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Review Article

Is apolipoprotein E4 an important risk factor for vascular dementia?

Troy T Rohn

Department of Biological Sciences, Boise State University, Room 228, Science Building, Boise, Idaho, USA

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Abstract: Despite the fact that vascular dementia (VaD) represents the seconding 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)

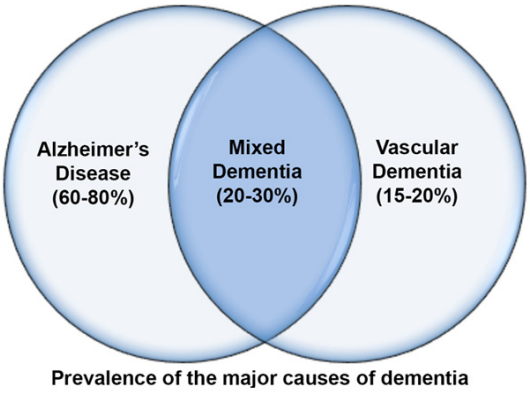

Figure 1. Overlap between AD and VaD is a common and often confounding factor in diagnosing VaD. The available evidence suggests that up to 20-30 percent of patients meeting pathological criteria for VaD also have concurrent AD pathology. This co-occurrence of symptoms between the two diseases has led to a lack of consensus about the best clinical criteria to identify VaD compounding the probability of misdiagnosing VaD as AD. Therefore, clear clinical and pathological criteria for the diagnosis of VaD will be critical in differentiating pure VaD from AD and mixed dementia.

large artery infarctions, 2) small artery infarctions or lacunes that are generally subcortical, and 3) chronic subcortical ischemia leading to selective loss of neurons, glial cells, and endothelial cells [9]. Two other commonly found features associated with VaD include cerebral amyloid angiopathy (CAA) and hippocampal sclerosis. CAA is characterized by the deposition and accumulation of beta-amyloid in small arteries of the brain. The accumulation of beta-amyloid leads to pathological changes within the vascular lumen that may precipitate the onset of ischemia and degeneration [10]. CAA is also commonly found in AD, however, it is an independent factor in approximately 10 percent of pure VaD cases without AD pathology [11-13]. Hippocampal neurons are highly susceptible to ischemic conditions and the loss of CA1 neurons as well as the accompanying gliosis in VaD has been correlated with lower hippocampal volume and memory score [14]. Thus, hippocampal sclerosis is a frequent pathological finding in VaD as documented by a recent cohort analysis showing approximately 28.5 percent of VaD subjects had the presence of hippocampal sclerosis [15]. Finally, VaD has been associated with white matter lesions. Specifically, white matter changes caused by microvascular disease not macroscopic infarction was significantly correlated with VaD [16]. 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,

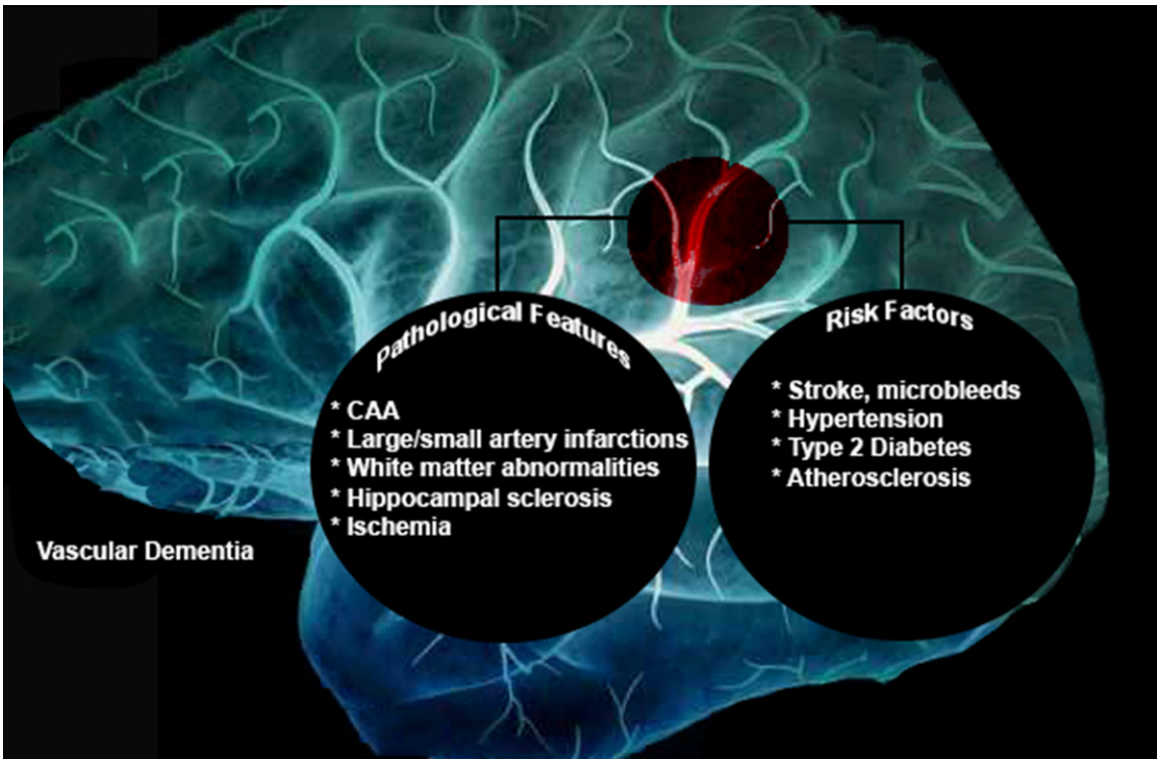

Figure 2. Overview of the known major pathological features and risk factors associated with VaD. A key feature of VaD is the presence of cerebral vasculature lesions that may lead to inadequate blood flow to neurons. Depending on the site of these lesions, neuronal degeneration may produce symptoms 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.

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].

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

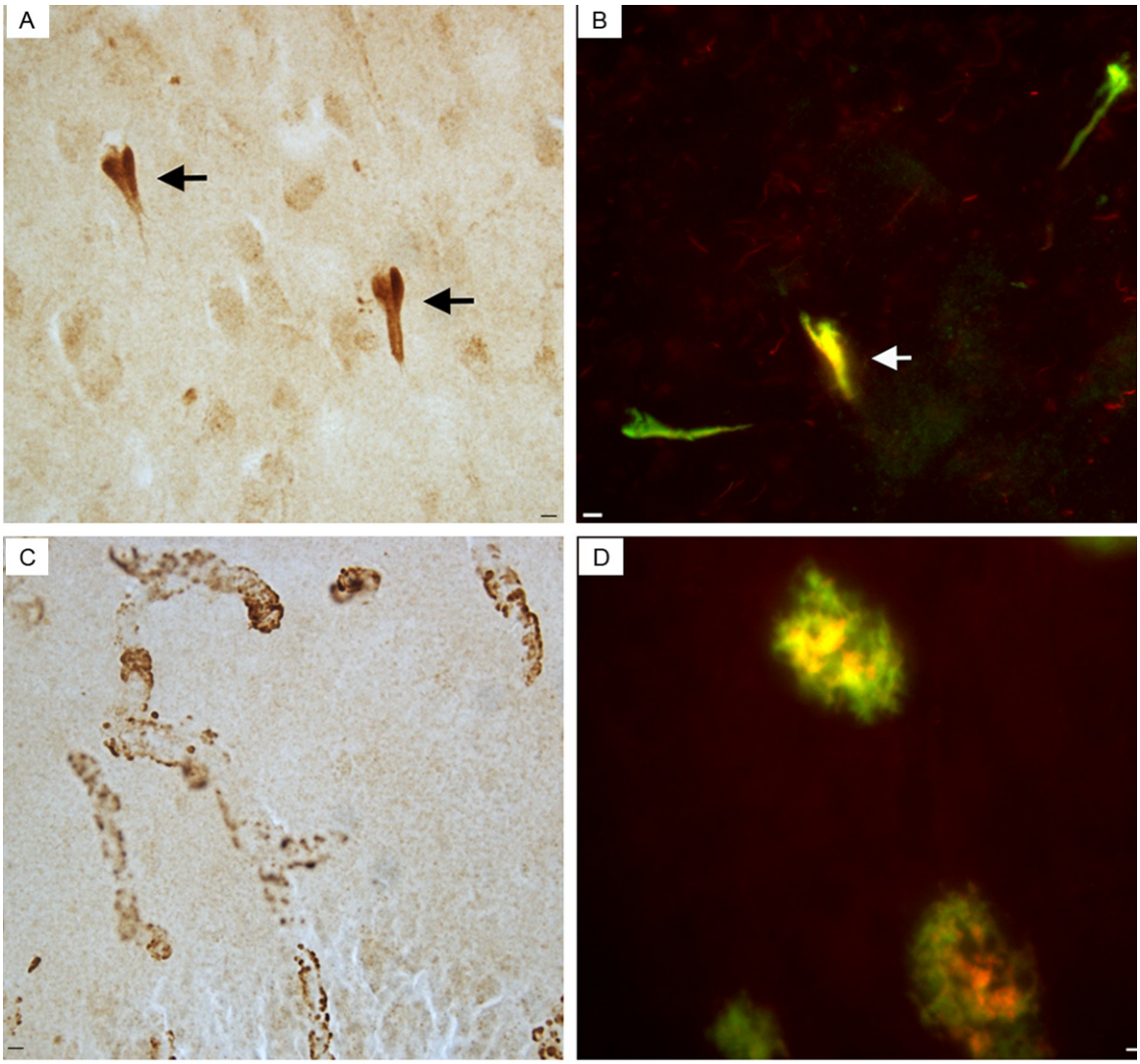

Figure 3. Evidence for apoE immunoreactive pathology in the human VaD brain. (A) Representative labeling utilizing a custom, in house antibody that specifically detects the amino-terminal fragment of apoE shows the presence of immunoreactivity within apparent NFTs in postmortem VaD brain tissue sections (arrows, A). (B) Confirmation of cleaved apoE within NFTs was confirmed following double-label immunofluorescence experiments with the cleaved apoE antibody (green) co-localizing with the tangle marker, PHF-1 (red), (arrow, B). Our custom apoE cleavage antibody also revealed punctate labeling within blood vessels. (C) Cleaved apoE was not evident within extracellular beta-amyloid plaques, although full-length APOE was readily present following co-localization with antibodies to full-length apoE4 (red) and an anti-Aβ antibody, 6E10 (green). (D) For details on these findings, please see the original article [66]. All scale bars represent 10 μm.

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

4 studies were from European populations [54-56, 59]. It is interesting to speculate on whether environmental and/or genetic factors may have played a role in these studies. For example, the relative distribution of *APOE* allele frequencies may vary across study populations, particularly in different ethnic and geographical groups. In addition, environmental factors may also provide a confounding factor in these studies including the role of diet. Diets rich in high saturated fat and cholesterol may confer added risk for the development of VaD, which would be aggravated even more in people carrying the *APOE4* alleles [61, 62]. On the other hand, carrying the *APOE4* allele does not increase the risk for dementia in countries where people have low fat diets, diets rich in omega-3 fatty acids, and more active lifestyles [63]. This may be the case for any one of the studies that found a negative association, for example if one considers the Mediterranean diet commonly found in Europe or high consumptions of fish in Asian populations. Taken together, the preponderance of data suggest that harboring one or both APOE4 alleles does confer an elevated risk for VaD, however, not to the same extent as observed in AD. A recent study evaluated the impact of *APOE4* on cognition in patients with VaD. In VaD patients, groups identified as being *APOE4* positive showed greater cognitive impairment [64], thus providing further support of the negative impact that the *APOE4* allele may have in VaD.

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 3**). 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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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Troy T Rohn, Department of Biological Sciences, Boise State University, 1910 University Drive, Boise, ID 83725, USA. Tel: 208-426-2396; Fax: 208-426-1040; E-mail: trohn@boisestate.edu

References

[1] Jellinger KA. The enigma of vascular cognitive disorder and vascular dementia. Acta Neuropathol 2007; 113: 349-388.
[2] Hebert R and Brayne C. Epidemiology of vascular dementia. Neuroepidemiology 1995; 14: 240-257.
[3] Jellinger KA. Pathology and pathogenesis of vascular cognitive impairment-a critical update. Front Aging Neurosci 2013; 5: 17.
[4] Kalaria RN. Comparison between Alzheimer's disease and vascular dementia: implications for treatment. Neurol Res 2003; 25: 661-664.
[5] Kalaria RN and Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord 1999; 13 Suppl 3: S115-123.
[6] Hachinski VC, Lassen NA and Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet 1974; 2: 207-210.
[7] Staekenborg SS, van der Flier WM, van Straaten EC, Lane R, Barkhof F and Scheltens P. Neurological signs in relation to type of cerebrovascular disease in vascular dementia. Stroke 2008; 39: 317-322.
[8] Staekenborg SS, Su T, van Straaten EC, Lane R, Scheltens P, Barkhof F and van der Flier WM. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. J Neurol Neurosurg Psychiatry 2010; 81: 547-551.
[9] Kalaria RN. Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. Stroke 2012; 43: 2526-2534.
[10] Gahr M, Nowak DA, Connemann BJ and Schonfeldt-Lecuona C. Cerebral Amyloidal Angiopathy--a disease with implications for neurology and psychiatry. Brain Res 2013; 1519: 19-30.
[11] Premkumar DR, Cohen DL, Hedera P, Friedland RP and Kalaria RN. Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. Am J Pathol 1996; 148: 2083-2095.
[12] Greenberg SM. Cerebral amyloid angiopathy and vessel dysfunction. Cerebrovasc Dis 2002; 13 Suppl 2: 42-47.
[13] Haglund M, Passant U, Sjobeck M, Ghebremedhin E and Englund E. Cerebral amyloid angiopathy and cortical microinfarcts as putative substrates of vascular dementia. Int J Geriatr Psychiatry 2006; 21: 681-687.
[14] Zarow C, Vinters HV, Ellis WG, Weiner MW, Mungas D, White L and Chui HC. Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. Ann Neurol 2005; 57: 896-903.
[15] Zarow C, Weiner MW, Ellis WG and Chui HC. Prevalence, laterality, and comorbidity of hippocampal sclerosis in an autopsy sample. Brain Behav 2012; 2: 435-442.
[16] Esiri MM, Wilcock GK and Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. J Neurol Neurosurg Psychiatry 1997; 63: 749-753.
[17] Leys D, Henon H, Mackowiak-Cordoliani MA and Pasquier F. Poststroke dementia. Lancet Neurol 2005; 4: 752-759.
[18] Aggarwal NT and Decarli C. Vascular dementia: emerging trends. Semin Neurol 2007; 27: 66-77.
[19] Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, Kawas C, Breitner JC, Fitzpatrick A and Dulberg C. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. Neurology 2005; 64: 1548-1552.
[20] Ross GW, Petrovitch H, White LR, Masaki KH, Li CY, Curb JD, Yano K, Rodriguez BL, Foley DJ, Blanchette PL and Havlik R. Characterization of risk factors for vascular dementia: the Honolulu-Asia Aging Study. Neurology 1999; 53: 337-343.
[21] in't Veld BA, Ruitenberg A, Hofman A, Stricker BH and Breteler MM. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001; 22: 407-412.
[22] Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y and Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002; 58: 1175-1181.
[23] Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE and Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 1996; 39: 1392-1397.
[24] Geroldi C, Frisoni GB, Paolisso G, Bandinelli S, Lamponi M, Abbatecola AM, Zanetti O, Guralnik JM and Ferrucci L. Insulin resistance in cog-

nitive impairment: the InCHIANTI study. Arch Neurol 2005; 62: 1067-1072.
[25] Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, Sulkava R and Kivipelto M. Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology 2010; 75: 1195-1202.
[26] van Oijen M, de Jong FJ, Witteman JC, Hofman A, Koudstaal PJ and Breteler MM. Atherosclerosis and risk for dementia. Ann Neurol 2007; 61: 403-410.
[27] Qiu C, Cotch MF, Sigurdsson S, Jonsson PV, Jonsdottir MK, Sveinbjrnsdottir S, Eiriksdottir G, Klein R, Harris TB, van Buchem MA, Gudnason V and Launer LJ. Cerebral microbleeds, retinopathy, and dementia: the AGES-Reykjavik Study. Neurology 2010; 75: 2221-2228.
[28] Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, Breteler MM and Vernooij MW. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. Neurology 2012; 78: 326-333.
[29] Weisgraber KH, Rall SC Jr and Mahley RW. Human E apoprotein heterogeneity. Cysteine-arginine interchanges in the amino acid sequence of the apo-E isoforms. J Biol Chem 1981; 256: 9077-9083.
[30] Eisenstein M. Genetics: finding risk factors. Nature 2011; 475: S20-22.
[31] Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurol 1993; 43: 1467-1472.
[32] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N and van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997; 278: 1349-1356.
[33] Pitas RE, Boyles JK, Lee SH, Hui D and Weisgraber KH. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E (LDL) receptors in the brain. J Biol Chem 1987; 262: 14352-14360.
[34] Michikawa M, Fan QW, Isobe I and Yanagisawa K. Apolipoprotein E exhibits isoform-specific promotion of lipid efflux from astrocytes and neurons in culture. J Neurochem 2000; 74: 1008-1016.
[35] Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A and Pfrieger FW. CNS synaptogenesis promoted by glia-derived cholesterol. Science 2001; 294: 1354-1357.
[36] Hayashi H, Campenot RB, Vance DE and Vance JE. Glial lipoproteins stimulate axon growth of central nervous system neurons in compartmented cultures. J Biol Chem 2004; 279: 14009-14015.
[37] Rohn TT. Proteolytic cleavage of apolipoprotein e4 as the keystone for the heightened risk associated with Alzheimer's disease. Int J Mol Sci 2013; 14: 14908-14922.
[38] Souza DR, de Godoy MR, Hotta J, Tajara EH, Brandao AC, Pinheiro Junior S, Tognola WA and dos Santos JE. Association of apolipoprotein E polymorphism in late-onset Alzheimer's disease and vascular dementia in Brazilians. Braz J Med Biol Res 2003; 36: 919-923.
[39] Liu X, Li L, Liu F, Deng S, Zhu R, Li Q and He Z. ApoE gene polymorphism and vascular dementia in Chinese population: a meta-analysis. J Neural Transm 2012; 119: 387-394.
[40] Bharath S, Purushottam M, Mukherjee O, Bagepally BS, Prakash O, Kota L, Krishnappa SB, Sivakumar PT, Jain S and Varghese M. Apolipoprotein E polymorphism and dementia: a hospital-based study from southern India. Dement Geriatr Cogn Disord 2010; 30: 455-460.
[41] Jones EL, Kalaria RN, Sharp SI, O'Brien JT, Francis PT and Ballard CG. Genetic associations of autopsy-confirmed vascular dementia subtypes. Dement Geriatr Cogn Disord 2011; 31: 247-253.
[42] Yin YW, Li JC, Wang JZ, Li BH, Pi Y, Yang QW, Fang CQ, Gao CY and Zhang LL. Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: a meta-analysis. Neurosci Lett 2012; 514: 6-11.
[43] Liu B, Shen Y, Cen L and Tang Y. Apolipoprotein E gene polymorphism in a Chinese population with vascular dementia: a meta-analysis. Dement Geriatr Cogn Disord 2012; 33: 96-103.
[44] Baum L, Lam LC, Kwok T, Lee J, Chiu HF, Mok VC, Wong A, Chen X, Cheung WS, Pang CP, Ma SL, Tang NL, Wong KS and Ng HK. Apolipoprotein E epsilon4 allele is associated with vascular dementia. Dement Geriatr Cogn Disord 2006; 22: 301-305.
[45] Frisoni GB, Bianchetti A, Govoni S, Trabucchi M, Calabresi L and Franceschini G. Association of apolipoprotein E E4 with vascular dementia. JAMA 1994; 271: 1317.
[46] Davidson Y, Gibbons L, Purandare N, Byrne J, Hardicre J, Wren J, Payton A, Pendleton N, Horan M, Burns A and Mann DM. Apolipoprotein E epsilon4 allele frequency in vascular dementia. Dement Geriatr Cogn Disord 2006; 22: 15-19.
[47] Chuang YF, Hayden KM, Norton MC, Tschanz J, Breitner JC, Welsh-Bohmer KA and Zandi PP. Association between APOE epsilon4 allele and

vascular dementia: The Cache County study. Dement Geriatr Cogn Disord 2010; 29: 248-253.

[48] Kalman J, Juhasz A, Csaszar A, Kanka A, Rimanoczy A, Janka Z and Rasko I. Increased apolipoprotein E4 allele frequency is associated with vascular dementia in the Hungarian population. Acta Neurol Scand 1998; 98: 166-168.

[49] Slooter AJ, Tang MX, van Duijn CM, Stern Y, Ott A, Bell K, Breteler MM, Van Broeckhoven C, Tatemichi TK, Tycko B, Hofman A and Mayeux R. Apolipoprotein E epsilon4 and the risk of dementia with stroke. A population-based investigation. JAMA 1997; 277: 818-821.

[50] Ji Y, Urakami K, Adachi Y, Maeda M, Isoe K and Nakashima K. Apolipoprotein E polymorphism in patients with Alzheimer's disease, vascular dementia and ischemic cerebrovascular disease. Dement Geriatr Cogn Disord 1998; 9: 243-245.

[51] Helisalmi S, Linnaranta K, Lehtovirta M, Mannermaa A, Heinonen O, Ryynanen M, Riekkinen P Sr and Soininen H. Apolipoprotein E polymorphism in patients with different neurodegenerative disorders. Neurosci Lett 1996; 205: 61-64.

[52] Kim KW, Youn JC, Han MK, Paik NJ, Lee TJ, Park JH, Lee SB, Choo IH, Lee DY, Jhoo JH and Woo JI. Lack of association between apolipoprotein E polymorphism and vascular dementia in Koreans. J Geriatr Psychiatry Neurol 2008; 21: 12-17.

[53] Nakayama S and Kuzuhara S. Apolipoprotein E phenotypes in healthy normal controls and demented subjects with Alzheimer's disease and vascular dementia in Mie Prefecture of Japan. Psychiatry Clin Neurosci 1999; 53: 643-648.

[54] Stengard JH, Pekkanen J, Sulkava R, Ehnholm C, Erkinjuntti T and Nissinen A. Apolipoprotein E polymorphism, Alzheimer's disease and vascular dementia among elderly Finnish men. Acta Neurol Scand 1995; 92: 297-298.

[55] Engelborghs S, Dermaut B, Goeman J, Saerens J, Marien P, Pickut BA, Van den Broeck M, Serneels S, Cruts M, Van Broeckhoven C and De Deyn PP. Prospective Belgian study of neurodegenerative and vascular dementia: APOE genotype effects. J Neurol Neurosurg Psychiatry 2003; 74: 1148-1151.

[56] Orsitto G, Seripa D, Panza F, Franceschi M, Cascavilla L, Placentino G, Matera MG, Paris F, Capurso C, Solfrizzi V, Dallapiccola B and Pilotto A. Apolipoprotein E genotypes in hospitalized elderly patients with vascular dementia. Dement Geriatr Cogn Disord 2007; 23: 327-333.

[57] Lin HF, Lai CL, Tai CT, Lin RT and Liu CK. Apolipoprotein E polymorphism in ischemic cerebrovascular diseases and vascular dementia patients in Taiwan. Neuroepidemiology 2004; 23: 129-134.

[58] Huang HM, Kuo YM, Ou HC, Lin CC and Chuo LJ. Apolipoprotein E polymorphism in various dementias in Taiwan Chinese population. J Neural Transm 2002; 109: 1415-1421.

[59] Traykov L, Rigaud AS, Caputo L, Couderc R, Coste J, Michot JL, de Rotrou J, Amouyel P, Forette F and Boller F. Apolipoprotein E phenotypes in demented and cognitively impaired patients with and without cerebrovascular disease. Eur J Neurol 1999; 6: 415-421.

[60] Kawamata J, Tanaka S, Shimohama S, Ueda K and Kimura J. Apolipoprotein E polymorphism in Japanese patients with Alzheimer's disease or vascular dementia. J Neurol Neurosurg Psychiatry 1994; 57: 1414-1416.

[61] Luchsinger JA, Tang MX, Shea S and Mayeux R. Caloric intake and the risk of Alzheimer disease. Arch Neurol 2002; 59: 1258-1263.

[62] Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M, Nissinen A, Tuomilehto J, Soininen H and Kivipelto M. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dement Geriatr Cogn Disord 2006; 22: 99-107.

[63] Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, Burke GL and Carlson MC. Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology 2005; 65: 1409-1414.

[64] McGuinness B, Carson R, Barrett SL, Craig D and Passmore AP. Apolipoprotein epsilon4 and neuropsychological performance in Alzheimer's disease and vascular dementia. Neurosci Lett 2010; 483: 62-66.

[65] Rohn TT, Catlin LW, Coonse KG and Habig JW. Identification of an amino-terminal fragment of apolipoprotein E4 that localizes to neurofibrillary tangles of the Alzheimer's disease brain. Brain Res 2012; 1475: 106-115.

[66] Rohn TT, Day RJ, Sheffield CB, Rajic AJ and Poon WW. Apolipoprotein E pathology in vascular dementia. Int J Clin Exp Pathol 2014; 7: 938-947.