Review Article
Is apolipoprotein E4 an important risk factor for vascular dementia?

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Abstract: Despite the fact that vascular dementia (VaD) represents the second leading cause of dementia in the USA, behind only Alzheimer’s disease (AD), there remains a lack of consensus on the pathological criteria required for diagnosis of this disease. A number of clinical diagnostic criteria exist but are poorly validated and inconsistently applied. It is clear that vascular risk factors play an important role in the etiology of VaD, including hypertension, stroke, diabetes, and atherosclerosis. Vascular risk factors may increase the risk for VaD by promoting inflammation, cerebral vascular disease, white matter lesions, and hippocampal sclerosis. Because vascular risk factors seem to impart a high degree of risk for conferring VaD, it seems logical that the apolipoprotein E (APOE) status of individuals may be important. APOE plays a critical role in transporting cholesterol in and out of the CNS and in AD it is known that harboring the APOE allele increases the risk of AD perhaps due to the improper functioning of this protein. The purpose of this review is to examine the important pathological features and risk factors for VaD and to provide a critical assessment of the current literature regarding whether or not apoE4 also confers disease risk in VaD. The preponderance of data suggests that harboring one or both APOE4 alleles elevates the risk for VaD, but not to the same extent as found in AD.

Keywords: Apolipoprotein E4 (APOE4), vascular dementia, pathology, risk factors, Alzheimer’s disease, neurofibrillary tangles, blood brain barrier, inflammation

Prevalence and clinical features of vascular dementia

According to a recent analysis, pure vascular dementia (VaD) accounts for roughly 15-20 percent of all types of dementia making it the second leading cause of dementia behind only Alzheimer’s disease in the USA [1]. The estimated prevalence of VaD varies from 1.2 to 4.2 percent of individuals over the age of 65 years and the incidence is estimated at 6-12 cases per 1,000 persons over 70 years of age per year [2]. One difficulty in measuring the prevalence of VaD is that it often coexists with Alzheimer-type lesions and other pathologies with 20-30 percent of demented subjects showing mixed pathologies [3] (Figure 1). Indeed, available data indicates that VaD and AD share several pathological features including the presence of neurofibrillary tangles (NFTs), amyloid or plaques, white matter lesions and cerebral amyloid angiopathy [4, 5].

Despite this co-occurrence of pathologies, it is possible to clinically distinguish pure VaD from mixed dementia or AD. The diagnosis of VaD and its differentiation from AD are based on the presence of vascular risk factors, neuroimaging, and clinical features such as acute onset, stepwise progression and emotional liability [6]. Behaviorally, patients with VaD show loss in executive functions as an initial symptom, whereas in AD memory loss is often associated with the earliest known symptoms. Other important symptoms of VaD include confusion, language deficits, restlessness and agitation, and gait disturbances [7]. In addition, an important behavioral component of VaD is the high rate of depression as well as apathy that is associated with the personality and mood changes that accompany this disease [8].

Pathophysiology of vascular dementia

There are at least three pathological features commonly associated with VaD that include: 1)
Collectively, all of these lesions lead to cerebrovascular disease (CVD), which represents the single most important unifying concept underlying the pathology of VaD. Figure 2 summarizes the common pathological features associated with VaD. It is noteworthy that a number of other pathological findings have also been documented in VaD including amyloid plaques, neurofibrillary pathology, and cholinergic deficits although to a lower degree than what is commonly found in AD [4].

Risk factors associated with vascular dementia

The expression “what’s bad for the heart is bad for the brain” fits aptly concerning VaD. Many of the important risk factors for cardiovascular disease have also been identified as being risk factors for VaD (Figure 2). Having a stroke doubles the risk of dementia [17] and according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Neurosciences (NINDS-AIREN), one of the criteria for a clinical diagnosis of vascular dementia includes evidence of cerebrovascular disease by focal signs on neurological examination consistent with stroke [18]. In addition, previous studies have shown that stroke specifically increases the risk for vascular disease [19]. The most common stroke subtype associated with VaD was lacunar stroke [20].

Because hypertension is a critical risk factor for stroke, it follows that hypertension would also be a risk factor for VaD. Indeed, using a cohort of the population based Rotterdam Study, it was demonstrated that antihypertensive drugs reduced the risk for VaD [21]. A previous study by Posner et al. showed that those with hypertension or heart disease alone had no increased risk for VaD. However, when both were present, there was a threefold increase in risk for VaD. In addition, a six-fold increase in risk was observed when both hypertension and diabetes were present [22]. Diabetes and insulin resistance has been confirmed to be an independent risk factor for VaD [23-25].

Related to stroke and hypertension is the role that atherosclerosis may have in the etiology of VaD. Atherosclerosis is a disease process that occurs over the lifetime of individuals and has a fundamental basis of chronic elevated cholesterol that leads to the formation of fatty streaks,
APOE and vascular dementia

Figure 2. Overview of the known major pathological features and risk factors associated with VaD. A key feature of VaD is the presence of cerebral vasculature lesions that may lead to inadequate blood flow to neurons. Depending on the site of these lesions, neuronal degeneration may produce symptoms of dementia. The potential risk factors that may trigger the pathological processes associated with VaD are shown, with many of these being important cardiovascular risk factors as well. See main text for details.

Is apolipoprotein E4 associated with vascular dementia?

Due to the inherent risk that hypertension, stroke, atherosclerosis and other metabolic factors have on the development of VaD, it is interesting to speculate on any putative role that apolipoprotein E (apoE) may have in this disease. Human apoE is polymorphic with three major isoforms, apoE2, apoE3, and apoE4, which differ by single amino acid substitutions involving cysteine-arginine replacements at positions 112 and 158 [29]. In AD, inheritance of the APOE4 allele greatly increases risk up to 10 fold if both alleles are present [30]. Harboring the APOE4 allele represents the most important genetic factor for late-onset AD with 65-80 percent of all AD patients carrying at least one APOE4 allele [31, 32]. Functionally, in the CNS, apoE is produced by a variety of cells including astrocytes, which function to transport cholesterol to neurons via apoE receptors that are members of the low-density lipoprotein (LDL) receptor family [33, 34]. It has been proposed that because apoE is the major cholesterol transporter in the brain (see below) and therefore is essential for synaptogenesis in neurons, then apoE-isoform-dependent differences in these processes may negatively impact synaptic plasticity or recovery of neurons from neurodegeneration as might occur in AD [35, 36]. In AD, one potential mechanism by

plaques, inflammation and eventual occlusion of effected blood vessels. In the cerebral vasculature, this will precipitate a stroke if the occluded blood vessels are sufficiently large enough to compromise brain function. Interesting, it is predominantly carotid atherosclerosis that is associated with an increase risk for VaD [26]. Equally problematic may be vascular occlusions involving smaller areas of the brain that may lead to microbleeds. Cerebral microbleeds are a prevalent finding in the aged brain. Cerebral microbleeds have been associated with worse cognitive function [27] and have been shown to be a risk factor for VaD [28].
which apoE4 confers disease risk is its propensity to undergo proteolytic cleavage generating N- and C-terminal fragments (for a recent review see, [37]). Cleavage of apoE4 may increase AD risk in two ways, either through a loss of function or gain of toxicity [37].

Whether apoE4 confers a similar risk for the development of VaD has been an area of intensive investigation with conflicting conclusions. For this review, analysis of 24 studies was undertaken all of which examined the potential association of APOE polymorphism in VaD. Of these studies (between the years 1994-2012), 14 showed a positive association between harboring the APOE4 allele and increased risk for VaD [38-51]. In contrast, 9 studies (between the years 1994-2008) found that APOE4 allele does not confer risk for VaD [52-60]. Examining the negative findings in more detail indicates that 5 of the 9 studies were found in Asian populations [52, 53, 57, 58, 60], whereas the other
ApoE4 pathology in vascular dementia

Based on the available data, it is not clear whether harboring the APOE4 allele equates to a greater risk for VaD. Another approach to answer this question would be to examine potential apoE4 pathology in VaD. It would be predicted that if APOE4 heightens the risk for VaD, there should be clear evidence for apoE pathology in the VaD brain. For example, previous studies in AD have shown that apoE4 has the propensity to be cleaved, which could provide either a toxic-gain or loss of function [37]. Surprisingly, however, a thorough search of the literature failed to yield even a single published study examining apoE pathology in VaD. Our own group has recently addressed this by examining apoE immunoreactive pathology in VaD utilizing a novel, site-directed antibody to the amino-terminal fragment of apoE [65].

Application of this antibody, termed the amino-terminal apoE cleavage fragment (nApoECF) antibody to AD frontal cortex brain sections revealed specific localization within neurofibrillary tangles (NFTs) that was dependent upon the APOE genotype: 4/4 ≥ 3/4 > 3/3 [65]. Recently, we reported for the first time the presence of cleaved apoE in the VaD brain [66]. The localization of an amino-terminal fragment of apoE, utilizing the nApoECF antibody, was determined to be largely confined within NFTs and blood vessels (Figure 3D). An interesting finding was the fact that cleaved apoE was not evident within extracellular beta-amyloid plaques, although full-length apoE was readily present [66] (Figure 3D). These results suggested that the cleavage of apoE most likely represents an intracellular event. The presence of cleaved apoE in VaD provides for pathological data supporting the potential link between APOE polymorphism and enhanced risk for VaD. In addition, the potential loss of function of apoE following cleavage may contribute to disease progression in a disorder whereby cerebral vascular risk factors play such an important role.

Concluding remarks

VaD is the second leading cause of dementia in the USA, and despite this fact, there has been a general lack of consensus on the pathological criteria required for diagnosing this disease. Clearly, vascular risk factors including hypertension, stroke, atherosclerosis may increase the risk for VaD and it follows that harboring the APOE4 allele may also lead to enhanced vulnerability. However, conflicting reports on APOE polymorphism and enhanced VaD risk have been documented although the preponderance of data suggest the presence of the APOE4 allele does increase risk albeit to a lower extent to what has been found in AD. Supporting these findings are the recent data showing widespread apoE immunoreactive pathology associated with the VaD brain that included evidence of fragmentation of the apoE protein [66]. The potential loss of apoE function following fragmentation may contribute to disease progression, particularly in a disorder whereby cerebral vascular risk factors play such an important role. Further studies are warranted to examine more clearly the potential connection between VaD and the APOE polymorphism.
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None.

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