SERUM HDL, LDL AND TOTAL CHOLESTEROL IN PATIENTS WITH LATE-LIFE ONSET OF ALZHEIMER'S DISEASE VERSUS VASCULAR DEMENTIA

Zlatko Trkanjec, Raphael Béné, Irena Martinić-Popović, Jelena Miljenka Jurašić, Marijana Lisak, Vesna Šerić and Vida Demarin

University Department of Neurology, Reference Center for Neurovascular Disorders and Reference Center for Headache of the Ministry of Health and Social Welfare of Republic of Croatia, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY - Patients with cerebrovascular risk factors are nowadays recognized as being at an increased risk of developing cognitive decline of both types. In this pilot study, we evaluated the levels of cholesterol (total, HDL, LDL) in patients with both vascular dementia (VD) and Alzheimer's type of dementia (AD). Cognitive decline was assessed using Mini Mental State Examination (MMSE) as a standardized method. The study included 66 patients diagnosed with dementia. AD was diagnosed in 43 patients (22 male and 21 female) mean age (±SD) 72.79±8.19 years and VD in 23 patients (mean age ± SD, 77.43±7.58 years). In AD group, 18 patients had cholesterol values within the normal range, whereas 25 patients had elevated levels of cholesterol. The mean value of total plasma cholesterol was 5.39 (SD=1.05), LDL cholesterol 3.33 (SD=0.95) and HDL cholesterol 1.41 (SD=0.34). In VD group, 11 patients had cholesterol values within the normal range, whereas 12 patients had elevated levels of cholesterol. In this group, the mean value of total plasma cholesterol was 5.78 (SD=1.66), HDL cholesterol 1.44 (SD=0.57) and LDL cholesterol 3.72 (SD=0.85). Total cholesterol, LDL cholesterol and HDL cholesterol levels were higher in the group of patients with VD, however, the difference was not statistically significant.

Key words: Alzheimer disease – etiology; Alzheimer disease – prevention and control; Alzheimer disease – risk factors; Hypercholesterolemia – complications; Dementia, vascular

Introduction

Dementia is a neurologic disease associated with aging. The incidence and prevalence of dementia is increasing as the population is growing older. There are several types of dementia. Alzheimer's disease (AD) is the leading cause of progressive dementia. Other degenerative neurologic diseases such as dementia with Lewy bodies, Parkinson's disease and Huntington's disease are known as causes of dementia. Vascular disorders such as vascular dementia (VD) seems to be the second most common cause of dementia, which is due to multiple strokes in the subcortical region of the brain. Other types of dementia can be triggered by infections that affect the central nervous system, such as HIV dementia complex and Creutzfeldt-Jakob disease, chronic drug use, depression as well as by some types of hydrocephalus.

AD causes 50%-70% of all cases of dementia and has become one of the most common chronic diseases in developed countries. Estimates indicate that, by 2050, one in eight men and almost one in four women in industrialized countries will develop AD during their lifetime.1

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1 Correspondence to: Raphael Béné, MD, University Department of Neurology, Sestre milosrdnice University Hospital, Vinogradarska c. 29, HR-10000 Zagreb, Croatia
E-mail: Raphaelpene.hr@gmail.com
Neurofibrillary tangles and senile plaques are the principal neuropathologic characteristics found at a significantly higher frequency in the frontotemporal cortex and hippocampus. In the early stages of both types of dementia, the most commonly recognized symptom is memory loss, such as difficulty in remembering recently learned facts. Vascular component appears to be significant in both AD and VD.

While memory impairment is essential for the diagnosis of AD, the clinical syndrome in VD is often characterized by executive dysfunction rather than memory impairment. VD is the second most common cause of dementia in the United States and Europe in the elderly, but it is the most common form in some parts of Asia. The prevalence of VD is 1.5% in Western countries and approximately 2.2% in Japan. It accounts for 50% of all dementias in Japan, 20% to 40% in Europe, and 15% in Latin America. The incidence of dementia is nine times higher in patients that have suffered a stroke than in controls, and 25% of stroke patients develop new-onset dementia within a year of stroke.

Cholesterol is an essential component of mammalian cell membranes and a precursor for synthesis of many biologically important substances. According to the lipid hypothesis, abnormally high cholesterol levels (hypercholesterolemia), or, more correctly, higher concentrations of LDL and lower concentrations of functional HDL are strongly associated with cardiovascular disease promoting atheroma development in arteries (atherosclerosis). This disease process leads to myocardial infarction (heart attack), stroke and peripheral vascular disease. Since higher blood LDL, especially higher LDL particle concentrations and smaller LDL particle size, contribute to this process more than the cholesterol content of the LDL particles, LDL particles are often termed ‘bad cholesterol’ because they have been linked to atheroma formation. On the other hand, high concentrations of functional HDL, which can remove cholesterol from cells and atheroma, offer protection and are sometimes referred to colloquially as ‘good cholesterol’. These balances are mostly genetically determined but can be changed by body build, medications, food choices and other factors.

**Patients and Methods**

The aim of this study was to evaluate serum levels of HDL, LDL and total cholesterol in patients with AD and VD, in order to compare cholesterol metabolism between VD, where higher levels of cholesterol and LDL are known to be an important risk factor, and AD, where there is still an open discussion about the role of cholesterol metabolism in the disease onset. The study included 66 patients with the diagnosis of dementia. AD was diagnosed in 43 patients (22 male and 21 female), mean age ± standard deviation (SD) 72.79±8.19 years, according to DSM-IV and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria. VD was diagnosed in 23 patients, mean age ± SD 77.43±7.58 years, according to the National Institute of Neurological Disorders and Stroke with Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria. We analyzed serum levels of total, LDL and HDL cholesterol in all patients.

**Results**

In the group of patients diagnosed with AD, 18 patients had cholesterol values within the normal range, whereas 25 patients had elevated levels of cholesterol. The mean value of total plasma cholesterol in this group was 5.39 (SD=1.05), LDL plasma cholesterol 3.33 (SD=0.95) and HDL plasma cholesterol 1.41 (SD=0.34).

In the group of patients diagnosed with VD, 11 patients had cholesterol values within the normal range, whereas 12 patients had elevated levels of cholesterol. In this group, the mean value of total plasma cholesterol was 5.39 (SD=1.05), LDL plasma cholesterol 3.33 (SD=0.95) and HDL plasma cholesterol 1.41 (SD=0.34).

Total cholesterol, LDL cholesterol and HDL cholesterol levels were higher in the VD group, however, the difference was not statistically significant.

**Discussion**

Our results are in line with two studies conducted in 1291 and 444 subjects, where high cholesterol in midlife was associated with a highly increased risk of AD in late-life. However, in the Framingham Study (77 AD cases), there was no association between total cholesterol or...
HDL cholesterol levels and AD risk (RR=0.95, 95% CI 0.87-1.04 per each 10 mg dL⁻¹ increase in total cholesterol; RR=1.10, 95% CI 0.93-1.31, for increasing HDL). In another study in Asiatic population, a decrease in total cholesterol from midlife to late-life was associated with an increased risk of AD in late-life.12

Relationship between total cholesterol and cognitive decline or cognitive impairment is more confounding. Results of the studies that investigated the association between total cholesterol and either cognitive decline or cognitive impairment are in contradiction. Two of these studies, with samples sizes of 93 and 12 subjects, found higher total cholesterol to be associated with a reduced risk of cognitive decline. Another three cognitive decline studies with sample sizes of 1147, 353 and 267 subjects found no association between this outcome and total cholesterol.13

Meta-analyses of late-life total cholesterol in relation to AD, VD, and any dementia did not reveal any significant associations, suggesting the possibility that the effect of total cholesterol on the risk of dementia may be limited to midlife. Two studies with 48 and 721 cases, respectively, have reported consistent relation between cholesterol and AD and examined mid-life cholesterol levels on an average of 21 and 27 years later.

Concerning the relationship between total cholesterol and VD, there is a small number of studies that included VD as an outcome, limiting the statistical power to detect a significant association between total cholesterol and VD.

No association between LDL and either AD or VD was found in western and in Japanese population.10,21

Data concerning the association between LDL and any dementia, cognitive decline or cognitive impairment were not available. However, ApoE seems to be the major lipoprotein present in the brain (which lacks apoB) and is involved in local recycling of cholesterol and phospholipids in response to disease or injury. On neuropathologic examination of AD affected brain, apoE is localized to senile plaques and neurofibrillary tangles. There are three polymorphisms of the apoE gene: apoE2, E3, and E4. Numerous epidemiological studies have implicated the apoE4 allele as a major genetic modifier that substantially increases the risk of developing sporadic AD.22

Cholesterol appears to be linked to the mechanism of cognitive deterioration in both AD and VD. The main mechanism seems to be the relationship between high cholesterol level and cerebrovascular disease. Many genes associated with Alzheimer's disease affect cholesterol or lipoprotein function and/or have also been implicated in atherosclerosis, concomitant to AD, explaining the links between vascular and cerebrovascular pathology in AD. Moreover, Ab, apoE, cholesterol, and cholesterol oxidase have been shown to co-localize in the core of fibrillary plaques in transgenic mice models of AD.23-26

Furthermore, cholesterol also modulates the production of amyloid beta. In the study by Frears et al., the addition of cholesterol to cell culture increased amyloid beta 1-40 by up to twofold, and cholesterol was necessary for any secretion of amyloid beta 1-42 (which appears to be the most toxic form of amyloid beta); similarly, a reduction of cholesterol levels in cell cultures decreased amyloid beta by 40%.27-30

Only two classes of medication have obtained FDA approval and are currently available for the treatment of AD, including acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine for mild to moderate cases, and the N-methyl-D-aspartate antagonist memantine for the treatment of moderate to severe dementia.

However, a decisive role for cholesterol metabolism in sporadic AD was recently confirmed by the findings that statins, therapeutic drugs that block endogenous cholesterol biosynthesis and thus lower systemic cholesterol concentrations, could reduce the risk of the onset of AD.31-33

Conclusion

Our pilot study demonstrated the correlation between cholesterol metabolism and onset of Alzheimer’s disease, by comparing serum levels of HDL, LDL and total cholesterol with those measured in patients with vascular dementia.

References


Sazetak

HDL, LDL i UKUPNI KOLESTEROL U SERUMU BOLESNIKA S NASTUPOM ALZHEIMEROVE BOLESTI U STARIJOJ DOBI U ODNOSU NA VASKULARNU DEMENCIJU

Z. Trkanjec, R. Bene, I. Martinić-Popović, J.M. Jurasić, M. Lisak, V. Šerić i V. Demarin

Danas je poznato kako su bolesnici s cerebrovaskularnim čimbenicima rizika u većoj opasnosti za razvoj obaju tipova spoznajnog propadanja. U ovom probnom ispitivanju procjenjivali smo razine kolesterolja (ukupnog, HDL i LDL) u bolesnika s vaskularnom demencijom (VD) i u onih s demencijom Alzheimerova tipa (AD). Spoznajno propadanje procjenjivalo se pomoću instrumenta Mini Mental State Examination (MMSE) kao standardnom metodom. U studiju je bilo uključeno 66 bolesnika s dijagnozom vaskularne demencije. AD je bila dijagnosticirana u 43 bolesnika (22 muškarca i 21 žena), srednje dobi 72,79 (±SD) 8,19 godina, a VD u 23 bolesnika (srednja dob ± SD, 77,43±7,58 godina). U skupini bolesnika s dijagnosticiranim AD 18 bolesnika je imalo vrijednosti kolesterolja unutar normalnog raspona, dok je 25 bolesnika imalo povišene razine kolesterolja. U ovoj skupini je srednja vrijednost ukupnog kolesterolja u plazmi bila 5,39 (SD=1,05), LDL kolesterol 3,33 (SD=0,95) i HDL kolesterol 1,41 (SD=0,34). U skupini bolesnika s dijagnosticiranim VD 11 bolesnika je imalo vrijednosti kolesterolja unutar normalnog raspona, dok je 12 bolesnika imalo povišene razine kolesterolja. U ovoj skupini je srednja vrijednost ukupnog kolesterolja u plazmi bila 5,78 (SD=1,06), LDL kolesterol 1,44 (SD=0,57) i HDL kolesterol 3,72 (SD=0,85). Dakle, razine ukupnog kolesterolja, LDL kolesterolja i HDL kolesterola bile su više u skupini bolesnika s VD, ali razlika među skupinama nije bila statistički značajna.

Ključne riječi: Alzheimerova bolest – etiologija; Alzheimerova bolest – prevencija i kontrola; Alzheimerova bolest – rizični čimbenici; Hiperkolesterolemija – komplikacije; Demencija, vaskularna