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Vascular predictors of cognitive decline in patients with mild cognitive impairment

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Abstract

Our aim in this study was to assess the relationship between the state of cerebral vessels and the risk of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD). We included 117 MCI patients. They underwent an ultrasonographic assessment of common carotid arteries intima-media thickness (IMT) and carotid plaque index. Cerebrovascular reactivity to hypercapnia in the middle cerebral arteries was calculated with the Breath-Holding Index (BHI). After a 12-month follow-up period, neuropsychological examinations demonstrated a progression to dementia in 21 patients. Pathological values of BHI and IMT significantly increased the risk of conversion (BHI: odds ratio, 5.80; 95% confidence interval, 1.83–18.37, $p < 0.05$; IMT: odds ratio, 3.08; 95% confidence interval, 1.02–9.33; $p < 0.05$, multinomial logistic regression analysis). Comparison between patients with all normal values and those with the simultaneous alteration of the 2 vascular indexes showed an increase in the risk of conversion from 9% to 33% (ordinal regression analysis). Our findings show that alterations of cerebral vessel functional and anatomic status increase the risk of conversion from MCI to dementia.

Keywords: Alzheimer's disease; MCI; Prognosis; Ultrasound

1. Introduction

Mild cognitive impairment (MCI) is a state affecting a large number of individuals, mainly characterized by the impairment of a single or multiple cognitive functions, not yet encompassing the definition of dementia (Petersen et al., 2001). A growing interest in MCI stems from the evidence that it can often be a precursor to Alzheimer's disease (AD) (Morris et al., 2001; Scheltens et al., 2002) with a rate of progression ranging between 10% and 15% on an annual basis (Petersen et al., 2001). The repeated observation that vascular risk factors facilitate AD occurrence and progression as well as the incidence of MCI and the rate of its progression to dementia, has stimulated the investigation of clinical and instrumental markers of increased risk for cerebrovascular disease in such conditions (Deschaintre et al., 2009; Li et al., 2011; Luchsinger et al., 2005). Lack of treatment that is able to modify long-term evolution of dementia strengthens the crucial role of preventive strategies in the early stages (de la Torre, 2010a, 2010b). In this respect, defining a role for vascular factors in the presentation and evolution of cognitive impairment in MCI patients would have important practical implications, especially as it would offer the opportunity of influencing the progression of decline by acting on them (Iadecola and Gorelick, 2003). Unfortunately, the simple assessment and conventional treatment of common vascular risk factors does not seem to be a fully satisfactory approach to adequately counteract the risk of developing dementia (Coley et al., 2008; Luzzi et al.,

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2010). This suggests that the aggressiveness of treatments should be modulated by taking into consideration some conditions like the individual predisposition to dementia development. Within such a theoretical frame, reliable prognostic markers of the risk of conversion from MCI to AD are not yet available. In this respect, the use of noninvasive diagnostic approaches to assess vascular status has been suggested to identify subjects with increased risk of cognitive impairment progression (de la Torre, 2010c).

Our aim in this study was to evaluate the morphological and functional characteristics of cerebral arterial vessels in patients with MCI. In particular, we sought to verify whether atherosclerotic changes and alteration in cerebral hemodynamics might influence the risk of conversion to AD.

2. Methods

2.1. Study population

Patients were selected from consecutive subjects referred by general practitioners to our dementia outpatient service during a 1-year period for suspected cognitive impairment. The only inclusion criterion was a diagnosis of MCI according to Petersen's criteria (Petersen et al., 2001). In order to select a more homogeneous sample, we only considered the amnesic form of MCI in the present investigation. We excluded all subjects with severe general or neurological conditions, focal neurological signs at physical examination, clinical history of cerebrovascular disease or cardiopathies, basal scores < 24 on the Mini Mental State Examination (MMSE) (Folstein et al., 1975) adjusted according to age and education as assessed for the Italian population (Grigoletto et al., 1999). All eligible patients were submitted to a brain magnetic resonance (MR) scan with a 1.5-T magnet using spin-echo T1-T2-weighted and fluid-attenuated inversion-recovery sequences. According to Wahlund's criteria for age-related white matter changes (Wahlund et al., 2001), we evaluated any white matter lesions and graded them; we only included patients without vascular lesions (grade 0) or with small subcortical focal lesions defined as areas of high signal intensity on T2-weighted images but isointense with normal brain parenchyma on T1-weighted images (grade 1). At baseline, after a careful physical examination, all the included patients went through a structured clinical interview on vascular risk factors (i.e., hypertension, diabetes, smoking, hyperlipidemia) and therapies. Moreover, we performed a standardized screening for vascular risk factor assessment including blood sample collection for laboratory tests and a cardiologic evaluation with electrocardiogram (ECG). In selected cases, transthoracic or transesophageal echocardiogram was obtained. Hypertension was defined as a history of high blood pressure, a systolic blood pressure $\geq$ 140 mm Hg, a diastolic blood pressure $\geq$ 90 mm Hg, or the use of an antihypertensive; dyslipidemia was defined as a history of dyslipidemia, a fasting serum total cholesterol $\geq$ 6.22 mmol/L (2.4 g/L) or triglycerides $\geq$ 2.26 mmol/L (2 g/L), or the use of a statin or fibrate; diabetes mellitus was defined as a history of diabetes mellitus, a fasting serum glucose $>$ 7.0 mmol/L (1.26 g/L), or the use of an oral antihyperglycemic or insulin; smoking was defined as a history of active tobacco smoking. Each subject received the best treatment for each vascular risk condition (Goldstein et al., 2011).

2.2. Neuropsychological evaluation

All patients went through an extensive neuropsychological assessment of their cognitive status that included the MMSE, the Mental Deterioration Battery, Trail Making A and B, and Test of Judgment.

2.3. Ultrasonographic evaluations

Every subject was submitted to an ultrasonographic morphological and functional evaluation of the neck and intracranial vessels. Neck vessels were evaluated with continuous wave Doppler and echo-color Doppler using high resolution 7.5 MHz transducers (iU22 Philips ultrasound, Bothell, WA, USA). According to the Mannheim Consensus, carotid plaques were defined (Touboul et al., 2007) as a focal structure protruding into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima media thickness (IMT) value or showing a thickness $>$ 1.5 mm measured from the media-adventitia interface to the intima-lumen interface. In each arterial segment, the plaque degree was quantified. Carotid plaques were defined as a thickening over 1.2 mm which does not include the whole vessel surface. In each arterial segment, the plaque degree was quantified as follows: 0, no plaque; 1, 1 small plaque $<$ 30% of vessel diameter; 2, 1 medium plaque between 30% and 50% of vessel diameter or multiple small plaques; and 3, 1 large plaque $>$ 50% of vessel diameter or multiple plaques with at least 1 medium plaque. The plaque index (PI) was calculated by adding the scores of the right and left carotid arteries (Sutton-Tyrrell et al., 1998). The measurements of IMT was performed on the segment of 1.5 cm of the common carotid that precedes the carotid bifurcation in agreement with the method described by O'Leary et al. (1999). A longitudinal image of the distal segment of common carotid arteries was taken, and the measurement was obtained with an automatic system at the thickest point where there were no plaques on the proximal and distal wall. IMT was defined as the mean of the maximum thickness for proximal and distal wall of the common carotid of both sides. Evaluation of intracranial circle was performed by means of transcranial doppler (TCD) (Multidop X DWL; Elektronische Systeme, GmbH, Germany) using the method described by Aaslid et al. (1982). Cerebrovascular reactivity to the hypercapnia (VMR) was measured with the Breath-Holding Index (BHI) (Markus and Harrison, 1992; Silvestrini et al., 2000). This index is obtained by dividing the percentage increase in mean flow velocity (MFV) occurring during