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Changes in vascular factors 28 years from midlife and late-life cortical thickness

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Abstract

We assessed midlife blood pressure (BP), body mass index, total cholesterol, and their changes over time in relation to cortical thickness on magnetic resonance imaging 28 years later in 63 elderly at risk of dementia. Participants in the population-based Cardiovascular Risk Factors, Aging, and Dementia study were first examined at midlife. A first follow-up was conducted after 21 years, and a second follow-up after an additional 7 years. Magnetic resonance images from the second follow-up were analyzed using algorithms developed at McGill University, Montreal, Canada. Midlife hypertension was related to thinner cortex in several brain areas, including insular, frontal, and temporal cortices. In elderly with thinner insular cortex, there was a continuous decline in systolic BP and an increase in pulse pressure after midlife, while in elderly with thicker insular cortex the decline in systolic BP started at older ages, paralleled by a decline in pulse pressure. No associations were found between body mass index, cholesterol, or apolipoprotein E ε4 allele and cortical thickness in this group of elderly at risk individuals.

Keywords: Blood pressure; BMI; Cholesterol; ApoE; MRI; Insular cortex; Cortical thickness

1. Introduction

Vascular factors, including elevated blood pressure (BP), body mass index (BMI), and cholesterol, have been associated with increased risk of cognitive impairment and dementia (Qiu et al., 2009). While the role of such factors at midlife is less controversial, their significance at older ages in relation to cognition is much debated (Anstey et al., 2008; Luchsinger and Gustafson, 2009; Qiu et al., 2009). Risk profiles predicting dementia development seem to be different at midlife compared with late-life (Barnes et al., 2009; Kivipelto et al., 2006). Diseases leading to dementia usually have a long preclinical phase, and current diagnostic criteria identify them only at a late stage. Distinguishing between true risk relations and reverse causality at older ages is thus difficult, and has generated a rich literature of conflicting findings. Several longitudinal population-based studies have reported a pattern of decline over time in BP, BMI, and total plasma cholesterol in people who develop cognitive impairment or dementia later on (Qiu et al., 2009), but underlying mechanisms are still unclear.

In addition to its widely accepted association with cerebrovascular lesions, elevated BP has also been linked to Alzheimer-type neuritic plaques and neurofibrillary tangles (DeCarli et al., 1999; Heijer et al., 2003; Petrovitch et al., 2000; Swan et al., 1998). Hypertension is known to have many effects on brain morphology (Jennings et al., 2012). It

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can act as a negative modifier of aging by accentuating brain morphological changes associated with advanced age, and it can also affect structures relatively uninfluenced by aging (Jennings et al., 2012). Long-term elevated BP has been associated with lower total brain weight and volume (DeCarli et al., 1999; Heijer et al., 2003; Petrovitch et al., 2000; Swan et al., 1998). Across studies using different analysis methods, temporal and frontal lobes have emerged as particularly vulnerable to the detrimental effects of hypertension (Chen et al., 2006; den Heijer et al., 2005b; Gianaros et al., 2006; Korf et al., 2004, 2005; Raz et al., 2003, 2005, 2007; Strassburger et al., 1997; Taki et al., 2008).

Elevated BMI was linked to lower brain volumes in longitudinal studies (Enzinger et al., 2005; Gustafson et al., 2004; Soreca et al., 2009) and several areas were associated with BMI such as hippocampus, precuneus, and frontal lobe (Pannacciulli et al., 2006; Raji et al., 2010; Taki et al., 2008; Walther et al., 2010). No association between total cholesterol and brain volumes was reported in some studies (Koschack et al., 2009; Wolf et al., 2004), and initial findings about high-density lipoprotein and morphological changes in hippocampus (Wolf et al., 2004) could not be replicated later in cognitively normal subjects (den Heijer et al., 2005a).

The brain is usually considered a target for the detrimental effects of vascular factors, but the relation is bidirectional. It seems that the brain is involved in the initiation of elevated BP, and is affected by early hypertension-related pathology as well (Jennings and Zanstra, 2009). Brain regions and processes important for dementia are also important for the neural regulation of food intake, energy metabolism, and consequently BMI (Luchsinger and Gustafson, 2009). The brain is the most cholesterol-rich organ in the human body, and the interactions between circulating and brain cholesterol are only beginning to emerge (Björkhem et al., 2009).

We have recently reported an association between more severe white matter (WM) lesions in late-life and midlife hypertension and decreasing BP during 2 decades after midlife in a subsample of participants in the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) study (Vuorinen et al., 2011). The aim of the present study is to assess the effects of midlife BP, BMI, total cholesterol, and their changes over time in relation to cortical thickness nearly 3 decades later in a group of elderly CAIDE participants at risk of dementia. A recent study has linked BP and cholesterol to cortical thickness (Leritz et al., 2011), but cortical thickness (a measure of gray matter integrity), has so far not been studied in relation to vascular factors and their variations over long periods of time. We hypothesized that hypertension, obesity and hypercholesterolemia at midlife but not late-life would be associated with lower cortical thickness in late-life, and that there would be different patterns of change in vascular factors from midlife in relation to late-life cortical thickness.

2. Methods

2.1. Subjects and study design

The design of the CAIDE study has been described previously (Kivipelto et al., 2001). Briefly, participants were examined at midlife (age approximately 50 years) within the framework of the North Karelia project and FINMONICA study (Finnish contribution of Multinational Monitoring of Trends and Determinants of Cardiovascular Diseases Study) in 1972, 1977, 1982, or 1987. In 1998, 2000 randomly selected survivors aged 65–79 years, and living in Kuopio and Joensuu in Finland, were invited for a first re-examination. Altogether 1449 (72.6%) subjects participated. A second re-examination was conducted between 2005 and 2008. Of the initial 2000 persons, 1426 were still alive and living in the region, and 909 (63.7%) participated. Participants were assessed using a 3-step protocol: screening, clinical phase, and differential diagnostic phase. In 1998, participants with $\leq$ 24 points on Mini Mental State Examination (Folstein et al., 1975) at the screening phase were referred for further evaluations. In 2005–2008, subjects with $\leq$ 24 points or decline $\geq$ 3 points on Mini Mental State Examination, or $<$ 70% delayed recall in the Consortium to Establish a Registry for Alzheimer's Disease word list (Morris et al., 1989), or with informant concerns about the participant's cognition were referred for further evaluations. In both re-examinations, the clinical phase included detailed medical and neuropsychological assessments, and the differential diagnostic phase consisted of brain imaging (magnetic resonance imaging; MRI/computed tomography), blood tests, and if needed, cerebrospinal fluid (CSF) analysis. A review board including the study physician, neuropsychologist, and a senior neurologist ascertained the primary diagnosis based on all available information. Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* 4th Edition criteria (American Psychiatric Association, 1994), and Alzheimer's disease (AD) according to the US National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984).

Because MRI investigation in 2005–2008 was available only at the differential diagnostic phase for participants from Kuopio, the 113 imaged subjects had poorer performance in cognitive tests compared with the rest of the CAIDE participants. Subjects with dementia were excluded from the present study, leaving a subsample of 63 elderly at risk of dementia, who had MRI of adequate quality for cortical thickness measurements. Of these, 27 subjects fulfilled criteria for mild cognitive impairment (Frisoni and Coleman, 2011). Of the 63 participants, 53 had also attended the 1998 CAIDE examination where 46 had been cognitively normal. The mean age ($\pm$ SD) of the 63 participants at baseline (midlife) was 49.8 ($\pm$ 6.0) years and 77.8 ($\pm$ 3.4) years at the 2005–2008 re-examination. The aver-