

# FRAILTY AND VASCULAR COGNITIVE IMPAIRMENT: MECHANISMS BEHIND THE LINK

SARA GLORIA AGUILAR-NAVARRO<sup>1\*</sup>, ALBERTO JOSÉ MIMENZA-ALVARADO<sup>2</sup>, ANTONIO ANAYA-ESCAMILLA<sup>2</sup>  
AND LUIS MIGUEL GUTIÉRREZ-ROBLEDO<sup>3</sup>

<sup>1</sup>Department of Geriatrics and <sup>2</sup>Neuro-Geriatric Program, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; <sup>3</sup>National Institute of Geriatrics, Mexico City, Mexico

## ABSTRACT

The relationship between frailty and cognitive impairment has been recognized for decades, but it was not until a few years ago that the interest in this relationship increased and is now being understood. Epidemiological evidence suggests that physical frailty may be linked to cognitive impairment since both conditions share pathophysiological mechanisms at the cellular and systemic levels. Aging itself promotes multiple vascular changes, making the brain susceptible to cognitive decline through mechanisms such as thinning of blood vessels, increased collagen accumulation, rupture of the blood-brain barrier, inflammation, and oxidative damage. The prevalence of frailty and cognitive decline increases as individuals become older, and cognitive impairment attributable to cerebrovascular disease has become a major public health problem since vascular dementia is now the second most common subtype of dementia. However, full understanding of the mechanisms underlying the relationship between frailty and vascular cognitive impairment remains fragmented. This review examines the link between frailty and vascular cognitive decline and also explores the role of vascular changes in the genesis of both conditions. (REV INVES CLIN. 2016;68:25-32)

**Key words:** Frailty. Vascular cognitive impairment. Molecular vascular risk.

## INTRODUCTION

The frailty syndrome is characterized by the loss of physiological reserves and resilience, leading older adults towards an elevated risk of declines in health and function. In the last two decades, the concept has gained general interest although its relationship with various biomarkers of aging remains debatable<sup>1</sup>. The frailty phenotype has been operationally defined by

the presence of at least three of the five following criteria: unintentional weight loss, weakness, exhaustion, slowness, and low level of physical activity. Identifying frailty in older adults is relevant as it helps clinicians recognize those at increased vulnerability for adverse health-related outcomes, including premature death, hospitalization, and disability<sup>2</sup>. Several studies have shown that frailty is associated with impaired cognitive performance and has been proposed

### Corresponding author:

\*Sara Gloria Aguilar-Navarro  
Department of Geriatrics  
Instituto Nacional de Ciencias Médicas y Nutrición  
Salvador Zubirán  
Vasco de Quiroga, 15  
Col. Sección XVI, Del. Tlalpan,  
C.P. 14000, Ciudad de México, México  
E-mail: sgan30@hotmail.com

Received for publication: 30-11-2015  
Accepted for publication: 30-12-2015

as a risk factor for both dementia and mild cognitive impairment (MCI)<sup>3,4</sup>. Pathophysiological mechanisms, such as subcellular disturbances (e.g., oxidative stress and protein misfolding), systemic disorders, as well as impaired maintenance of mitochondrial function (failures in chaperone proteins, autophagy) are common features in frail and cognitively impaired people as well<sup>5</sup>. Disturbances in hematological and inflammatory pathways leading to a catabolic status and endothelial dysfunction could also be responsible for the association between frailty and multiple cardiovascular diseases including vascular dementia<sup>6</sup>. On the other hand, cerebrovascular disease (CVD) is a well-known determinant of cognitive decline in older adults. Cerebrovascular disease is a marker of atherosclerosis; for example, an increased thickness of the carotid intima-media has been associated with a greater presence of silent cerebral infarcts, higher white matter hyperintensity (WMH), and further decline of cognition<sup>7,8</sup>.

Despite being biologically plausible, the relationship between frailty and cognitive impairment has been inconsistently reported, and the pathophysiological bases remain under consideration<sup>9,10</sup>. Recent evidence suggests that CVD, via vascular endothelial dysfunction (e.g., impaired signaling molecules), is present among both cognitively impaired and frail persons. In this regard, the altered synthesis of nitric oxide (NO) by the endothelium has been implicated as a potential factor in the genesis of CVD<sup>11</sup>. Even though the relationship between frailty and Alzheimer's disease (AD) is yet to be clarified, the one between frailty and vascular dementia has proven more consistent<sup>12,21</sup>. In fact, a cognitive domain has been proposed as another criterion of frailty; as it adds cognition to the conventional frailty phenotype, it improves its predictive value for adverse health-related outcomes. Furthermore, frail individuals have a higher risk of cognitive decline and dementia in comparison to their non-frail counterparts and *vice versa*<sup>13</sup>. The purposes of this review are to examine the mechanisms underlying the relationship between frailty and cognitive decline and to explore the role of vascular changes in these conditions.

## FRAILITY AND COGNITIVE IMPAIRMENT

A number of epidemiological studies have reported that frailty increases the risk of cognitive decline and that cognitive impairment in turn elevates the risk of being

frail, suggesting that both conditions interact within a cycle of an aging-associated decline<sup>13</sup>. It is biologically plausible that both conditions share pathophysiological mechanisms, but previous research remains inconclusive around this issue<sup>14</sup>.

The concept of a frailty phenotype is relatively well understood in the context of aging, and has been used in studies conducted over the past two decades. However, how the cognition domain should be included within this concept is still under debate. The term "cognitive frailty" has emerged and is attractive as a suggestion of an existing parallel between aging, physical frailty, and cognitive function. Although cognitive frailty may seem useful in common practice, its actual use remains controversial. Kelaiditi, et al. state that cognitive frailty must be considered as being independent of dementia or pre-existing brain disorders, even if both conditions share several pathophysiological mechanisms and risk factors<sup>15,16</sup>.

The important role of the central nervous system in frailty manifestations has been postulated since the central components of frailty, such as problems in gait or balance, can be related to neurological disturbances. Previous investigation has shown that impaired physical performance (measured by walking speed or the Short Physical Performance Battery [SPPB]) is an independent risk factor for cognitive decline<sup>17</sup>. Execution of the SPPB test (including walking speed, balance, and chair stands) requires the complex interplay of sensory, cognitive, and motor functions, which could be impaired early in the pathway to cognitive decline<sup>18</sup> and be expressed as frailty. A secondary analysis of the Rush Memory and Aging Project (a cohort study of aging and dementia) showed a postmortem association between common age-related brain disorders (including cerebral infarctions, Lewy body pathology, and AD pathology) and the frailty phenotype. Their results showed that subjects who were frail before death had more postmortem evidence of AD pathology compared to non-frail participants, an association independent of a previous dementia diagnosis<sup>19</sup>.

Considering the cognition domain (in the frailty phenotype) has improved the identification of frail persons at risk of adverse health-related outcomes. Avila-Funes, et al. proved that cognitively impaired frail individuals had higher risk of disability and incidental hospitalization compared with their non-frail counterparts, even

after adjusting for potentially confounding variables<sup>20</sup>. Nevertheless, it seems that a frail status is more strongly associated with the risk of incident vascular dementia even after adjustment for many potential confounders<sup>21</sup>. Within the same line of study, Gray, et al. in the Adult Changes in Thought (ACT) Study explored the association between frailty and incident AD and non-AD dementia type. In this population-based study, frailty was associated with a 2.6-fold increased risk for non-AD dementia subtypes, but the authors are inconclusive about the underlying mechanisms<sup>22</sup>. The relationship between frailty and cognitive impairment could be bidirectional, but in light of these studies, the frailty phenotype probably represents a physiological state that occurs before non-AD cognitive impairment, suggesting that frailty is a prodromal state of non-degenerative dementia.

On the other hand, cognitive performance probably plays a role in the prognosis of frail individuals. A recent study conducted in Hong Kong aiming to establish the transition between the different frailty states showed that at baseline, among pre-frail older adults (Fried's criteria 1 or 2), 23.4% of men and 26.6% of women improved to non-frail status after two years of follow-up, and 11.1% of men and 6.6% of women worsened to frailty<sup>23</sup>. In this study, among pre-frail men, a higher Mini-Mental State Examination (MMSE) score was inversely associated with frailty, suggesting that a lower cognitive performance could be a marker for future frailty. Another study suggests a low cognitive performance as a risk factor for dementia rather than frailty *per se*, since the risk was seen only in the subject subgroups that presented both frailty syndrome criteria in addition to low cognitive performance, and the risk was not present in those showing only frailty phenotype<sup>20</sup>.

## VASCULAR COGNITIVE IMPAIRMENT

Vascular pathology of the aging brain and AD includes cerebral amyloid angiopathy, which leads to lobar mass hemorrhages, small or recurrent bleeds and ischemic infarcts, microvascular degeneration, disorder of the blood-brain barrier, white matter lesions, microinfarcts, lacunes, and cerebral hemorrhages<sup>24</sup>. Beyond the possible role of vascular risk factors and vascular-related diseases, there are several potential pathways by which frailty could contribute to cognitive decline.

Cognitive impairment attributable to CVD has been termed "vascular cognitive impairment" (VCI), which is related not only with cortical or subcortical infarcts, but also with small vessel disease (WMH, lacunar infarcts, and microbleeds) inducing ischemic and hemorrhagic brain injury<sup>25</sup>. Recently, hypertension<sup>26</sup>, diabetes<sup>27</sup>, and dyslipidemia<sup>28</sup>, among others, have been identified as risk factors of CVD as well as cognitive impairment, explaining a large proportion of cases of small vessel disease, but not all. Although several monogenic forms in early onset of small vessel disease have been described among patients with VCI, most are sporadic cases with an increased frequency in the familial aggregation, but with no clear Mendelian inheritance pattern<sup>29,30</sup>.

The most widely investigated genetic variants are the single nucleotide polymorphisms (SNP), which are bi-allelic variants in the human genome involving a nucleotide exchange. Certain SNPs have been associated with lesion development in the cerebral white matter. A meta-analysis of Paternoster, et al. identified 46 genetic studies of polymorphisms in 19 genes in a total of  $\approx 19,000$  subjects<sup>31</sup>. The CHARGE (Cohorts for Health and Aging Research in Genomic Epidemiology) consortium is an investigator-initiated collaboration to facilitate genome-wide association studies (GWAS) meta-analyses among multiple large and well-phenotyped cohort studies, with cerebral magnetic resonance imaging (MRI) and genome data<sup>32</sup>. Seven community-based cohorts included in this study performed a GWAS for WMH burden in 9,361 stroke-free European descent individuals; results identified six novel risk-associated SNPs in one locus of chromosome 17q25 all encompassing six known genes: WBP2, TRIM65, TRIM47, MRPL38, FBF1, and ACOX1. The most significant association with cerebral white matter lesion was rs3744028. Other polymorphisms of a single nucleotide were rs9894383, rs936393, rs3744017, and rs1055129. Variant alleles at these loci conferred a small increase in WMH burden (4-8% of the overall mean WMH). This study provides the first characterization of this new locus on chromosome 17 as a possible factor contributing to pathophysiology associated with WMH burden of individuals of European descent<sup>33</sup>.

Apolipoprotein E (*APOE*) is a gene that has been linked to the vascular and amyloid metabolism. The homozygosity for *APOE*  $\epsilon 4$  allele has been associated with the presence of small vessel disease, higher volumes of WMH, and lacunar infarcts. In addition, the results

of the Austrian Stroke Prevention study suggest an association between *APOE*  $\epsilon$ 2 expression and the presence of WMH and lacunar infarction, while the Rotterdam scan study also reported higher prevalence of cerebral microbleeds among *APOE*  $\epsilon$ 4 allele carriers<sup>34-36</sup>.

On the other hand, the genes involved in VCI must be of two non-reciprocal exclusive classes: (i) those which predispose to CVD, and (ii) those which determine the tissue response to CVD (e.g., genes conveying tolerance or susceptibility to ischemia or the ability to recover from ischemia). The two best-studied monogenetic forms of CVD are the cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and the hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D). In contrast, little is known about the second class of genes, but evidence of their existence is seen in patients with a similar vascular pathology load (type of injury, number, and location), differing in the severity of cognitive impairment<sup>37</sup>.

It is also possible that some genetic factors contribute to the development of conventional cardiovascular risk factors (such as hypertension, diabetes, or hyperhomocysteinemia), which may also interact with environmental factors or contribute directly to an intermediate phenotype<sup>38</sup>.

The *NOTCH3* gene has been associated with development of CVD. The *NOTCH3* gene (a heterodimer composed of a large extracellular fragment and a smaller transmembrane intracellular fragment) is normally expressed in vascular smooth-muscle cells and pericytes (including those of the cerebral vasculature). *NOTCH3* encodes a cell-surface receptor related to cellular proliferation and to differentiation and survival of vascular smooth muscle. Mutations in the *NOTCH3* gene have been associated with the development of CADASIL. About 95% of patients with CADASIL have missense mutations that cluster in exons 3-4 and consist in changes of cysteine residues, but the pathogenic mechanism associated with this mutation is still unknown<sup>39</sup>.

## CONTRIBUTION OF VASCULAR DISTURBANCE TO NEURODEGENERATION

Neuroinflammation is a key component in AD and CVD, involving the proliferation of microglia and astrocytes,

transcription factor activation (nuclear factor kappa beta [NF- $\kappa$ β]), and upregulation of inflammatory cytokines (tumor necrosis factor alpha [TNF- $\alpha$ ], interleukin [IL]-1 $\beta$ , prostaglandin E2, reactive oxygen and nitrogen species)<sup>40</sup>.

Based on epidemiological studies, Thiel, et al. propose two hypothesis linking AD and CVD. The first is the hypothesis of "independence", which assumes that multiple cortical or subcortical ischemic events cause neuronal loss, leading to a decrease in neuronal connectivity and a sudden decrease in cognitive function, from which patients could recover. In case of additional presence of AD pathology, these vascular ischemic processes decrease the cerebral reserve's capacity to compensate the ongoing neurodegeneration as well as to restore cognitive function<sup>41</sup>. The second is the hypothesis of "interaction", which states that patients with cognitive impairment at the time of a stroke have a higher risk of developing dementia, suggesting that ischemic stroke triggers additional pathways to degenerative processes and accelerates ongoing neurodegeneration<sup>42,43</sup>.

## THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) plays an important role in vascular regulation, inflammation, oxidative stress, and apoptosis. RAS contributes to the pathogenesis of several human diseases that have a clear association with advanced aging, including hypertension, myocardial infarction, congestive heart failure, atrial fibrillation, coronary artery disease, diabetes, nephropathy, stroke, dementia, and even frailty<sup>44</sup>. The RAS disturbances may be involved in the occurrence of cerebral vascular lesions. Hypertension induces damage to brain microcirculation, contributing to the development of dementia. However, evidence of benefit from RAS blockers on cognitive function has been controversial. RAS is a major regulator of systemic blood pressure and cerebral blood flow; therefore, gene polymorphisms in the RAS coding are excellent candidates for cerebral small vessel disease. The plasmatic angiotensinogen (AGT, GenBank ID183) synthesized by the liver is converted to angiotensin II (Ang II) by the serial action of renin and angiotensin-converting enzyme (ACE GenBank ID1636). The association between ACE I/D (insertion/deletion) polymorphism and WMH has been investigated in nine

studies, and the deletion-deletion genotype is a significant predictor of WMH. The most frequently studied SNP in the *AGT* gene is the M235T; it is possible, however, that this polymorphism *per se* is not the causal mechanism but a functional variant. One of them might be a haplotype (-6:a, -20:c, -153:g, -218:g, positions relative to transcriptional start site) at the *AGT* promoter. The Austrian Stroke Prevention Study described the association between this haplotype and greater severity of WMH, which was independent of hypertension, and the haplotype enhanced the basal transcriptional activity of the *AGT* promoter in astrocytes but not in hepatocytes, suggesting that this association is mediated by disturbances in activity of cerebral and not the systemic RAS<sup>45</sup>. Another study showed that the rate of progression of WMH in elderly males is influenced by polymorphisms in genes of angiotensinogen (*AGTR1* and *AGTR2*). Homozygous individuals for the 1166A allele in the *AGTR1* gene had less changes in cerebral white matter in comparison with carriers of the 1166C allele<sup>46</sup>.

## AGING AND NEUROVASCULAR UNIT

Pericytes, microglia, mast cells, oligodendroglia, and neurons respond to an ischemic event or an inflammatory stimulus by activation. While the individual features of specific cell responses are known, it is not understood how they respond as a whole. It is essential to understand these interactions because processes leading to injury in one compartment of the neurovascular unit (which includes perivascular neurons, astrocytes, endothelial cells, and vascular smooth muscle cells) probably affect other compartments, potentially irreversibly unless the initial event is limited. Furthermore, aging could modify these inflammatory responses in unclear ways. Interactions between components of the neurovascular unit and their responses to external stimuli are an open field for research<sup>47</sup>.

Vascular disturbances may precede neuronal changes in dementia syndromes. A decline in cerebrovascular function includes a decrease in cerebral blood flow in different parts of the brain such as limbic and association cortex<sup>48</sup>. Studies have shown that in comparison with subjects without the *APOE*  $\epsilon$ 4 allele, carriers of the *APOE*  $\epsilon$ 4 allele without neurological disease have lower cerebral blood flow in several brain regions, rendering them more vulnerable to AD pathology<sup>46</sup>.

## NEUROVASCULAR PATHOLOGY AND AGING

Aging leads to normal vascular changes, including thinning of blood vessels, decreased capillary density, increased endothelial pinocytosis, decreased mitochondrial content, increased collagen accumulation, and rupture of the blood-brain barrier (BBB)<sup>49</sup>. Reduction in the BBB of GLUT1-mediated glucose transport across the plasmatic membranes decreases glucose uptake by the BBB, which predisposes to cerebral atrophy and impairment of cognitive function<sup>50,51</sup>.

Furthermore, angioneurins are growth factors with neurotrophic properties. Vascular endothelial growth factor regulates vessel formation, neuronal survival, and axonal growth. Ephrin, semaphorin, and netrins are factors that regulate the function of axons as well as the development of the vascular system<sup>52</sup>.

An important aspect in the pathophysiology of VCI is the role of inflammation: the incidence of VCI is influenced by gene polymorphisms of inflammatory mediators (IL-1, IL-6, TNF- $\alpha$ , toll-like receptor 4, E and P selectin, and C-reactive protein), lipid metabolism (*APOE*), NO, and extracellular matrix (matrix metalloproteinase)<sup>53</sup>. During a stroke, the microglia increases brain inflammation, releasing a wide variety of inflammatory mediators and free radicals until ultimately reaching its quiescent state. All of these mechanisms contribute to neuronal damage and eventually lead to cellular death. The development of VCI may then result from various pathological processes, including vascular damage, predisposition to cognitive impairment, as well as the number and type of vascular injuries (small or large vessel)<sup>48</sup>. Figure 1 shows neurovascular changes and their effect on VCI.

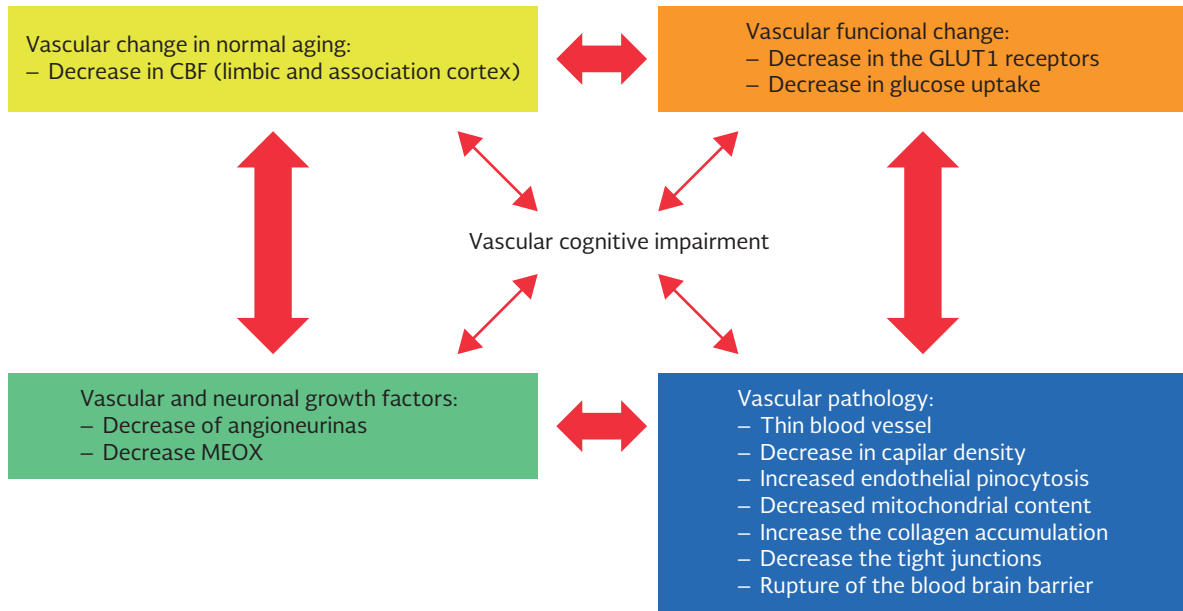
## POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS BETWEEN FRAILTY AND VASCULAR COGNITIVE IMPAIRMENT

The mechanisms linking cognitive impairment and frailty could be associated to endothelial dysfunction within a pro-inflammatory environment with increased oxidative stress<sup>54</sup>. Atherosclerosis could be a common biological pathway that explains how frailty and CVD are inter-related, as could also be the interaction between multiple factors such as aging, inflammation, and activation of the blood coagulation and fibrinolytic systems<sup>55</sup>.

Figure 1. Neurovascular changes and their effect on vascular cognitive impairment.

Vascular cognitive impairment is a consequence of vascular aging. This determines changes in vascular function (such as decrease in GLUT 1 receptors, resulting in decrease in glucose uptake). Also, others factors reduce vascular and neuronal growth; furthermore, through the vascular aging, changes in the blood vessels (thinning, decrease in capillary density, increased accumulation of collagen, among others). All these changes are related to each other and converge in the pathophysiological process of the vascular cognitive impairment.

CBF: cerebral blood flow.



It is difficult, however, for only one mechanism to explain incident VCI or even frailty. Frailty is related with multiple chronic diseases and a functional decline, which requires a greater amount of energy; this condition could then explain why mitochondrial metabolism produces higher quantities of free radicals<sup>56</sup>. At the same time, this increased production of free radicals could also activate the NF- $\kappa$ B pathway, which in turn leads to inflammation<sup>57</sup>. Immune disturbances have a systemic impact. The accumulation of mitochondrial and nuclear DNA damage can compromise the integrity of the cell, leading to loss of myocytes and muscle wasting, both cornerstone features of frailty<sup>58</sup>. Chronic inflammation as a process of aging (inflamm-aging) has been associated with poor physical performance and weakness. A recent review also suggested that since the central nervous system and the immune system are in constant interaction, inflammation in one area of the body might promote inflammation in the brain. An inflammatory response in cerebrovascular areas may trigger another response in the blood-brain barrier and release inflammatory cytokines into the brain<sup>59</sup>. For example, IL-6 interrupts adult neurogenesis and, considering IL-6 receptors are expressed

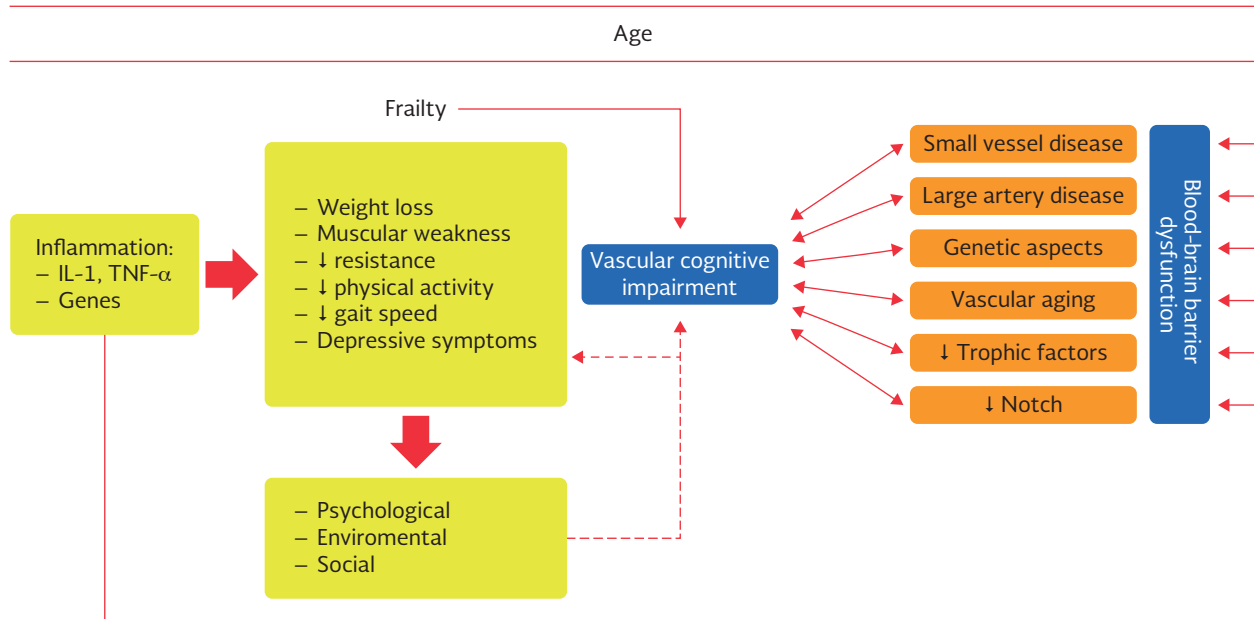
in the hippocampus and pre-frontal cortex, this constant inflammatory state could have serious consequences for cognitive function, particularly in memory and executive functions<sup>60,61</sup>.

## CONCLUSIONS

Frailty and cognitive impairment are closely related. Aging promotes cellular and molecular accumulative damage, which can be evidenced through laboratory measurements and histopathology. Hypertension, diabetes, and hypercholesterolemia are well-known risk factors for cognitive impairment such as AD and VCI in later-life. The increased permeability of the blood-brain barrier in people with WMH plays a causal role in the development of lacunar infarcts. VCI and frailty are closely inter-related. Understanding the relationship between cognition and frailty is useful because frail individuals have a higher risk of cognitive impairment and vice versa. In addition, understanding the link between frailty and VCI may lead to interventions aimed at preventing and treating both conditions. Clinical trials on any type of dementia should consider including frail



Figure 2. Possible interaction between frailty and vascular cognitive impairment. IL: interleukin; TNF: tumor necrosis factor.



elderly subjects since frailty appears to lead to an expression of disease that may be the neuropathological key to expressing the deleterious effects in classic dementia (Fig. 2).

## REFERENCES

- Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med*. 2010;26:275-86.
- Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-56.
- Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc*. 2010;58:248-55.
- Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment—a review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12:840-51.
- Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci*. 2014;69:1536-44.
- Inglés M, Gambini J, Carnicero JA, et al. Oxidative stress is related to frailty, not to age or sex, in a geriatric population: lipid and protein oxidation as biomarkers of frailty. *J Am Geriatr Soc*. 2014;62:1324-8.
- Avila-Funes AJ, Meillon C, González-Colaço Harmand M, Tzourio C, Dartigues JF, Amieva H. Association between frailty and carotid central structure changes: The Three-City Study. *J Am Geriatr Soc*. 2014;62:1906-11.
- Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2672-713.
- Halil M, Cemal Kizilarlanoglu M, Emin Kuyumcu M, Yesil Y, Cruz Jentoft AJ. Cognitive aspects of frailty: mechanisms behind the link between frailty and cognitive impairment. *J Nutr Health Aging*. 2015;19:276-83.
- Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosom Med*. 2007;69:483-9.
- Alonso-Bouzon C, Carcaillon L, García-García FJ, Amor-Andrés MS, El Assar M, Rodríguez-Mañas L. Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. *Age (Dordr)*. 2014;36:495-505.
- Song X, Mitnitski A, Rockwood K. Age-related deficit accumulation and the risk of late-life dementia. *Alzheimers Res Ther*. 2014;6:54.
- Woods AJ, Cohen RA, Pahor M. Cognitive frailty: Frontiers and challenges. *J Nutr Health Aging*. 2013;17:741-3.
- Samper-Ternent R, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Relationship between frailty and cognitive decline in older Mexican Americans. *J Am Geriatr Soc*. 2008;56:1845-52.
- Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17:726-34.
- Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment: A review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12:840-51.
- Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. *J Neurol Neurosurg Psychiatr*. 2007;78:929-35.
- Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332:556-61.
- Bennett DA, Wilson RS, Arvanitakis Z, Boyle P, Toledo-Morrell L, Schneider J. Selected findings from the Religious Orders Study and Rush Memory and Aging Project. *J Alzheimers Dis*. 2013;33(Suppl 1):S397-403.
- Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the Three-City Study. *J Am Geriatr Soc*. 2009;57:453-61.
- Avila-Funes JA, Carcaillon L, Helmer C, et al. Is frailty a prodromal stage of vascular dementia? Results from the Three-City Study. *J Am Geriatr Soc*. 2012;60:1708-12.
- Gray SL, Anderson ML, Hubbard RA, et al. Frailty and incident dementia. *J Gerontol A Biol Sci Med Sci*. 2013;68:1083-90.
- Lee JS, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. *J Am Med Dir Assoc*. 2014;15:281-6.
- Jellinger KA. Alzheimer's disease and cerebrovascular pathology: an update. *J Neural Transm*. 2002;109:813-36.

25. Jellinger KA. Morphologic diagnosis of "vascular dementia" - a critical update. *J Neurol Sci.* 2008;270:1-12.
26. Kimura S, Saito H, Minami M, et al. Pathogenesis of vascular dementia in stroke-prone spontaneously hypertensive rats. *Toxicology.* 2000;153:167-78.
27. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. *Nat Rev Endocrinol.* 2011;7:108-14.
28. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry.* 2008;16:343-54.
29. Schuur M, Swieten JCV, Schol Gelok S, et al. Genetic risk factors for cerebral small vessel disease in hypertensive patients from a genetically isolated population. *J Neurol Neurosurg Psychiatry.* 2011;82:41-4.
30. Freudenberger P, Schmidt R, Schmid H. Genetics of age-related white matter lesions from linkage to genome-wide association studies. *J Neurol Sci.* 2012;322:82-6.
31. Paternoster L, Chen W, Sudlow CLM. Genetic determinants of white matter hyperintensities on brain scans; a systematic assessment of 19 candidate gene polymorphisms in 46 studies in 19,000 subjects. *Stroke.* 2009;40:2020-6.
32. Psaty BM, O'Donnell CJ, Gudnason V, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet.* 2009;2:73-80.
33. Fornage M, Debette S, Bis JC, et al. Genome-wide association studies of cerebral white matter lesion burden: the CHARGE Consortium. *Ann Neurol.* 2011;69:928-39.
34. Hirono N, Yasuda M, Tanimukai S, Kitagaki H, Mori E. Effect of the apolipoprotein E epsilon4 allele on white matter hyperintensities in dementia. *Stroke.* 2000;31:1263-8.
35. Schmidt R, Schmidt H, Fazekas F, et al. Apolipoprotein E polymorphism and silent microangiopathy-related cerebral damage. Results of the Austrian Stroke Prevention Study. *Stroke.* 1997;28:951-6.
36. Poels MMF, Vernooij MW, Ikram MA, et al. Prevalence and risks factors of cerebral microbleeds: an up-date of the Rotterdam scan study. *Stroke.* 2010;41(Suppl 10):S103-6.
37. Ungaro C, Mazzei R, Conforti FL, et al. CADASIL: extended polymorphisms and mutational analysis of the *NOTCH3* gene. *J Neuroscience Res.* 2009;87:1162-7.
38. Dichgans M. Genetics of ischemic stroke. *Lancet Neurol.* 2007;6:149-61.
39. Ikram MA, Seshadri S, Bis JC, et al. Genomewide Association Studies of Stroke. *N Engl J Med.* 2009;360:1718-28.
40. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol.* 2009;8:1006-18.
41. Thiel A, Cechetto DF, Heiss W-D, Hachinski V, Whitehead SN. Amyloid Burden, neuroinflammation and links to cognitive decline after ischemic stroke. *Stroke.* 2014;45:2825-9.
42. Rist PM, Chalmers J, Arima H, et al. Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. *Stroke.* 2013;44:1790-5.
43. Huang KL, Lin KJ, Ho MY, et al. Amyloid deposition after cerebral hypoperfusion: evidenced on [(18)F]AV-45 positron emission tomography. *J Neurol Sci.* 2012;319:124-9.
44. Abadir PM. The frail renin-angiotensin system. *Clin Geriatr Med.* 2011;27:53-65.
45. Schmid H, Freudenberger P, Seiler S, Schmidt R. Genetics of subcortical vascular dementia. *Exp Gerontol.* 2012;4:873-7.
46. Taylor WD, Steffens DC, Ashley-Koch A, et al. Angiotensin receptor gene polymorphisms and 2 year change in hypertensive lesion volume in men. *Mol Psychiatry.* 2010;15:816-22.
47. Thambisetty M, Beason HL, An Y, Kraut MA, Resnick SM. APOE epsilon4 genotype and longitudinal changes in cerebral blood flow in normal aging. *Arch Neurol.* 2010;67:93-8.
48. Del Zoppo GJ. Aging and the neurovascular unit. *Ann NY Acad Sci.* 2012;1268:127-33.
49. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci.* 2011;12:723-38.
50. Popa-Wagner A, Buga AM, Popercu B, Muresanu D. Vascular cognitive impairment, dementia, aging and energy demand. A vicious cycle. *J Neural Transm.* 2015;122:547-54.
51. Brown WE, Thore CR. Review: Cerebral microvascular pathology in aging and neurodegeneration. *Neuropathol Appl Neurobiol.* 2011;37:56-74.
52. Mosconi L, De Santi S, Li J, et al. Hippocampal hypometabolism predicts cognitive decline from normal aging. *Neurobiol Aging.* 2008;29:676-92.
53. Lemolo F, Duro G, Rizzo C, Castiglia L, Hachinski V, Caruso C. Pathophysiology of vascular dementia. *Immun Ageing.* 2009;6:1-13.
54. Rodriguez-Mañas L, El-Assar M, Vallejo S, et al. Endothelial dysfunction in aged humans is related with oxidative stress and vascular inflammation. *Aging Cell.* 2009;8:226-38.
55. Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. *J Nutr Health Aging.* 2011;15:857-62.
56. Searle SD, Rockwood K. Frailty and the risk of cognitive impairment. *Alzheimers Res Ther.* 2015;7:54.
57. Piette J, Piret B, Bonizzi G, et al. Multiple redox regulation in NF-kB transcription factor activation. *J Biol Chem.* 1997;272:1237-45.
58. Jensen GL. Inflammation: roles in aging and sarcopenia. *J Parenter Enteral Nutr.* 2008;32:656-9.
59. Rosano C, Marsland AL, Gianaros PJ. Maintaining brain health by monitoring inflammatory processes: a mechanism to promote successful aging. *Aging Dis.* 2012;3:16-33.
60. Chung HY, Cessari M, Anton S, et al. Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Res Rev.* 2009;8:18-30.
61. Leblanc GG, Meschia JF, Stuss DT, Hachinski V. Genetics of vascular cognitive impairment: The opportunity and the challenges. *Stroke.* 2006;37:248-55.