Importance of Apolipoprotein E in Vascular Dementia, Stroke Prevalence and Associated Cognitive Dysfunction

Dandekar MP* and Shaoling Huang
Division of Cardiology, Department of Internal Medicine, The University of Texas Health Science Center at Houston (UTHealth), McGovern Medical School, Houston, USA

Abstract
Atherosclerosis, cerebral hypoperfusion or hypertension is the most common pathogenic risk factors in about half of all stroke, and also causative to vascular cognitive impairment (VCI). While the precise underlying mechanisms of the VCI are poorly understood, vascular dementia associated with Alzheimer’s disease (AD) and heart disease has shared a genetic link with Apolipoprotein E (APOE). Typically, APOE is well known for its effects on regulation of cholesterol metabolism. Epidemiological surveys also emphasized the improper functioning of an APOE harboring the allele epsilon4 (APOE4) genotype in the pathogenesis of cardiovascular disease, atherosclerosis and AD. Moreover, enhanced expression of APOE has been reported by astrocytes and oligodendrocytes in injured brain structures. The preclinical and clinical studies demonstrated a strong correlation between the APOE polymorphism and development of vascular disease and dementia. This paper summarizes an intriguing role of APOE4 genotype in the sick heart, prevalence of stroke and their association with occurrence of cognitive deterioration.

Keywords: Hypertension; Atherosclerosis; Dementia; Astrocytes; Vascular cognitive impairment

Short Communication

Background
Cardiovascular disease (CVD) is a leading cause of death and disability worldwide [1]. The hemodynamic changes associated with CVD like heart failure, hypertension and atherosclerosis reported to alter the cognitive ability [2,3]. The cerebral hypoperfusion caused due to cardiac disease [4,5] also invariably linked to cognitive deficits in attention and memory and can lead to neurodegenerative disorders like Alzheimer’s disease (AD) [6-8]. It has been reported that, nearly 50% of AD risk is associated with traditional vascular risk factors and post-mortem cases of AD have some form of vascular pathology [3,9]. Thus, therapeutic implications of controlling such vascular abnormalities in AD have presumed to be one of the most important inroads in the search to lower the rising prevalence of AD and vascular dementia [9,10]. While the underlying mechanisms of the vascular cognitive impairment (VCI) are poorly understood, many people have assume that AD and heart disease share a genetic link associated with Apolipoprotein E (APOE). Epidemiological surveys also support the neuropathologic link between presence of APOE harboring the allele epsilon4 (APOE4) genotype in cardiac abnormalities such as amyloid angiopathy and development of AD in elderly population. This article summarizes an intriguing role of APOE4 genotype in the sick heart, prevalence of stroke and their association with occurrence of cognitive deterioration.

Role of APOE in Cognitive Dysfunction
APOE is a 34-kDa glycosylated protein that plays a critical role in the metabolism of fats in the peripheral parts and central nervous system (CNS). In addition to its well-characterized role in cholesterol metabolism, APOE has been up-regulated by astrocytes and oligodendrocytes in the injured brain structures, suggesting its role in the neural injury and repair [11,12]. Several studies proposed the improper functioning of APOE4 genotype in the pathogenesis of CVD, atherosclerosis and AD. With reference to AD, APOE4 has been shown to binds with amyloid β (Aβ) protein and facilitates its uptake, as well as enhances the production of Aβ and synergizes with Aβ toxicity [13,14]. The APOE knock out (APOE-/-) is a classic mouse model mainly employed to study the atherosclerosis, these mice also displayed an impairment of spatial memory compared with wild-type animals in the Morris water maze (MWM) assay indicating cognitive dysfunction, a core symptoms of AD. Additionally, APOE-/- mice showed several hallmarks of AD such as an increased inflammation, increased blood brain barrier permeability, micro vessel degeneration, reduction of neurogenesis and synapses, reduced clearance of Aβ and the presence of hyperphosphorylated tau [15]. Moreover, vascular hypothesis proposed by [16] showed that advanced aging, a former head injury and APOE4 genotype became critical risk factors to AD by virtue of their potential to lower blood flow to the brain [17].

That being said, APOE4 genotype polymorphisms may be a strongest genetic risk factor for dementia and accelerated cognitive decline seen in patients with sporadic- and late-AD [18-25], which was also associated with a higher degree and faster rate of neurodegeneration [25,26], a greater amyloid deposition and changes in cerebrospinal fluid measures of amyloid and tau [27]. In AD, inheritance or clearance of the APOE4 greatly increases AD risk by several folds if both alleles are present [28]. A positive association of APOE4 polymorphism and increased risk for vascular dementia has been demonstrated in 14 out of 24 studies [28]. In contrast, 9 studies reported that APOE4 allele does not confer risk for vascular dementia [29]. Although the functional activity of APOE4 varies considerably, Baltimore longitudinal study of aging reported that carriers of this genotype had greater decline in cerebral blood flow [30]. These findings underscore the importance of APOE genotype when considering biomarkers in early stages of AD or dementia [31].

*Corresponding author: Dandekar MP, Division of Cardiology, Department of Internal Medicine, The University of Texas Health Science Center at Houston (UTHealth), McGovern Medical School, Houston, USA, Tel: +1 713-500-5116; E-mail: md_manoj1@rediffmail.com

Received January 18, 2018; Accepted February 05, 2018; Published February 12, 2018


Copyright: © 2018 Dandekar MP. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
The deficiency of APOE leads to several cellular and molecular changes in the important brain structures associated with memory formation including the hippocampal CA1 and caudoputamen. Yet while an estimated 3.5 million of Americans suffer with AD, this CNS disorder is far less common than CVD. More than 85 million people in the USA are living with some form of CVD or the aftereffects of stroke, which also affects brain function. A meta-analysis of randomized controlled trials of antihypertensive therapy in the elderly indicated that lowering of the blood pressure led to decrease risk of stroke by 35% [32]. The role of APOE4 allele has been reported in the risk of both ischemic and hemorrhagic stroke [33]. However, most cases of dementia after stroke may be described under the umbrella term of VCI that needs to be explored in detail.

Role of APOE in Stoke and Vascular Dementia

Globally, stroke is the leading cause of long-term disability among adults and the second leading cause of death [34]. The enhanced risk of cognitive impairment and incident dementia has also been reported in the stroke survivors [35-37]. Cognitive impairment is one of the most common sequelae following stroke with 40%-75% of stroke survivors experiencing some sort of cognitive deficit [38]. The high cumulative risk of dementia or stroke or both conditions has been shown by the Framingham study [39] and the urgent need to improve knowledge regarding cognition and vascular conditions has been emphasized in a specific meeting providing harmonized standards [40]. While involvement of APOE in CVD-associated stroke and cognitive impairment is enigmatic, APOE deficiency has been shown to worsen the ischemic outcome [12] and displayed increased neuronal damage following an episode of global cerebral ischemia [41]. The infusion of APOE in APOE-deficient mice reversed these brain insults [40]. In Canadian study of health and aging, the joint presence of stroke and APOE4 was associated with a greater risk of dementia compared with absence of these two factors [39]. Although stroke and APOE4 were considered an independent risk factors for dementia [42], their combined effect is still debatable [43,44]. In aged stroke patients with early cognitive impairment, the presence of an APOE4 allele is associated with greater progression of cognitive decline [45]. The presence of one or two APOE4 alleles may be a significant independent risk factor for cognitive impairment in the early phase after stroke [46-53]. Collectively, APOE genotype and recurrent stroke may affect the relationship between a history of stroke and incident dementia risk.

Conclusion

Atherosclerosis, cerebral hypoperfusion or hypertension is the most common identified pathogenic risk factors for stroke and VCI (Bink et al., 2013). Indeed, cognitive dysfunction after stroke is a frequent observation but neglected consequence compared to other neurological deficits (Jacova et al., 2012). Herein, independent role of APOE genotype has been discussed in stroke prevalence as well as in patients with vascular dementia. The small vessel disease associated genetic traits, severe white matter changes and medial temporal lobe atrophy have been identified in the development of dementia after stroke injury. Although the direct influence of any specific genetic factor(s) is not clear, the putative role of APOE4 genotype in cognitive impairment after stroke has been suggested in the literature. However, it is early to decide which effects are due to atherosclerosis and which are due to direct effects of ApoE in the brain (i.e. Aβ clearance and deposition) (Mahley and Huang, 2012). Importantly, post-stroke cognitive impairment reduces quality of life in survival and early detection of causative biomarkers as well as it management is warranted.

References


