Chapter 5
The Role of Cerebrovascular Disease in Cognitive Decline

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Abstract Vascular risk factors and cerebrovascular disease are recognized factors implicated in the evolution toward dementia, not only of vascular origin but also degenerative dementia as Alzheimer's disease. Even among nondemented subjects, hypertension, diabetes, and stroke are associated with worse performance in attention, executive functions, and speed and motor control. Influence of vascular risk factors in cognition starts early in life. Treatment and control of vascular risk factors since early ages has a key role in order to prevent cognitive impairment associated with aging. Cerebral white matter changes have gained attention in the last decades and can represent a potential outcome in experimental studies aiming to reduce cerebrovascular burden.

Keywords Vascular risk factors • Hypertension • Diabetes • Stroke • White matter changes • Lacunes • Microbleeds

Vascular risk factors and cerebrovascular disease of the brain are recognized factors that influence cognition and are implicated in the evolution toward dementia, not only of vascular origin but also degenerative dementia as Alzheimer's disease.

This chapter has two different sections. The first section covers the impact of main vascular factors in cognition and in the risk of dementia. As small vessel disease is closely linked to vascular risk factors and represents one of the consequences of several vascular risk factors measured in the brain; we approach, in the second section, the impact of cerebral small vessel disease in cognition and in dementia.

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Role of Vascular Risk Factors in Cognition

Vascular risk factors have been implicated in cognitive decline and dementia (including degenerative dementia). Among the whole spectrum of vascular risk factors, hypertension, stroke, and diabetes seem to play the most important role [1–12]. Before exploring evidence that supports the relationship between some of the major risk factors and cognitive impairment, we present two concepts that have evolved in past years. The first is that cognitive decline is insidious and slowly developing starting early in life, around the fourth decade [13]. This is probably one of the explanations for many of the controversial data concerning some of the vascular risk factors, namely, cholesterol blood levels and body mass index [14–18]. It is likely that these pathologies contribute to cognitive decline mainly when present in midlife.

The second concept is that the interaction between several cardiovascular risk factors contributes more strongly for cognitive decline than isolated risk factors [4, 16]. A systematic review stressed that the risk of dementia in diabetes is increased when associated with other vascular risk factors, phenomena that were also identified for other risk factors [4, 16, 19], mainly if they are concomitantly present in midlife [4, 20].

Role of Diabetes in Cognition

Diabetes has increasingly been identified as a risk factor for cognitive impairment and dementia [12, 21, 22], including Alzheimer's disease [23]. Among nondemented subjects, diabetics have worse cognitive performance when compared to nondiabetics [7, 22, 24] in global tests of cognition [25], attention, executive functions, processing speed and motor control, and also memory, praxis, and language [25, 26], independently of other confounders. Diabetic subjects have a twofold increase in risk for mild cognitive impairment and dementia compared with diabetics [7, 12, 27, 28].

Diabetes has several pathways to be implicated in the progression for dementia, not only due to the higher risk of vascular disease but also mediated through metabolic changes due to the insulin and glycemia pathways that are implicated in the metabolic production of beta-amyloid protein and tau protein [21], promoting neuronal degeneration [29] and thus implicated in pathogenesis of Alzheimer's disease [7, 30, 31]. Moreover, recent data suggest a genetic link between diabetes and the pathogenesis of Alzheimer's disease [32, 33].

Role of Stroke in Cognition

Stroke is a well-recognized risk factor for cognitive impairment in prospective community studies [1, 8, 28, 34, 35] and is associated with a twofold risk of dementia [35], not only for vascular dementia and vascular cognitive impairment but also for degenerative dementias such as Alzheimer's disease [35].

The higher risk of dementia in stroke survivors can be partially explained by concomitant vascular factors [36] and by prestroke dementia, but this is not the only explanation [35–37]. Nondemented stroke survivors have worse performance in tasks of attention and executive functions [25] compared with subjects without stroke. On the other hand, small vessel disease predicts vascular dementia [38], even without clinical stroke.

The clear impact of stroke on the development of degenerative types of dementia is not well established. Although a higher risk of Alzheimer's disease is associated with stroke, the pathological association between the two diseases is not clear.

Neuropathological data suggested that vascular disease could affect cognition, not only through the effects on subcortical connections and white matter disease but also exacerbating cortical atrophy [34, 39]. One of the likely explanations could be that vascular acute events anticipate incipient cognitive impairment due to concomitant amyloid pathology or otherwise have a synergistic or additive effect to develop degenerative dementia.

Role of Hypertension in Cognition

There is a considerable controversy between studies approaching some of the vascular risk factors and cognitive decline. One of the examples is the effect of hypertension. One of the most important variables that explain differences between studies considering hypertension is age of included subjects in those studies. Hypertension in midlife has been consistently associated with later development of cognitive decline and dementia. Although the strongest association is with vascular dementia, there is also an increased risk of degenerative dementia as Alzheimer's disease [1, 4, 11, 40–43]. Recently, it was indeed suggested that hypertension was associated with greater amyloid burden not only in middle-aged but also among older adults [44]. Treatment with antihypertensive treatment was associated with reduced hippocampus atrophy in hypertensive subjects [45] and with less Alzheimer's disease neuropathology [46].

However, the relationship between late-onset hypertension and cognitive decline and dementia is less clear: some studies were negative for this association [5, 6, 47] or sustain that a very low systolic and/or diastolic value was associated with higher risk of cognitive decline [41, 42].

In cross-sectional studies among nondemented subjects, hypertension in late life was associated with worse performance in several cognitive tests mainly related with executive functions and attention, digit symbol test, and word fluency [48] but also difficulties in some global cognitive functioning tests [27, 49, 50]. The most likely explanation for these discrepancies is that the deleterious effect of hypertension is due to chronic vascular damage starting in midlife that later originates cognitive impairment [43]. Results from trials focusing on the prevention of dementia using antihypertensive medication have failed to show a consistent protective effect, sustaining this explanation [51, 52]. From the six main randomized placebo-controlled

studies, four were negative for a protective effect [53–56], one found a small effect on the prevention of dementia [57], and the other [58] found a protective effect only for poststroke dementia. In fact those studies were probably performed in older ages than what was desirable to prevent dementia, and, additionally, the follow-up was short.

Role of Alcohol Intake and Smoking in Cognition

The influence of alcohol intake on brain structure and cognition has been a focus of interest in late years. In the Leukoaraiosis And DISability (LADIS) study [25], among subjects with white matter changes free of dementia and living independently, mild and moderate alcohol consumption was associated with better performance on global measures of cognition compared to nondrinkers (included never drinkers), but this relation was lost overtime [25, 38]. Low or moderate alcohol intake was associated with reduced risk of Alzheimer's disease in a systematic review with meta-analysis, compared to the risk of dementia in nondrinkers [59]. In this review, nondrinkers had a small higher risk compared also with excessive drinkers. However, nondrinkers could include former excessive drinkers that stopped consuming due to health problems [59]. Recently, a study conducted among older subjects could not find evidence that moderate alcohol intake could prevent cognitive decline [60]. Considering imaging data, brain atrophy was associated with alcohol intake even for low drinkers [61], and controversial effects on white matter changes (WMC) and infarcts were associated with alcohol consumption in the same study [61].

Risk of dementia associated with smoking has also been studied. Smoking habits could have a theoretical beneficial effect in cognition, mediated through the stimulating effect of nicotine. In fact, the acute administration of nicotine in nonsmoking young adults with attentional deficit was associated with improvement in attention, executive functions, and working memory, probably mediated through the activation of the cholinergic system [62]. Indeed, in a study with elderly people from Taiwan, a better cognitive profile was observed in smokers [63]. Very recently, an improvement in measures of attention, memory, and mental processing was found after 6 months of transdermal nicotine in nonsmoking subjects with amnestic mild cognitive impairment, in a double-blind randomized trial [64]. However, the deleterious effect of smoking, mediated through oxidative stress, triggering atherogenesis and inflammation could, even indirectly, mediate increased risk for cognitive decline. In a meta-analysis of 19 observational prospective studies, smoking increased the risk for dementia, not only vascular dementia but also for degenerative dementias, an effect found mainly comparing active smokers against never smokers [65]. This risk could potentially be more pronounced among persons without the apolipoprotein E type 4 allele (*APOE-* ε 4) than among *APOE-* ε *4* carriers [66].

Role of Small Vessel Disease in Cognition

Small vessel disease is a broad concept used in several contexts and involves the cognitive, clinical, and imagiological consequences of the pathological changes of the small vessels of the brain [67]. As small vessels are not visualized in vivo, visible imagiological consequences of small vessel disease are usually considered as the marker of the disease. Clinical expression of small vessel disease is not uniform, as it includes lacunar infarcts, white matter changes, or hemorrhagic events as microbleeds (Fig. 5.1). Moreover, definition of small vessel disease definition varies between the different studies. In this section we will focus on the cognitive implications of small vessel disease.

White matter changes designate the changes of the radiological appearance of the white matter of the brain, detected through computed tomography (CT) or magnetic resonance imaging (MRI), of probable vascular etiology, that are frequently described in older subjects with or without cognitive deficit [68–79]. White matter changes do not follow specific vascular territories and are usually described as periventricular and subcortical but can also appear infratentorial in the pons. Age is the most frequent risk factor, but white matter changes are increased in subjects with hypertension and stroke [80]. Clinical manifestations of white matter changes include cognitive decline, gait disturbances, urinary dysfunction, and personality and mood changes [67]. The knowledge of an implication of white matter changes in cognition has more than a century, but it was only after the advent of brain imaging that this concept gained interest, and the term leukoaraiosis was introduced [81]. Periventricular white matter changes are frequent in demented subjects, independently of the type of dementia [71]. White matter changes are associated with worse cognitive performance among nondemented older subjects, mainly in executive functions, attention, and processing speed and motor control [25, 72, 73, 82] but also in global measures of cognition [12–14], independently of other confounders. WMC severity is implicated in higher risk of cognitive impairment and dementia [38, 75–78], and the relation is stronger with vascular dementia [38, 79–84].

Lacunes are frequently described in CT and MRI of elderly subjects and have been implicated in higher risk of dementia [85]. Similarly to white matter changes, lacunes have been implicated in worse executive functioning [86], processing speed and motor control [87] among demented and nondemented subjects, with or without previous clinical stroke. The higher frequency of lacunes in nondemented subjects [88] and the coexistence of other small vessel disease types [89] make it difficult to determine the exact influence of lacunes in cognition.

Specific locations, such as thalamic and basal ganglia lacunes, can have a specific impact in cognition [80], but further studies are needed to understand the individual effect of lacunes, even considering other concomitant confounders.

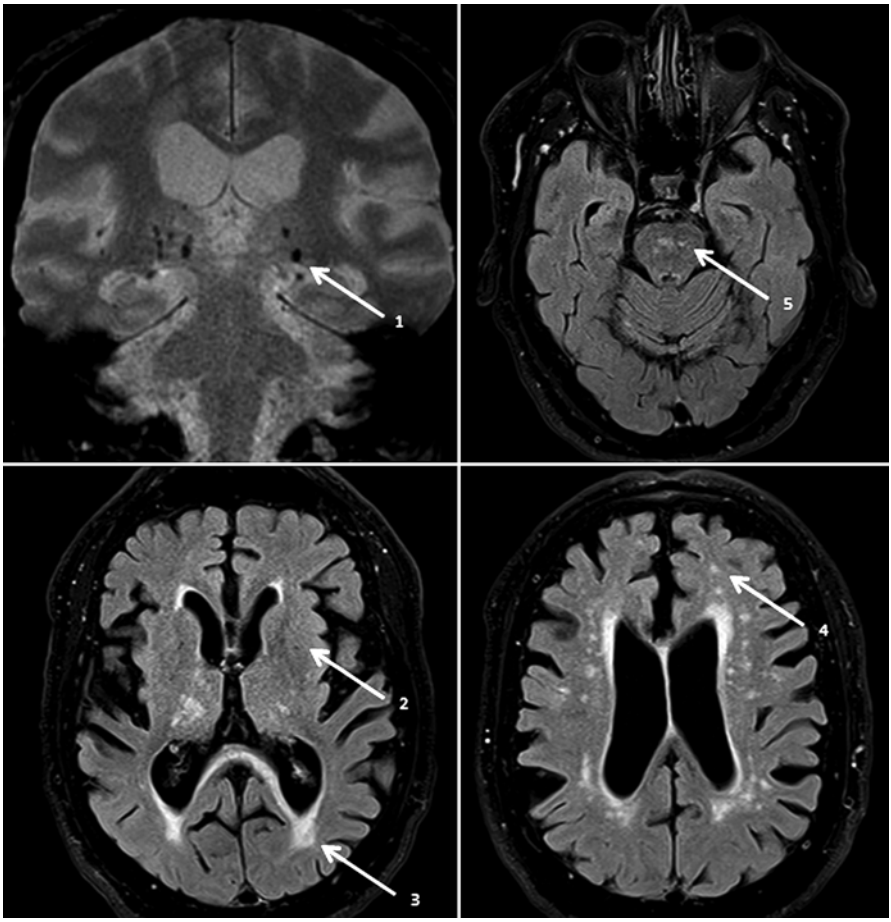

Fig. 5.1 Different expressions of small vessel disease in the same patient. *1* Microbleeds, *2* lacunes, *3* periventricular white matter changes, *4* subcortical white matter changes, *5* white matter changes in the pons

Cerebral microbleeds have been progressively described using specific susceptible MRI sequences. Prevalence data are highly variable, lower in community studies (7–36 %), higher among demented subjects, and mainly in subcortical vascular dementia (up to 85 %) [90–92].

Cerebral microbleeds have been associated with worse performance mainly in executive functions [93–95], processing and motor speed [95, 96], and attention [97], but the individual impact in cognition is not settled yet. It is not clear if different localizations are associated with specific profiles of cognitive deterioration, but increasing number of microbleeds seem to be associated with an increasing cognitive decline [95, 98].

Conclusion

Vascular risk factors are associated with an increased risk of cognitive decline and dementia, including degenerative dementia, and even among nondemented subjects are associated with worse cognitive performance. Treatment and control of vascular risk factors since at an early age has a key role in order to prevent cognitive impairment associated with aging. Nowadays, enough evidence sustains treatment of diabetes, prevention of stroke and stroke recurrence, and also treatment of hypertension in midlife, in order to prevent progression toward dementia. Further studies are needed to determine the type of intervention in each subject, considering other vascular risk factors. Small vessel disease is increased in subjects with vascular risk factors, can be monitored with brain imaging, is associated with cognitive decline, and can be used as a hallmark of cerebral vascular disease. In future studies white matter changes (and other expressions of small vessel disease) could be used as a potential end point of experimental studies.

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