Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer’s disease

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Abstract

Serum apolipoprotein (apo) AI concentration was studied in 98 Alzheimer’s disease (AD) patients (77.56 ± 8.83 years) and 59 healthy, elderly controls (75.37 ± 5.27 years). ApoAI levels were significantly lower ($p < 10^{-7}$) in AD patients. An apoAI cutoff value of 1.50 g/L, could distinguish between the two groups with a sensitivity of 71% and a specificity of 69%. ApoAI levels were highly correlated with mini-mental state (MMSE) scores of patients ($p < 0.0001$). These relationships remained significant after adjustment for multiple testing. Our findings raise the question of the potential implication of apoAI in the etiopathology of AD and bring serum apoAI concentration to the fore as an important biochemical marker. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Apolipoprotein A-I; Alzheimer’s disease; Biochemical marker; Mini-mental score

1. Introduction

Apolipoprotein (apo) AI is one of the $\text{A}\beta$-binding proteins, the major component of senile plaques in the brain of AD patients, which includes apoE, ApoJ, transthyretin, and $\alpha$-antichymotrypsin. $\text{A}\beta$ is supposed to be under equilibrium among all factors that are thought to maintain the solubility of this peptide or to promote its deposition within the brain in some pathological conditions. ApoAI is the major component of high-density lipoprotein (HDL). Several antiatherogenic functions have been attributed to apoAI including reverse cholesterol transport and protection against thrombosis and oxidation [13]. In cerebrospinal fluid (CSF), apoAI is also found in HDL-like particles [1,12]. Expression of apoAI was recently reported in the brain of AD patients [5]. No significant difference in apoAI brain expression [5] or in CSF levels were found between AD patients and controls [15]. However, as shown in two studies [7,9], plasma apoAI are reduced in AD and dementia patients. We therefore decided to re-evaluate the role of apoAI as a peripheral biochemical marker for AD and to assess its relationship with the severity of disease, as estimated by the mini-mental score (MMS) [3].

2. Materials and methods

2.1. Subjects

The population studied included 98 late-onset AD patients (70 females and 28 males with mean age of 77.56 ± 8.85 years) as defined by the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III-R) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association of probable AD (NINCDS-ADRDA) criteria. The control group was composed of 59 supposed healthy elderly subjects (31 females and 28 males with mean age of 75.37 ± 5.27 years) who were being
followed at the Center for Preventive Medicine in Nancy-France.

2.2. Biochemical measurements

Blood was collected by venipuncture after an overnight fasting. Total serum cholesterol and triglycerides were measured in fresh serum by using standard enzymatic methods (Merck, Darmstadt, Germany), automated on AU5000 (Olympus, Tokyo, Japan). Serum apoAI and apoB were determined by immunonephelometry on Behring Nephelometer Analyzer, with Behring reagents (Rueil-Malmaison, France), HDL cholesterol (HDL-C) was determined using reagents from Boehringer Mannheim, Germany on COBAS MIRA (Roche Diagnostics-System, Neuilly-sur-Seine, France). DNA extraction and apoE genotyping were performed as described elsewhere [6,11]. Data shown are presented as mean ± SD.

3. Results

Serum apoAI levels were significantly lower \((p < 10^{-7})\) in AD patients compared to controls (Table 1). The difference remained significant even when we took into account other parameters such as age, sex, and albumin as covariants. Serum levels of apoB did not differ significantly between AD patients and controls (Table 1). The levels of HDL-C-like apoAI levels, were also significantly reduced in AD patients \((p < 10^{-7})\), suggesting a high association between these two parameters. The gender repartition between control and AD was different (e.g., same ratio of women and men in the control group, and 2.5-fold more women in the AD group). Gender had no effect in serum apoAI concentrations \((p = 0.48)\), allowing us to evaluate our results in the study groups regardless of gender. Fig. 1a shows the distribution of apoAI levels in the sera of AD patients and controls. To evaluate the diagnostic potential of apoAI as a marker of AD, a cutoff point was established by constructing a receiver operating characteristic curve (Fig. 1b). A cutoff value of 1.50 g/L of apoAI had a sensitivity of 71% and a specificity of 69%. A cutoff value of 1.4g/L gave a sensitivity of 61% and a specificity of 80%. Considering that sensitivity is important in the early diagnosis of AD, we chose the cutoff value of 1.5 g/L.

Our study demonstrated that apoAI concentrations were highly correlated \((p < 0.0001,\) Fig. 2) with the severity of Alzheimer’s disease, as reflected by the patients’ MMS [3]. This relationship was independent of all other parameters studied (age, gender, albumin, apoE genotypes). In the AD patients, apoAI concentrations seemed to be slightly increased \((p = 0.06,\) Table 2) in patients with 1 or 2 \(e4\) allele(s) compared to those without the allele. This tendency was not seen in the control group \((p = 0.85)\). ApoAI levels were significantly and consistently lower in AD patients, independent of \(e4\) status \((p < 0.001 in the group without e4 and p < 0.05 in the group with e4, Table 2).
4. Discussion

Two previous studies reported decreased levels of plasma ApoAI in AD patients [7,9]. Our work adds to these results by studying a larger number of patients and by demonstrated for the first time that serum apoAI are highly linked to the severity of Alzheimer’s disease, as reflected by the MMSE. ApoAI levels have been also evaluated in vascular dementia [9]. In fact, apoAI levels decreased simultaneously in both vascular dementia and Alzheimer’s diseases and cannot be used for differential diagnostic. The latter needs to be assessed by other clinical and biological tests that can distinguish clearly between AD and vascular dementia.

Interestingly, studies in the elderly have shown that high levels of serum apoAI and HDL-C are associated with low total mortality and enhanced longevity [10]. Our results suggest that the AD patients with higher serum apoAI concentrations have less cognitive impairment. Considering the anti-atherogenic properties of high density lipoprotein, it is possible to identify an analogy between biochemical markers of atherosclerosis (apoE4, apoAI, HDL, etc.) and markers of Alzheimer’s disease.

The relationship between apoAI and the presence of an ε4-allele is interesting. A metabolic interaction between apoE and apoAI, leading to apoE4-dependant turnover of apoAI/E-containing lipoproteins in AD-linked conditions is plausible. However, no relationship between apoE genotype and apoAI levels has been found in the previous study [7]; this could be due to the inclusion of a smaller number of patients (45 vs. 95 in our study). Future studies are needed to further address this issue.

In contrast to plasma apoAI, the levels in the CSF do not seem to vary between AD patients and controls [15]. An increase of apoAI passage to the CSF or the housekeeping function of the blood-brain barrier could explain this finding. Many lines of evidence support this idea. The need for apoAI is increased in the experimental regenerative conditions [2]. CSF-apoAI levels have been shown to increase with the severity of macaque brain injury [14], whereas those in serum decrease with inflammation due to shorter half-life [17]. We cannot exclude enhanced passage of apoAI to the CSF in our AD patients due to alterations of the blood-brain barrier.

Our results suggest that changes in metabolic conditions, reflected by apoAI and HDL levels, may take place in AD patients. ApoAI could be involved in the pathology of AD in at least three ways. A first mechanism would entail the formation of amyloid-like fibrils. ApoAI has been shown in vivo to participate in the amylogenesis process by binding to Aβ [8] and to form amyloid-like fibrils [18]. A second role of apoAI with implications in the genesis of AD, relates to neuron maintenance. ApoAI is one of the exchangeable apolipoproteins that are actively involved in the regeneration process of neuron cells occurring after injury [2]. Finally, the association between apoAI and other proteins such as apoJ [16], could contribute to the pathogenesis of AD. ApoJ, for example, is one of the major Aβ-binding proteins in the CSF [4] and exerts a remarkable permeability effect at the blood-brain barrier [19,20]. The physiological association between apoAI and apoJ with a constant molar ratio in HDL particles [16], suggests a strict metabolic control in the formation of this complex. We propose that the decrease of total apoAI levels in sera may affect apoJ

Table 2
Serum concentrations of apoAI (mean ± SD) according to the apoE genotype

<table>
<thead>
<tr>
<th>ApoE Genotypes</th>
<th>without ε4</th>
<th>with ε4</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2/2</td>
<td>2/3</td>
<td>3/3</td>
</tr>
<tr>
<td>AD group</td>
<td>0.97 ± 0.0</td>
<td>1.33 ± 0.16</td>
<td>1.28 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>(n = 2)</td>
<td>(n = 5)</td>
<td>(n = 40)</td>
</tr>
<tr>
<td></td>
<td>1.28 ± 0.28 (n = 47)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1.80 ± 0.42</td>
<td>1.61 ± 0.25</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>(n = 0)</td>
<td>(n = 4)</td>
<td>(n = 38)</td>
</tr>
</tbody>
</table>

* Comparison of apoAI levels in AD or control group according to apoE genotypes

** P < 0.001 and ** P < 0.05, comparisons with control groups with the same apoE ε4 status.
structure and/or function in AD, especially in regards to maintaining the solubility of Aβ and/or affecting its transport across the blood-brain barrier. Other pathologic mechanisms are possible and would need to be further evaluated in future AD studies.

The strong and independent relationship between serum apoAI concentration and MMSE score in AD patients is of potential importance. It is, however, necessary to further investigate the role of apoAI in AD in the context of other cognitive tests. ApoAI may contribute to enhance the accuracy of an AD diagnosis, and may also constitute a target for pharmacological treatment of the disease.

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References


