Research article

Lipoprotein profile in older patients with vascular dementia and Alzheimer's disease

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Abstract

Background: Some alterations of the lipoprotein profile have been associated with cerebrovascular disease. Recently, it has been suggested that cerebrovascular disease might play a role in the pathogenesis of both vascular dementia (VD) and Alzheimer's disease (AD). Nevertheless, the possible association of dyslipidemias with VD or AD is still a controversial issue.

Methods: We investigated the lipoprotein profile in 100 older patients with vascular dementia (VD; n°: 60) or Late Onset Alzheimer’s Disease (LOAD; n°: 40). The patients were compared with 54 community dwelling non-demented older controls.

Results: After adjustment for functional status, blood sedimentation rate, and serum albumin levels, no differences in lipoprotein profile emerged between the three groups, with the exception of HDL-C that was lower in VD compared with controls. Low HDL-C (< 45 mg/dL) was associated with VD (O.R.: 6.52, C.I. 95%: 1.42–30.70 vs controls, and 4.31, C.I. 95%: 0.93–19.82 vs LOAD), after multivariate adjustment. No differences in plasma lipid levels emerged between the three groups after stratification for apo E4 genotype.

Conclusions: In this cross-sectional study low HDL-C levels are associated with VD, but not with LOAD, in a sample of older subjects.

Background

Some alterations of lipoprotein profile, such as hypercholesterolemia and reduced levels of high-density lipoprotein cholesterol (HDL-C), are considered risk factors for cardiovascular disease, and perhaps for cerebrovascular disease [1–3].

In the last few years several authors have investigated the possible role of dyslipidemias in the pathogenesis of vascular dementia (VD) and Alzheimer's disease (AD); indeed, it has been recently suggested that cerebrovascular disease might play a role not only in VD but also in determining the presence and severity of AD [4].
Reduced HDL-C [5,6] and apo A-I levels [7], as well as increased levels of lipoprotein (a) [7–9] have been reported in VD by some authors, but not by others [9,10]; furthermore, dementia "with stroke" has been associated with high levels of total (TC) and low-density lipoprotein (LDL) cholesterol in a large longitudinal survey [9]. Conflicting results have been obtained in AD: indeed, both increased and reduced TC values [11–13], HDL-C levels [7,14,15], and LDL-C levels [11,15] have been reported in different studies. High Lp(a) values have also been found in AD patients [16].

On the whole, the possible association of dyslipidemias with VD or AD is still a controversial issue, probably due to: 1) the very small number of patients included in most of the studies, and 2) the exclusion from the analysis of some important factors that might induce significant modifications in lipoprotein profile. As regards to this aspect, several conditions are known to modify plasma lipids in the elderly including age itself, gender, apoprotein E phenotype [17], impaired functional status [18], a condition of "frailty" [19], and an inflammation state [20].

In the present study we investigated the lipoprotein profile in a sample of older patients with VD or AD, and compared them with a group of older non-demented controls, before and after adjustment for some potential confounding factors.

Materials and methods

Subjects

Three groups of subjects were enrolled in the present study:

1. Sixty consecutive patients with "probable" vascular dementia by the NINDS-AIREN criteria [21]. All subjects had an Hachinski ischemic score over 7 [22]. By CT scan, forty subjects (66.6%) had small-vessel disease, 14 (23.4%) subjects had large-vessel disease, and 6 (10%) had both small and large vessel disease.

2. Fourty consecutive patients with "probable" late-onset Alzheimer's disease (LOAD) by the NINCDS-ADRDA criteria [23].

The diagnosis of VD and LOAD was made by trained geriatrarians; for neuropsychological assessment all subjects were given a battery of standardized tests.

3. Fifty four community dwelling older subjects without dementia. These subjects had a negative history for cardiovascular and thyroid disease, renal or hepatic insufficiency, and chronic inflammatory diseases. They did not follow an hypolipemic diet.

No patients with VD and LOAD, or control subjects were treated with lipid lowering drugs.

Plasma lipids

Blood samples were obtained after 12 hour overnight fasting, kept at 4°C for 1 h, and centrifuged at 3000 rpm for 10 m’ at 4°C to obtain serum or plasma. Total cholesterol (TC) and triglycerides (TG) were assayed by the Trinder method. HDL-C was determined after selective precipitation of apoprotein B-containing lipoproteins with MgCl2-phosphotungstic acid. Apoproteins A-I and B were measured by nephelometry. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation (LDL-C: TC – TG/5 – HDL-C). Lipoprotein (a) was measured by ELISA (kit Immunozym Lp(a), Immuno, GMBH). Apo E genotype was evaluated on genomic DNA by polymerase chain reaction by the method of Hixon & Vernier.

Clinical chemistry

Serum albumin was measured by nephelometry. Blood sedimentation rate (BSR) was determined by the Wintrobe method. BSR is typically increased during acute phase; although it is not an absolutely specific marker, it is currently utilized in literature as an acute phase indicator [24].

Functional status

Basic activities of daily living (BADLs) were measured by the Barthel index [25] with a score ranging from 0 (severe disability) to 20 (no disability).

Statistical analysis

Data are reported as mean ± standard error (SE) or standard deviation (SD) as reported. Due to the "skewed" distribution of values, Lp(a) was expressed as median (range). The χ2 test was used to compare the categorical variables. Means were compared by ANOVA. ANCOVA was used to compare lipoprotein parameters including Barthel index score, blood sedimentation rate, and serum albumin levels as covariate. Lp(a) levels were compared by the Kruskal-Wallis test.

The odds ratio (VD vs LOAD, VD vs C, and LOAD vs C) was calculated by multivariate logistic regression analysis. HDL-C was transformed into a categorical variable (cut-off: 45 mg/dL); albumin, BSR, and Barthel score were included as confounders.

Systat for Windows version 5.0, and SPSS for Windows version 7.0 statistical packages were used.

Results

The principal characteristics of the three groups are reported in table 1. No differences emerged in age and gender...
distribution. As expected, subjects with VD and LOAD had lower MMSE and Barthel index score compared with controls, while no differences were found between VD and LOAD. Serum albumin was lower in VD compared with controls (p: 0.01); BSR was higher in both VD and LOAD compared with controls (p: 0.04). Unadjusted lipoprotein parameters are compared in table 2. Total and LDL cholesterol were lower in VD compared with controls (p: 0.001), while HDL-C was lower in VD compared with both LOAD (p:0.04) and controls (p: 0.001).

The prevalence of the ε4 allele was 13.3% in VD, 17.5% in LOAD, and 9.2% in controls; the results reported in table 2 didn’t change after stratification for the presence/absence of ε4 allele (data not shown).

In table 3, the lipoprotein parameters are compared after adjustment for Barthel score, blood sedimentation rate, and serum albumin levels. No differences emerged between the three groups, with the exception of the HDL-C that was significantly lower in VD compared with controls (p: 0.04).

Low HDL-C (< 45 mg/dL) was associated with VD: the odds ratio was 6.52 (C.I. 95%: 1.42–30.70) compared with controls, and 4.31 (C.I. 95%: 0.93–19.82) compared with LOAD, after adjustment for albumin, BSR, and Barthel score. The odds ratio for LOAD was 1.13 (C.I. 95%: 0.24–6.26) compared with controls.

**Discussion**

The main result of this study is the finding of lower HDL-C levels in patients with VD compared with controls, before and after adjustment for possible confounders.

The neglect of confounding factors is a major limitation when comparing plasma lipids among groups of older subjects; indeed, lipoprotein metabolism is influenced by a number of conditions that are typical of the elderly population. Different studies reported lower lipid levels in older subjects with comorbidity, disability, or with markers of acute phase [18,26,27,20]. Recently, Corti et al. [19] suggested that the consideration of indicators of poor health and markers of frailty, i.e. serum albumin and iron levels, may help to clarify the role of cardiovascular risk factors in various diseases in older subjects.

Our data are in good agreement the findings of other authors. Kurijama et al. reported lower HDL-C levels in 43 VD patients compared with controls [5], while Katzman et al. found lower HDL-C levels in older men with dementia "with a vascular component" [28]. Munckle et al. found lower HDL-C values in five VD compared with twelve LOAD patients [6], and proposed a possible role of HDL-C in the differential diagnosis of these two forms of dementia; nevertheless, although HDL-C was slightly lower in VD versus LOAD in our sample, it was not useful in discriminating VD from LOAD.

It has not been established the possible mechanism linking low HDL-C and VD. A first possibility is that low HDL-C levels might be the result of the cross-sectional design of this study and of the effect of dementia on plasma lipid levels. We cannot exclude this possibility; nevertheless, if this is the case we should not observe significant differences between VD and LOAD.

A second possibility is that low HDL-C levels might be involved in the pathogenesis of VD. Many epidemiological studies have found a negative association between HDL-C levels and risk of ischemic stroke [29], but the pathogenesis of different subtypes of ischemic stroke may differ. Most of our VD patients were affected by lacunar strokes, and of consequence we might hypothesize a possible association between low HDL-C values and small vessels disease. It has been suggested that HDL particles might

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**Table 1: Principal characteristics of demented (VD and LOAD) and control subjects.**

|                      | VD      | LOAD    | CONTROLS |
|----------------------|---------|---------|----------|
| **Number**           | 60      | 40      | 54       |
| **Age (years)**      | 81.3 ± 0.8 | 79.1 ± 1.0 | 82.2 ± 0.8 |
| **Female gender**    | 55%     | 68%     | 66%      |
| **MMSE**             | 16.4 ± 0.7 | 14.8 ± 0.8 | 26.5 ± 0.6° |
| **Barthel index**    | 8.2 ± 0.7 | 10.9 ± 1.0 | 18.6 ± 0.7° |
| **Serum albumin (mg/dL)** | 3.79 ± 0.5 | 4.01 ± 0.48 | 4.06 ± 0.5 ^ |
| **BSR (mm/1h)**      | 32.6 ± 0.8 | 29.9 ± 0.7 | 17.8 ± 0.8 § |

VD: vascular dementia; LOAD: late onset Alzheimer’s disease MMSE: mini mental status examination; BSR: blood sedimentation rate ° p: 0.001 C vs VD and LOAD; ^ p: 0.01 C vs VD; § p: 0.04 C vs VD and LOAD
play a role in the removal of excess cholesterol from the brain by interaction with apo E and heparan sulfate proteoglycans in the subendothelial space of cerebral microvessels [30]. It is also known that HDL particles favour endothelium dependent vasorelaxation by inhibiting the action of oxidized LDL particles [31], and interfere with induction of endothelial cell adhesion molecules [32]; these mechanisms might be involved in the pathogenesis of small vessels disease. Interestingly, Bonarek et al. recently found that, in a nested case-control study, elevated HDL-C levels were associated with a decreased risk of dementia at multivariate analysis [33]; nevertheless, in their sample the majority of subjects were affected by AD.

A second result of this study is the lack of significant differences in lipoprotein parameters when comparing LOAD patients and controls. In unadjusted analysis HDL-C was higher in LOAD compared with VD, but this difference was no more significant after adjustment. Plasma lipids have been investigated in LOAD patients by several authors in the last few years, but on the whole the results are controversial. Our data seem to confirm the findings of some authors which found no differences in TC and LDL-C [9,14,34], nor in HDL-C [9,34] levels between LOAD and controls.

**Conclusions**

In this cross-sectional study we found that older subjects with VD, are characterized by lower HDL-C levels compared with controls. Longitudinal studies are needed in order to elucidate the possible role of HDL particles in the pathogenesis of this disease.

**Competing interests**

None declared

**References**

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**Table 2: Unadjusted lipoprotein parameters in demented (VD and LOAD) and control subjects (ANOVA).**

| (mg/dL) | VD | LOAD | C |
|--------|----|------|---|
| TC     | 193.5 ± 63° | 214.7 ± 54 | 237.7 ± 47 |
| TG     | 133.4 ± 89   | 118.7 ± 68  | 130.3 ± 50   |
| HDL-C  | 38.2 ± 13%^  | 48 ± 12.3    | 55.8 ± 16    |
| LDL-C  | 120 ± 38 §   | 135.4 ± 44   | 155.8 ± 40.3 |
| TC/HDL | 5.1 ± 1.9    | 4.5 ± 1.6    | 4.5 ± 1.3    |
| Lp(a)  | 16 (1.2–124) | 17(1.5–140)  | 21 (1–142)   |

VD: vascular dementia; LOAD: late onset Alzheimer’s disease; C: controls ° VD vs C p: 0.001; ^ VD vs C p: 0.001; § VD vs LOAD p: 0.04; § VD vs C p: 0.001

**Table 3: adjusted lipoprotein parameters in demented (VD and LOAD) and control subjects (Barthel score, blood sedimentation rate, and serum albumin covariates).**

| (mg/dL) | VD | LOAD | CONTROLS |
|--------|----|------|----------|
| TC     | 206.9 ± 60  | 208.5 ± 46 | 226.8 ± 55 |
| TG     | 138.4 ± 84  | 103.6 ± 64 | 126.1 ± 54 |
| HDL-C  | 42.7 ± 12°  | 47.1 ± 11  | 54 ± 15   |
| LDL-C  | 134.3 ± 37  | 144.6 ± 41 | 146.7 ± 43 |
| TC/HDL | 4.4 ± 1.8   | 4.9 ± 1.4  | 5.0 ± 1.2 |

VD: vascular dementia; LOAD: late onset Alzheimer’s disease ° VD vs C p: 0.04
