., 1996). For each segment, the plaque score was defined as 0: no plaque, 1: one small plaque $<30\%$ of vessel diameter; 2: one medium plaque between 30 and 50% of vessel diameter or multiple small plaques; and 3: one large plaque $>50\%$ of vessel diameter or multiple plaques with at least one medium plaque. The plaque index (PI) was calculated by adding the scores of the right and left carotid arteries (Sutton-Tyrrel et al., 1998).

Measurements of intima–media thickness (IMT) were performed on the CCAs over ≈ 1.5 cm proximal to the flow divider, with a method similar to the one previously described

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