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Plasma oxidized low-density lipoprotein levels and risk of Alzheimer's disease

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ABSTRACT

This study examines the association of plasma oxidized low-density lipoprotein (OxLDL) levels with all-cause dementia, including Alzheimer's disease (AD) and vascular dementia. Data are taken from the Canadian Study of Health and Aging, a population-based study of a representative sample of persons aged more than 65 years conducted from 1991 to 2002. The present study sample included 670 subjects of which, 155 developed all-cause dementia with 109 cases of AD and 32 of vascular dementia. In Cox regression models, no association between OxLDL and risks of dementia or subtypes was found. A triple interaction between OxLDL, sex, and history of cardiovascular disease on the risk of AD ($p = 0.0077$) was found. Increased levels of OxLDL were significantly associated with an increased risk of AD in men with a history of cardiovascular disease (hazard ratio = 1.11; 95% confidence interval 1.04–1.19); no association in women was found. These findings suggest that increased levels of OxLDL are not associated with the risk of dementia, AD, and vascular dementia. The association of OxLDL with AD in men with a history of cardiovascular disease merits further investigation.

1. Introduction

The definite causes of Alzheimer's disease (AD) are not well established yet. The 2 main hallmark pathologic features of AD are the abnormal accumulation of amyloid-beta (Aβ) peptides leading to senile plaques (Selkoe, 1993) and the hyperphosphorylation of the protein tau forming intracellular neurofibrillary tangles (Selkoe, 2004; Sobów et al., 2004). Aβ deposits and neurofibrillary tangles are important stimuli for the inflammatory mechanisms observed in the brains of AD patients. Cumulated over many years, the inflammatory mechanism is likely to exacerbate the pathogenic processes that gave rise to it (Akiyama et al., 2000).

In parallel to these processes, increased regional levels of oxidative stress (Markesbery, 1997; Zhu et al., 2005) and evidence of oxidative damage, mainly oxidized lipids, proteins (Smith et al., 1995), and nucleic acids (Mecocci et al., 1993), can be found in neurodegenerative disorders. Whether oxidative stress plays a key role in the pathogenesis of AD or is just its pathologic manifestation is still controversial (Markesbery, 1997), but some studies indicate that the increase in oxidative stress is one of the earliest changes occurring several years before the disease (Nunomura et al., 2001). Similar signs like an increase in antioxidant levels in the cerebrospinal fluid (CSF) (Kankaanpää et al., 2009) and elevated indices of protein oxidation and lipid peroxidation (Picklo et al., 2002; Sayre et al., 2001; Subbarao et al., 1990) are detectable in AD patients and in cases of mild cognitive impairment (MCI) (Keller et al., 2005).

Low-density lipoproteins (LDL) are key molecules in the cholesterol transport mechanisms and are susceptible to oxidation into oxidized LDL (OxLDL). OxLDL are immunogenic and also cytotoxic to endothelial cells. Beside their highly atherogenic characteristics (Bhakdi et al., 1995; Steinberg, 1995; Young and McEneny, 2001), OxLDL are also associated with the development of coronary and vascular diseases (Holvoet et al., 2003; Toshima et al., 2000; Tsimikas et al., 2003; Zhu et al., 2007). The presence of atherosclerosis has been related to AD in postmortem studies (Jellinger, 2010; Jellinger and Mitter-Ferstl, 2003). It has been suggested that atherosclerosis, coronary heart disease, and AD may have certain risk factors in common including dyslipidemia, hypertension, oxidative stress, and elevated oxidation levels of LDL (Kivipelto et al., 2001; Pappolla et al., 2003; Sparks, 1997; Steinberg, 1997).

Unlike its links with coronary heart disease and atherosclerosis, the association between OxLDL levels and AD is still relatively novel and has been less often investigated in the literature. Koyama et al.

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(2013) evaluated the association between serum OxLDL levels and cognitive impairment in older women and found negative results. The aim of the present study was to evaluate the association between plasma levels of OxLDL and the incidence of all-cause dementia including AD and vascular dementia (VaD) in both sexes. The modification effect of sex, history of cardiovascular disease, and apolipoprotein E e4 allele (apoE4) on the association was also tested.

2. Methods

2.1. The Canadian Study of Health and Aging

The Canadian (CSHA) is a 3-phase, population-based longitudinal study of the epidemiology of dementia in Canada. In 1991/1992 (CSHA-1), representative samples of persons aged 65 years or more were drawn from 36 cities in all the Canadian provinces along with their rural areas (Canadian Study of Health and Aging Working Group, 1994). The initial sample included 10,263 men and women in total, 9008 were living in the community and 1255 in institutions. All participants coming from the community underwent a screening test with the 100-point Modified Mini-Mental State Examination (3MS) (Teng and Chui, 1987), followed by a standardized clinical examination. A consensus diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) for dementia (American Psychiatric Association, 1987); the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for AD (McKhann et al., 1984), and the World Health Organization International Classification of Diseases, 10th Revision criteria for VaD (World Health Organization, 1987). Information on risk factors was collected using a self-administered questionnaire in nondemented subjects.

A similar screening and re-evaluation process was carried out in 1996/1997 (CSHA-2) and 2001/2002 (CSHA-3) (Lindsay et al., 2004). In the latter 2 phases, the diagnosis for both dementia and AD followed the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) (American Psychiatric Association, 1994), while that of VaD was based on the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Román et al., 1993). In all, 2914 subjects underwent the clinical examination at CSHA-1, 2305 at CSHA-2, and 1386 at CSHA-3.

2.2. Blood samples

At each phase, clinically assessed subjects were invited to provide blood samples to be frozen at −20 °C and stored for future analysis. At CSHA-1, 9 research centers participated to the blood sampling, at CSHA-2 and -3, all the centers participated, and all the clinically assessed subjects were asked to provide blood samples except for those who already did in a previous phase.

2.3. Study sample

Of 10,263 subjects at the beginning of CSHA-1, 1132 subjects were already demented and 500 were screened positive but refused to be clinically evaluated; 8631 nondemented subjects were eligible for a prospective analysis. Of these, 1219 nondemented subjects provided blood samples and underwent a clinical evaluation either at CSHA-1 or CSHA-2. Among these, 450 died, 68 went missing before having any follow-up and 701 subjects were left for chemical analyses. Finally, 31 subjects were excluded because they had no whole blood available for another analysis (Kröger et al., 2009). Among the 670 subjects that were retained for analysis, 115 were from CSHA-1 and 555 from CSHA-2. Out of the 115 subjects of CSHA-1, 68 had only 1 follow-up and 47 subjects had 2 follow-ups. There was no difference concerning age and sex between subjects in the final study sample and those who were excluded; subjects from the study sample had slightly fewer years of education than those not included (mean [standard deviation]: 9.8 (4.1) and 10.3 (3.8) years, respectively; $p = 0.01$).

2.4. OxLDL dosage

OxLDL dosage was realized using frozen samples stored in polypropylene microtubes. Plasma levels (U/L) of OxLDL were measured in EDTA-treated plasma using a Mercodia Oxidized-LDL Enzyme Linked Immunosorbent Assay containing mAb-4E6 antibody and has a detection limit of <1 mU/L and a variation coefficient of 8%. The samples were analyzed in 2007 at the Lipid Research Centre of the CHU de Québec, in Quebec City.

2.5. Statistical analyses

Comparison between the subjects who developed all-cause dementia and those who remained cognitively normal were performed using χ^2 tests for categorical variables and t tests or Wilcoxon rank-sum test for continuous variables. Plasma OxLDL concentration was treated as a continuous variable and in tertiles. To examine the association between OxLDL levels and outcomes, Cox proportional hazards regression models with age as the time scale were used in 3 different models (basic; model 1), semi-, or fully adjusted (models 2 and 3, respectively).

The proportionality and linearity assumption of the models were tested and found to be satisfied. Age at the onset of disease was defined as the midpoint between the last follow-up without dementia and the next one with dementia. Follow-up time was calculated from time of blood provision and until the time of event, loss of follow-up, or end of the study. When OxLDL concentration was treated as categorical, the first tertile was used as the reference. The semi-adjusted model included 2 covariates: sex and education (continuous variable, in years) and the fully-adjusted model additionally controlled for apoE4 status (yes or no, defined as the presence or not of at least 1 e4 allele), history of cardiovascular disease (yes or no, defined as history of stroke or myocardial infarction), history of diabetes mellitus (yes or no), hypertension (yes or no, defined as supine blood pressure >160 mm Hg systolic or 95 mm Hg diastolic, or a physician's diagnosis of hypertension), ever smoking (yes or no), regular alcohol consumption (yes or no). Information on these covariates was obtained from either the risk factor questionnaire at baseline and/or from the clinical examination at the time of blood sampling. Effect modification of sex, history of cardiovascular disease, and apoE4 was tested in all-cause dementia and AD according to model 2 and with OxLDL as a continuous variable to test with the highest statistical power. Given the small number of incident cases of VaD, effect modification was not tested. Statistical analyses were performed using SAS 9.1.3 software.

3. Results

Over 4.8 years of follow-up (range, 2.2–10.3 years), 515 remained cognitively normal and 155 developed dementia; this included 109 cases of AD, 32 cases of VaD, and 14 cases of other types. OxLDL levels were normally distributed with a mean (standard deviation) of 38.7 (11.2) U/L. No significant colinearity was found between any of the independent variables. There was no significant difference in the initial characteristics between subjects who remained cognitively normal and those who developed