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Blood-Based Biomarkers

Plasma clusterin levels and risk of dementia, Alzheimer's disease, and stroke

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Abstract

Introduction: Genetic variation in the clusterin gene has been associated with Alzheimer Disease (AD), and the clusterin protein is thought to play a mechanistic role. We explored the associations of clusterin plasma levels with incident dementia, AD, and stroke.

Methods: Plasma clusterin was assessed in 1532 nondemented participants from the Framingham Study Offspring cohort between 1998 and 2001 (mean age, 69 ± 6; 53% women). We related clusterin levels to risk of incident dementia, AD, and stroke using Cox-proportional hazards models and examined potential interactions.

Results: A significant interaction of plasma clusterin levels with age was observed. Clusterin was significantly associated with increased risk of dementia among elderly persons (>80 years; hazard ratio [HR], 95% confidence interval = 6.25, 1.64–23.89; P = .007) and with decreased risk of dementia (HR = 0.53, 0.32–0.88; P = .013) and stroke (HR = 0.78, 0.63–0.97; P = .029) among younger participants.

Discussion: The association between plasma clusterin levels and risk of dementia and stroke may be modified by age or an age-related factor.

Keywords: Epidemiology; Plasma clusterin; Dementia; Alzheimer's disease; Stroke; Risk factors

1. Introduction

Genetic variation within the clusterin (*CLU*, also previously called apolipoprotein J, ApoJ) gene has been associated with risk of Alzheimer's disease (AD) in multiple independent genome-wide association studies of diverse ethnic groups [1]. In addition, among healthy participants in the Baltimore Longitudinal Study of Aging, carriers of the protective *CLU* allele showed slower rates of decline in memory performance relative to carriers of the risk allele [2]. However, our knowledge is very limited regarding the mechanisms through which genetic variation in the clusterin gene modifies the risk of AD. Some evidence suggests that the clusterin protective variant is associated with elevated gene expression and higher plasma clusterin levels [3–6]. In turn, there is substantial evidence suggesting neuroprotective roles for clusterin in AD pathogenesis. For instance, clusterin acts as a chaperone to alter amyloid beta (aβ) aggregation and toxicity, it has a role in aβ clearance as well as in lipid metabolism in the brain, and it modulates inflammation and inhibits apoptosis [7–9]. In contrast, clusterin mRNA and protein levels have been shown to be higher in AD [5,6,10,11] and mild cognitive impairment [11,12] in some but not all [4,6,13] studies. Clusterin

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protein levels in plasma are also increased with increasing severity of the disease [6,10] as well as in persons showing a more rapid decline [6]. Even in nondemented individuals, clusterin levels are negatively correlated with performance on tests of global cognition and attention/processing speed [12], with greater brain atrophy [6,12] and with a greater decline in white-matter volume [12]. These findings have led to the hypothesis that clusterin is elevated in response to brain pathology to exert its neuroprotective effect. In contrast, in vitro studies suggest that clusterin can promote amyloid aggregation and toxicity when the clusterin/aβ ratio is low [14,15]. Furthermore, in a longitudinal study of 241 old individuals, clusterin levels in the cerebrospinal fluid (CSF) have been related to a greater entorhinal cortex atrophy rate, and this relationship was observed only among CSF aβ1-42-positive individuals but not among CSF aβ1-42-negative individuals [16]. We postulate that one reason for these apparently contradictory findings may be variation in the role of circulating clusterin with increasing age, inflammation, and amyloid pathology.

It is not clear whether clusterin levels in plasma can serve as an early predictor of dementia and AD among cognitively healthy individuals. The discovery of a well-established peripheral AD biomarker that is easily accessible and cost effective is of great importance because AD incidence increases as the population ages, and the ability to identify high-risk populations is thought to be crucial for the success of current and future therapies. We tested the hypothesis that elevated plasma levels of clusterin are associated with a higher risk of new-onset dementia and AD in cognitively healthy participants. We then examined whether age and sex modify this association. An interaction of clusterin levels with plasma aβ was also tested, as the impact of clusterin may depend on aβ burden [16]. Furthermore, because clusterin has been shown to play a significant role in inflammation and immune responses [17], we assessed whether its relationships with dementia/AD risk differ in individuals with low compared to high serum C-reactive protein (CRP) levels. Finally, we have explored the relationship between clusterin levels and the risk for stroke in the current analysis, as both stroke and dementia share common risk factors and etiologies [18]. Moreover, clusterin also has been shown to alter the risk of cardiovascular and metabolic diseases [19].

2. Methods

2.1. Study sample

The FHS is a longitudinal community-based cohort study that was initiated in 1948 with the enrollment of 5209 participants aged 28–62 years. In 1971, offspring of the first generation participants and spouses of these offspring were enrolled as the Offspring cohort (n = 5124, age = 12–58 years). Since their recruitment, participants from the Offspring cohort have had 9 serial examinations including standardized interviews, physician examinations, and laboratory testing [20].

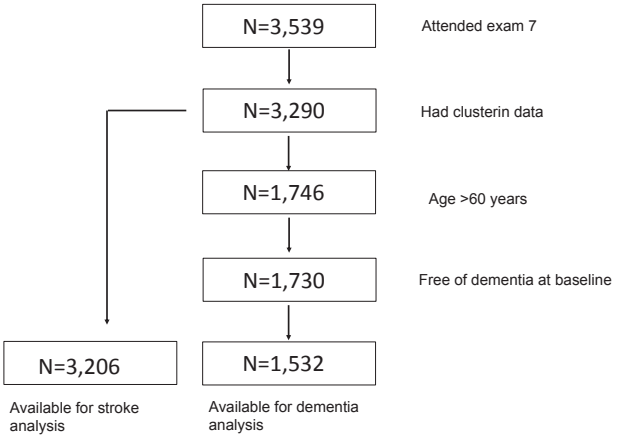

Fig. 1. Flow diagram of study participants.

The study design is described in Fig. 1. Clusterin was measured in blood drawn from Offspring participants at the 7th offspring examination between 1998 and 2001, and of 3539 who attended that examination, 3290 had blood samples available for plasma clusterin assay. We excluded persons age <60 years because *CLU* has been associated only with late-onset dementia, and persons with prevalent dementia at the 7th Offspring examination. Therefore, 1730 participants remained, of whom, 1532 also had further follow-up information on cognitive status for at least 1 year and thus constitute our study sample. For analyses of stroke outcome, we did not exclude younger participants, so after excluding 84 participants with prevalent stroke, 3206 of the 3290 persons with plasma clusterin data were available for analysis.

2.2. Laboratory measurements of clusterin, aβ, and CRP

Whole blood was collected in fasting state using a 21-gage needle. For serum preparation, blood was collected into red top tubes and was allowed to clot in a vertical position at room temperature for 30 minutes before centrifugation. For plasma preparation, blood was collected to EDTA-treated tubes and gently inverted 5–10 times. All tubes underwent centrifugation at 3000 rpm/1850 g for 30 minutes at 4°C. Serum and plasma were then apportioned into 0.5-mL aliquots and stored at −80°C.

All samples were analyzed for beta-amyloid levels at the Department of Molecular Pharmacology and Experimental Therapeutics of the Mayo Clinic, Jacksonville, FL. Quantification of aβ in plasma was performed using INNO-BIA assays (Innogenetics, Ghent, Belgium), which is a multiplex microsphere-based Luminex xMAP technique. Intra-assay coefficients of variations (CVs) for $a\beta_{1-40}$ and $a\beta_{1-42}$ were 3.2% and 2.6%, and inter-assay CVs were 10.5% and 7.6%, respectively. Plasma clusterin