Role of Cerebrovascular Disease in Cognition

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Abstract

Vascular risk factors and cerebrovascular disease are recognized factors implicated in the evolution towards dementia, not only of vascular origin, but also of degenerative dementia as Alzheimer's disease. Even among nondemented subjects, hypertension, diabetes, and stroke are associated with worse performance in attention, speed and motor control, and executive functions. Influence of vascular risk factors in cognition starts early in life. Recently, several publications expressed that intervention in potential modifiable risk factors should receive special attention in order to delay or prevent dementia. Current scientific evidence sustains that policy actions should be conducted in order to reduce vascular risk factors in middle life, with population and community-level measures. Cerebral small vessel disease, which can be expressed by white matter changes, lacunes, and microbleeds, has gained clinical relevance in the last decades. Intervention in prevention of this previously overlooked disease can represent a potential outcome in experimental studies aiming to reduce cerebrovascular burden.

Keywords

Vascular risk factors · Hypertension · Diabetes · Stroke · Cerebral small vessel disease · White matter changes · Lacunes · Microbleeds

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Introduction

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

In the last few years several publications have stressed acknowledge of an overlap between risk factors for vascular disease and neurodegeneration and dementia [1]. On this behalf, efforts should be done in order to improve research and population recognition of vascular risk factors [1–3]. Recently, in an initiative funded by the Joint Programme for Neurodegenerative Disease Research, a survey was conducted within a group of international experts. The results and recommendations for the study of vascular disease and its contribution to cognitive decline and neurodegeneration retrieved from that survey were published, and the interested reader may find it in a quite fine comprehensive review [4]. There are other publications made upon this approach, but this chapter does not aim to be an exhaustive bibliographic review under the topic. The author proposes a reflection based on selected bibliographic references and his own clinical experience, aiming to share the concern about a (although) frequent, sometimes neglected topic in daily practice.

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.

Role of Vascular Risk Factors in Cognition

Vascular risk factors have been implicated in cognitive decline and dementia. A recent review that considered the most frequent vascular risk factors (diabetes, midlife hypertension, midlife obesity, physical inactivity, and smoking) plus depression and educational level, concluded that even among degenerative dementia, around a third of Alzheimer's disease cases might be attributable to potentially modifiable risk factors [5]. Moreover, midlife vascular risk factors were associated with higher amyloid deposition in the brain [6]. Among the whole spectrum of vascular risk factors, hypertension, stroke, and diabetes seem to play the most important role [7–18]. Before exploring evidence that support the relationship between some of the major risk factors and cognitive impairment, we present two concepts that have evolved in the last years. The first is that cognitive decline is insidious and slowly developing starting early in life, around the fourth decade [19]. 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 [20–24]. 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 [10, 22]. A systematic review stressed that the risk of dementia in diabetes is increased when

associated with other vascular risk factors, a phenomenon that was also identified for other risk factors [10, 22, 25], mainly if they are concomitantly present in midlife [10, 26].

Role of Diabetes in Cognition

Diabetes has increasingly been identified as a risk factor for cognitive impairment and dementia [18, 27–30], including AD [31]. Among nondemented subjects, diabetics have worse cognitive performance when compared to nondiabetics [13, 28, 32] in global tests of cognition [33], attention, executive functions, processing speed, and motor control, and also memory, praxis, and language [33, 34], independently of other confounders. Diabetic subjects have a twofold increase in risk of mild cognitive impairment and dementia comparing to nondiabetics [13, 18, 35], an effect that stands long time after diabetes diagnosis [30].

Diabetes has several pathways to be implicated in the progression of dementia: not only due to the higher risk of vascular disease, but also mediated through metabolic changes due to the insulin and glycemia pathways, interfering with imbalance of glucagon/insulin homeostasis [36] that is implicated in the metabolic production of beta-amyloid protein and tau protein [27], promoting neuronal degeneration [37] and thus implicated in pathogenesis of AD [13, 38, 39]. Moreover, recent data suggest a genetic link between diabetes and the pathogenesis of AD [40, 41] and that insulin may modulate distribution of amyloid beta 40 and 42 in the brain [42].

Role of Stroke in Cognition

Stroke is a well-recognized risk factor for cognitive impairment in prospective community studies [7, 14, 35, 43, 44] and is associated with a twofold risk of dementia [44], not only for vascular dementia and vascular cognitive impairment, but also for degenerative dementias such as AD [44].

The higher risk of dementia in stroke survivors can be partially explained by concomitant vascular factors [45] and by pre-stroke dementia, but this is not the only explanation [44–46]. Nondemented stroke survivors have worse performance in tasks of attention and executive functions [33] comparing to subjects without stroke. On the other hand, small vessel disease predicts vascular dementia [47], 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 AD 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 [48–50]. 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. In line with this hypothesis, amyloid pathology was associated with more severe and rapid post-stroke/TIA cognitive decline in a recent publication [51]. However, so far, no evidence exists that stroke per se leads to increase of amyloid deposits [52]. On the other hand, in the DEDEMAS study [53], the majority of post-stroke cognitively impaired patients were not due to amyloid pathology, as deficits developed in the absence of amyloid pathology [53]. These findings suggest an alternative explanation implicating stroke as the direct cause of cognitive decline. In the same line, in a mouse model of recurrent photothrombotic stroke, recurrent infarcts (parietal cortex) were recently associated with progressive cognitive decline, with histopathologic evaluation showing remote astrogliosis of the hippocampus [54].

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, with midlife hypertension being the cue for the explanation of the impact in cognition [55]. Hypertension in midlife has been consistently associated with later development of cognitive decline and dementia, with a higher effect in non-treated hypertensive subjects [56]. Sustained midlife hypertension was also associated with brain atrophy [57]. Although the strongest association is with vascular dementia, there is also an increased risk of degenerative dementia as Alzheimer's disease [7, 10, 17, 56, 58–60]. It was indeed suggested that hypertension was associated with greater amyloid burden not only in middle aged but also among older adults [61]. Treatment with antihypertensive treatment was associated with reduced hippocampus atrophy in hypertensive subjects [62] and with less AD neuropathology [63].

However, the relationship between late-onset hypertension and cognitive decline and dementia is less clear: some studies were negative for this association [11, 12, 64] or sustain that a very low systolic and/or diastolic value was associated with higher risk of cognitive decline [58, 59].

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 [33] but also difficulties in some global cognitive functioning tests [65, 66]. 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 [60]. Results from trials focusing on the prevention of dementia using antihypertensive medication have failed to show a consistent protective effect, sustaining this explanation [67–69] and precluding a recommendation [69]. From the six main randomized placebo-controlled studies, four were negative for a protective effect [70–73], one found a small effect on the prevention of dementia [74], and the other [75] found a protective effect only for post-stroke dementia. Other studies,

with concomitant treatments other than hypertension therapy, failed to show an effect in cognition [76], and from three recent studies approaching multifactorial intervention including hypertension control risk, in different settings, only one had a positive outcome [77–79]. 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

Influence of alcohol intake on brain structure and cognition has been a focus of interest in the two last decades. In the LADIS study [33], 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 non-drinkers (included never drinkers), but this relation was lost over time [33, 47]. Low or moderate alcohol intake was associated with reduced risk of AD in a systematic review with meta-analysis, compared to the risk of dementia in non-drinkers [80]. In this review, non-drinkers had a small higher risk compared also to excessive drinkers. However, non-drinkers could include former excessive drinkers that stopped consuming due to health problems [80]. These favorable results were replicated in a recent overview of systematic reviews under the topic [81]. However, a study conducted among older subjects could not find evidence that moderate alcohol intake could prevent cognitive decline [82]. Moreover, higher alcohol consumption and drinking have been associated with increased risk of dementia (both for vascular and Alzheimer's dementia) [83]. A recent review approached alcohol dose associated with a stratified risk of dementia and found that low dose (6 g/day for best association and 12.5 g/day maximum dosage for benefit) had the best association with low risk for dementia [84]. High risk of dementia was particularly found with dosages above 23 drinks/week or 38 g/day [84]. Considering imaging data, controversial data exists considering brain atrophy: brain atrophy was associated with alcohol intake even for low drinkers [85], but a recent study suggested that wine (among different types of alcohol beverages) was associated with larger total brain volume [86]. Direct effect of alcohol consumption on WMC and infarcts remains unclear [85].

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 non-smoking young adults with attention deficit was associated with improvement in attention, executive functions, and working memory, probably mediated through the activation of the cholinergic system [87]. In a pilot study, an improvement in measures of attention, memory, and mental processing was found after 6 months of transdermal nicotine in non-smoking subjects with amnestic mild cognitive impairment, in a double-blind randomized trial [88]. Nevertheless, 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 [89]. This risk could potentially be more pronounced among persons without the APOE4 allele than among APOE4 carriers [90]. In a small study using estimates of relative risk, an increased relative risk was found between cigarette smoking and AD [91].

Role of Small Vessel Disease in Cognition

Small vessel disease is a broad concept used in several contexts and involves the cognitive, clinical, and imaging consequences of the pathological changes of the small vessels of the brain [92]. As small vessels are not visualized in vivo, visible imaging consequences of small vessel disease are usually considered as the marker of the disease. Clinical expression of small vessel disease is not uniform; to make it more complex, definition of small vessel disease varies between the different studies. Expression of small vessel disease includes lacunar infarcts, white matter changes, or hemorrhagic events, as microbleeds (Fig. 5.1). More recently, perivascular spaces that are mostly visible through MRI gained attention as an additional marker of small vessel disease. In a recent study, using genome-wide association study data from two different large sets of cases and controls, Traylor et al. found results supporting a shared pathophysiological process between AD and specifically small vessel disease strokes [93]. Location of MRI-visible perivascular space may potentially be different in these two pathologies [94].

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 CT or MRI, of probable vascular etiology, that are frequently described in older subjects with or without cognitive deficit [95–106]. 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 [107]. Traditional clinical manifestations of white matter changes include cognitive decline, gait disturbances, urinary dysfunction, personality, and mood changes [92]. 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 [108]. Periventricular white matter changes are frequent in demented subjects, independently of the type of dementia [98]. White matter changes are associated with worse cognitive performance among nondemented older subjects, mainly in executive functions, attention, processing speed, and motor control [33, 99, 100, 109] but also in global measures of cognition [33, 99, 109], independently of other confounders. WMC severity is implicated in higher risk of cognitive impairment and dementia [47, 49, 102–105], and the relation is stronger with vascular dementia [47, 106–111]. Recently, Kandiah N et al. showed that white matter changes increased over the

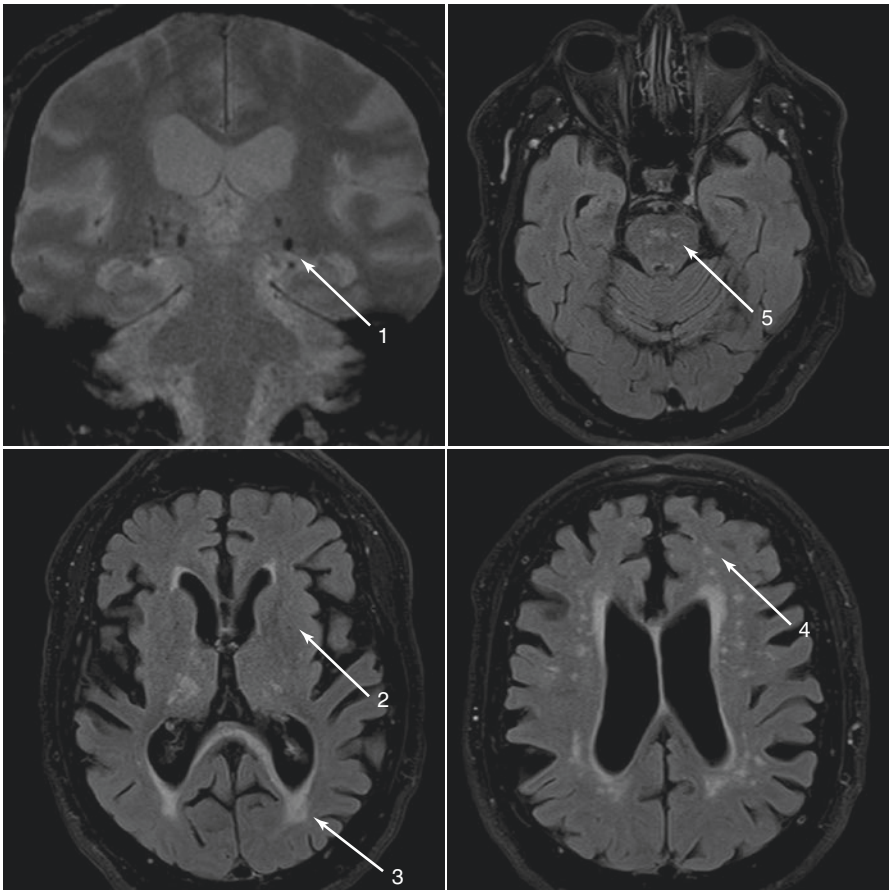

Fig. 5.1 Different expressions of small vessel disease, in the same patient. (1) Microbleeds. (2) Lacunes. (3) Periventricular white matter changes. (4) Subcortical white matter changes. (5) White matter changes in the pons

continuum of mild cognitive impairment and mild AD evolution, suggesting a synergistic effect between white matter changes and amyloid pathology [112]. Moreover, white matter changes were associated with cortical thickness [113], and effect found associated with other vascular lesions, as incident subcortical infarcts [114] and acute infarcts [50], and association eventually mediated through remote disconnecting phenomena. A nice summary of these effects is described in the METACOHORTS Consortium Statement [4].

Lacunes are frequently described in CT and MRI of elderly subjects and have been implicated in higher risk of dementia [115]. A recent systematic review and meta-analysis found an increased risk of mild cognitive impairment and dementia after lacunar stroke, the same risk described in other clinical non-lacunar strokes [116]. Similarly to white matter changes, lacunes have been implicated in worse

executive functioning [117], processing speed, and motor control [118] among demented and nondemented subjects, with or without previous clinical stroke. The high frequency of lacunes in demented and nondemented subjects [119], and the coexistence to other small vessel disease types with lacunes [120] difficult the exact influence of lacunes in cognition. Specific locations, such as thalamic and basal ganglia lacunes, can have a specific impact in cognition [107], but further studies are needed to understand the individual effect of lacunes, even considering other concomitant confounders.

Cerebral microbleeds have been progressively described using specific susceptible MRI sequences. Prevalence data is highly variable, lower in community studies (7–36%), higher among demented subjects, mainly in subcortical vascular dementia (up to 85%) [121–124], but also in AD, where cerebral microbleeds are located more frequently in lobar areas [125].

Cerebral microbleeds have been associated with worse performance mainly in executive functions [122, 126–128], processing and motor speed [129–131], and attention [130]. Some recent evidence sustains a specific association between lobar microbleeds and memory deficit [132], and an association between cerebral microbleeds and cerebrospinal fluid biomarkers, emphasizing the link with amyloid pathology [131]. The increasing number of microbleeds seems to be associated with an increasing cognitive decline [127, 132], including AD [132].

Conclusions

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 in midlife 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 towards dementia. Further studies are needed to determine the type of intervention in each subject, considering other vascular risk factors [132]. 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, small vessel disease, namely, white matter changes, represents a potential end point of experimental studies.

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