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REVIEW ARTICLE

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Why are stroke patients prone to develop dementia?

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Abstract Stroke patients are more likely to develop dementia than age- and sex-matched controls but the pathogenesis of dementia remains unresolved in most of them. The aim of this review is to determine, from the available literature, the theoretical reasons for a stroke patient to become demented. We found three distinct factors that may explain the occurrence of dementia after a stroke. Firstly, post-stroke dementia may be the direct consequence of the vascular lesions of the brain: this is the most likely cause in patients with normal cognitive functions before a strategic infarct, especially in young patients, in Icelandic-type hereditary amyloid angiopathy and in cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy. Secondly, post-stroke dementia may be due to an associated asymptomatic Alzheimer pathology; the reasons for such an association are that (1) some cases of dementia occurring after a stroke are progressive and Alzheimer's disease (AD) is the most frequent cause of progressive dementia; (2) age and *APOE ε 4* genotype are risk factors for both AD and ischaemic stroke; (3) a vasculopathy is often associated with AD. Lastly, white matter changes may also contribute to dementia because they often indicate small-vessel disease and a higher risk of stroke recurrence, and may lead to slight cognitive impairment. Finally, the summation of vascular lesions of the brain, white matter changes, and Alzheimer pathology might lead to dementia, even when each type of lesion, on its own, is not severe enough to induce dementia. Therefore, in patients followed up after a stroke, the term "post-stroke dementia" is probably more appropriate than that of vascular dementia because it includes all possible causal factors.

Key words Dementia · Stroke · Vascular dementia · Alzheimer's disease · White matter

Introduction

Stroke patients are at risk for dementia; the prevalence of dementia 3 months after an ischaemic stroke, in patients aged over 60 years, was found to be 26.3%, i.e. ninefold higher than in controls [83]. One year after stroke, the probability of new-onset dementia is 5.4% in patients over 60 years and 10.4% in patients over 90 years [82]. Four years after a first lacunar infarct, 23.1% of patients develop dementia, i.e. 4–12 times more than controls [52]. These studies have not taken into account the cognitive state of the patients before stroke onset. However, even after exclusion of patients who are demented 3 months after an ischaemic stroke, the relative risk of dementia within 4 years remains 5.5 [84]. Previous stroke and cor-

tical atrophy are associated with a higher risk of post-stroke dementia [51, 52, 84]. Stroke is considered as the direct cause of only one-half of post-stroke dementia [83]. In some stroke patients, dementia has a progressive onset and course suggesting a degenerative process [84]. White matter changes, often associated with stroke and Alzheimer's disease (AD), might also contribute to cognitive decline [32, 36, 50]. Dementia due to vascular disease is one of the rare preventable dementias [30] but, when Alzheimer pathology is associated, secondary prevention may have less effect on cognitive decline. Moreover, these patients require a different kind of management. This review aims to discuss the putative mechanisms of post-stroke dementia.

Direct consequence of the cerebrovascular lesions

A "pure" vascular dementia may occur irrespective of the underlying cause of stroke [48]. The underlying vascular pathology of stroke is outside scope of this review and will not be detailed. In large-vessel diseases and in cardiac sources of cerebral ischaemia, dementia is often overshadowed by the severity of neurological sequelae. Although the total volume of cerebral infarction probably contributes to the pathogenesis of dementia, the volume of functional tissue loss may be more important because it also includes the effect of "incompletely infarcted tissue" and deafferented cortex [57]. Therefore, dementia is the prominent problem mainly in lacunar infarcts. In the following four circumstances, cerebrovascular lesions are likely to be the only cause of dementia.

Strategic infarcts with previous normal cognitive functioning

Sometimes, cognitive state, likely to be normal before stroke, is impaired immediately after stroke and does not decline over time: the dementia is then related to a single infarct located in a "strategic" area [59, 66] such as the thalamus [26, 90], the angular gyrus [3] and the caudate nucleus [56]. The term "focal form of vascular dementia" has been suggested [55] because dementia is usually the consequence of the occlusion of a single artery.

Lacunar state

Lacunar infarcts are related to lipohyalinosis and segmental fibrinoid degeneration of the wall of the deep perforators without typical features of atheroma [21]. Age and arterial hypertension are the main risk factors of this vasculopathy [21]. Repeated lacunes produce the lacunar state [54] which may sometimes lead to cognitive decline.

Hereditary cystatin C amyloid angiopathy

Hereditary cystatin C amyloid angiopathy, formerly called "hereditary cerebral hemorrhages with amyloidosis, Icelandic type", is an autosomal dominant disorder that has been described in several families from Iceland [44]. Recurrent cerebral haemorrhages occur before the age of 40 years [5, 44] and can lead to dementia [44]. At autopsy, patients have extensive intracerebral haemorrhages, widespread hyalinization of the walls of small arteries, extensive amyloid deposits in the walls of the cerebral and leptomeningeal arteries, without Alzheimer features [27].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

CADASIL is an autosomal dominant disease of the small arteries of the brain leading to lacunar infarcts and dementia [13, 86]. Genetic analysis demonstrated linkage to chromosome 19q12 [86]. The first clinical symptoms usually occur between 30 and 50 years of age [8]. Most patients are free of vascular risk factors. Dementia usually has a stepwise course and may also develop progressively without clinical cerebrovascular episodes [13, 68]. Magnetic resonance imaging shows lacunar infarcts and confluent and symmetrical areas of increased signal intensity in the subcortical white matter, sparing the U fibrer [8, 86]. The underlying lesion is a widespread vasculopathy affecting the penetrating arteries of less than 400 μm in diameter, which are thickened by a granular, eosinophilic, non-amyloid, electron-dense material in the media which differs from arteriosclerotic and amyloïd deposits.

In these four circumstances, dementia is likely to be the direct consequence of the vascular lesions of the brain, although the contribution of white matter changes is possible in the last three.

Associated Alzheimer pathology

Arguments for an associated degenerative pathology.

Some post-stroke dementias have a progressive course which suggests a degenerative rather than a vascular process [60, 84]. In addition, mild progressive dementia may be present before stroke and unrecognized by the family: in community studies, the prevalence of all types of dementia is of 2% in the ages between 65 and 74 years, and above 10% in the age between 75 and 84 years [64]; therefore, similar figures are expected by chance in stroke patients. As suggested by Hénon et al. [33] unrecognized pre-stroke dementia may contribute to the 50% increase in the incidence rate of AD 1 year after a first ischaemic stroke reported by Kokmen et al. [46]. The prevalence of

pre-stroke dementia has been evaluated in only one study [33]. It has been estimated to be 18% (95% confidence interval: 11–25%) in patients with a mean age of 73 years [33]. The slowly progressive course of symptoms in pre-stroke dementia strongly suggests a degenerative origin [33].

Arguments for associated Alzheimer pathology

AD is the most frequent cause of degenerative dementia [64]. Moreover, AD and stroke have common genetic risk factors. The ε 4 allele of the apolipoprotein E gene (*APOE*) is associated with a higher risk of ischaemic stroke or coronary heart diseases [25, 47, 91], and of so-called vascular dementia [23, 76]. The *APOE ε 4* allele has also been firmly established as a major risk factor for late-onset AD [23, 61, 70] with an odds ratio of 4 for the ε3 /ε 4 genotype and of 16 for the ε 4/ε 4 genotype. For heart diseases, the odds ratio is 1.5, without evidence of a gene dose effect [25]. The possibility that AD and ischaemic stroke may share a common genetic risk factor suggests pathogenic relationships between brain ischaemia and AD [14]. It is known that amyloid precursor protein accumulates in regions of neurodegeneration following focal cerebral ischaemia in the rat [78]. An unifying explanation of the association of the ε 4 allele with both stroke and AD might involve the role of *apoE* isoforms in the repair processes in the nervous system and play a role in normal brain lipid metabolism [62, 67]. Albert et al. [2] showed a strong association between the ε 4 genotype and a poor neurological outcome after intracerebral haemorrhage. It can be hypothesized that different insults, either degenerative or vascular, might result in greater damage when a particular *apoE* isoform allele is present [23]. A synergistic relationship between stroke and a marker of genetic susceptibility to AD could therefore exist.

Moreover, several data suggest than AD patients have some degree of vascular change. Cerebral amyloid angiopathy, a frequent factor of non-hypertensive intracerebral haemorrhage [89], is more frequent in AD patients than in controls [92]. The amyloid angiopathy of AD may lead to cerebral haemorrhages [16, 53] and to cerebral infarcts [16]. Therefore, amyloid angiopathy may lead to a vascular component of Alzheimer dementia. Moreover, dementia in hereditary cerebral haemorrhages with amyloidosis of the Dutch type is a combination of vascular and Alzheimer lesions [28, 29]. Non-specific fibrohyaline thickening of the wall of the small perforating intracerebral arteries is observed in AD patients [63] even when there is no vascular risk factor [49]. This arteriolopathy may lead to lacunes [21] and may be associated with white matter changes in patients with stroke [36, 50] and in AD patients [50, 63]. In the Rotterdam study, AD patients had an increased common intima-media thickness in the common carotid artery [37]. This finding was associated with an increased risk of stroke in the community [6]. Therefore, AD patients could be considered at risk for stroke. In a community-based study, Ferrucci et al. [20] found a higher risk of stroke in elderly subjects with dementia than in non-demented subjects; however, the presumed cause of dementia was not detailed. Alzheimer and vascular neuropathological lesions are frequently associated. In a study performed before the NINDS-AIREN criteria for vascular dementia were established, approximately 20% of patients with clinically diagnosed "multi-infarct dementia" and 14% of those classified as having "mixed dementia" fulfilled histopathological criteria for AD [43]. Ten to 18% of Alzheimer patients have associated cerebrovascular lesions [38, 43]. On the other hand, Alzheimer-type pathology is often associated with cerebral amyloid angiopathy [94] and with infarcts [38].

Therefore, the link between stroke and AD seems to be closer than expected by chance.

White matter changes

White matter abnormalities are often associated with stroke [36, 39, 50] and with risk factors for stroke such as age [39], arterial hypertension [9, 73], cardiac disease [34] and diabetes mellitus [36, 74]. Moreover, some data suggest that they are associated with subtle neuropsychological [16, 73] and behavioural [69, 80] changes. Therefore, the contribution of white matter changes to post-stroke dementia should be considered.

White matter changes are associated with a higher risk of dementia after adjustment on other variables

Leukoaraiosis, which refers to white matter changes on CT scans, is more frequent in so-called vascular dementia than in other types of dementia and the normal elderly [1, 19, 39, 72]. However, these studies [1, 19, 39, 72] were conducted before the NINDS-AIREN criteria for "vascular dementia" [66] were established. Therefore the causal relationship between stroke and dementia remained to be clarified in many cases. Large coalescent hyperintense areas extending from the periventricular region far into the deep white matter in demented patients are one of the imaging hallmarks of a cerebrovascular disease associated with dementia [19, 45, 51, 72]. However, less frequently, white matter changes are also found in AD patients [18, 50, 63], especially with late onset [11, 71], even after the exclusion of potential risk factors for stroke [50, 71]. Moreover, leukoaraiosis was an independent predictor of post-stroke dementia in most studies [51, 58, 84].

In stroke patients, leukoaraiosis is more frequent in those with lacunes [12, 36, 50] or deep haemorrhages [12, 36, 40, 50]. The relationship between leukoaraiosis and

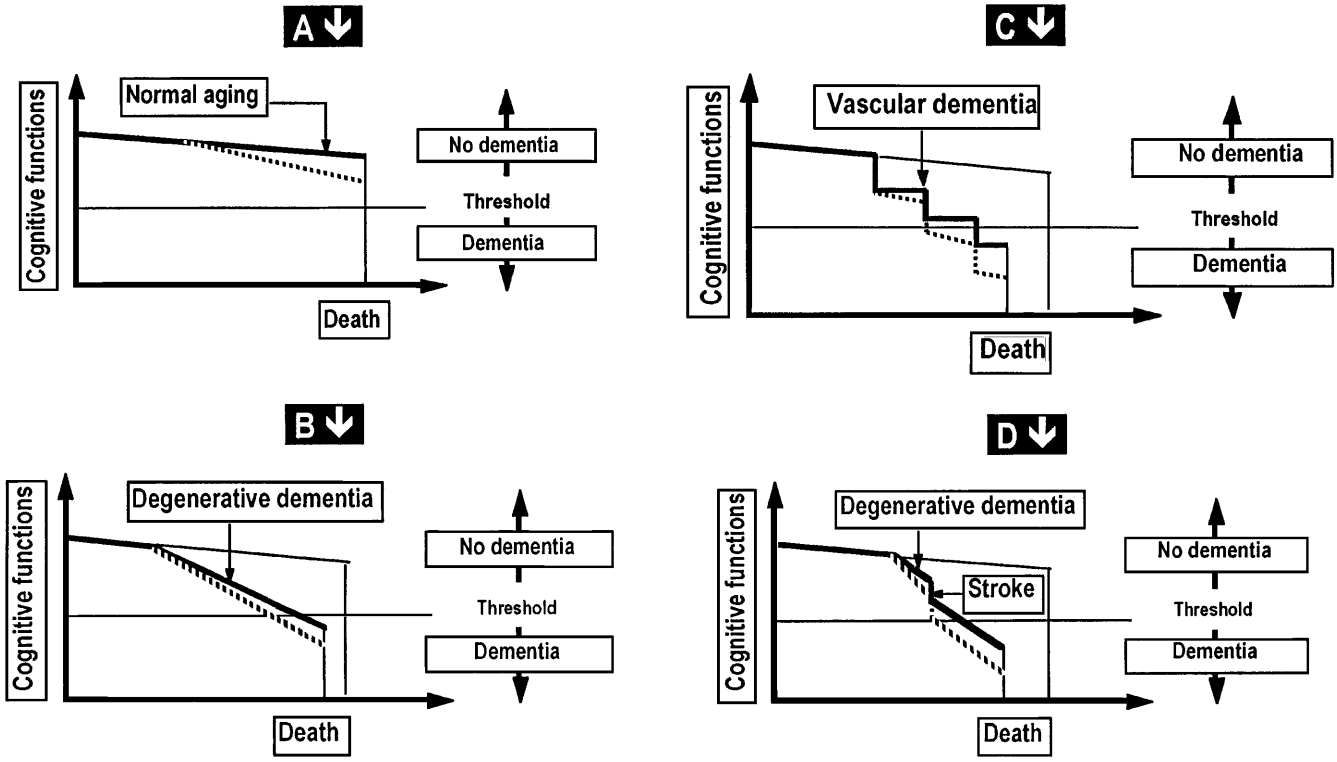

Fig. 1A–D Evolution of cognitive capacities over time. *Hatched lines* represent patients with white matter changes. **A** In normal aging, the loss of cognitive capacities remains moderate and never reaches the threshold of dementia during life. **B** In Alzheimer's disease (AD), the slope of the line is modified and, after a period of preclinical AD, the threshold of dementia is reached. **C** In "pure" vascular dementia, each stroke leads to a sudden loss of cognitive functions; in this example the first two strokes did not induce cognitive changes severe enough to reach the threshold of dementia but the third did, in a stepwise fashion. **D** When a stroke occurs at a preclinical stage of AD, and does not induce a loss of cognitive capacities severe enough to induce dementia, the period of preclinical AD is shortened by the summation of vascular and Alzheimer lesions; the threshold of dementia is reached earlier than in patients with "pure" AD. In all circumstances, white matter changes lead to a moderate increase in the loss of cognitive functions due to aging, AD or stroke and white matter changes probably contribute independently to dementia

lacunes or deep cerebral haemorrhages is stronger than that with arterial hypertension [12, 36, 50], suggesting that arterial hypertension leads to leukoaraiosis only after having caused small-vessel disease to such a degree that lacunes or deep cerebral haemorrhages are almost always present [36, 50]. Therefore, among stroke patients, those who have the highest risk of having white matter changes are patients with lacunes, i.e. those who have the highest risk of becoming demented. The so-called Binswanger's disease [4] may be the end-stage pathology of a lacunar state [22, 50, 65].

Among stroke patients, those with leukoaraiosis have a higher risk of stroke recurrence after adjustment for age and other vascular risk factors [41, 58, 88]. If leukoaraiosis is associated with a higher risk of stroke recurrence, it is also likely to be associated with a higher risk of dementia.

White matter changes may induce specific cognitive decline

The functioning of neurons depends on the myelination of their axons. Any abnormality within the cerebral white matter may induce clinical disorders. Although the NINDS-AIREN criteria state that white matter changes alone may lead to dementia when the abnormalities involve 25% of the total volume of the white matter [66], this hypothesis has never been tested and the cut-off of 25% is somewhat arbitrary.

In studies performed in large groups of healthy individuals, white matter hyperintensities are associated with subtle neuropsychological deficits especially for memory [15, 73], attention capacities [87] and frontal lobe cognitive function [15]. A threshold of white matter hyperintensity areas is required before cognitive deficits are observed in healthy elderly individuals [7]. Mild disturbance in attention and increased perseveration may represent frontal or subcortical functions (or both) that are most susceptible to disruption, and therefore decline first. The areas correspond to white matter hyperintensities [6, 75, 87, 93]. In non-demented stroke-free subjects randomly selected from the Rotterdam cohort, those who had white

matter hyperintensities performed worse in tests measuring executive control functions, mental speed and delayed verbal recall [10]. These findings suggest that white matter hyperintensities are primarily related to impairment of subcorticofrontal functions. However, cerebral atrophy may, at least in part, be a confounding factor [35, 48]. It is wise to consider patients with white matter changes as prone to develop neuropsychological deficits, although several of them will probably remain free of any clinical abnormality [48].

As in normal subjects, white matter changes may probably also induce neuropsychological disturbances in demented patients, but these are usually masked by the dementia syndrome [32]. In demented patients, white matter changes are correlated to the severity of dementia [32, 43, 51, 77, 79] but brain atrophy may be a confounding factor, as in normal subjects [79]. The location of white matter changes may influence cognitive functions: patients with lacunes and dementia have more white matter lesions in the frontal lobes and their severity correlates with the cognitive decline [24, 42]. Lower perfusion rates of frontal and temporal cortical regions are seen in demented patients with multiple cerebral infarcts [85]. Underlying leukoaraiosis causing cortical disconnections was held responsible.

Summation of vascular, degenerative and white matter lesions

This review suggests that many post-stroke dementia are multifactorial. They may be the consequence of the additive effect of the cerebrovascular lesions, Alzheimer pathology, white matter changes and aging. Even when these changes, on their own, do not lead to dementia, their summation may reach the threshold of lesions required to induce dementia [7, 17].

We suggest the following mechanism: in aging, the cognitive decline does not reach the threshold of dementia (Fig. 1A); in patients with "pure" Alzheimer pathology, the slope of the cognitive decline is dramatically modified and the threshold of dementia is reached after a period of preclinical AD (Fig. 1B); in "pure" vascular dementia, each stroke leads to a sudden cognitive impairment leading to dementia in a stepwise fashion (Fig. 1C); when a stroke occurs in a patient with asymptomatic Alzheimer pathology, the period of preclinical AD is shortened by the summation of vascular and Alzheimer lesions and the threshold of dementia is reached earlier than in patients with "pure" AD (Fig. 1D): these patients develop progressive dementia with a time-course suggestive of AD. White matter changes slightly increase the cognitive impairment due to these various mechanisms and probably independently contribute to dementia (Fig. 1A–D).

Conclusion

The concept of vascular dementia encompasses many mechanisms and refers only to the latest stage of the cognitive decline occurring after a stroke [31]. Therefore, in patients followed up after a stroke, the term "post-stroke dementia" is probably more appropriate: this is a descriptive term which has no implied meaning and includes all possible mechanisms of dementia. However, recognition of a vascular component in a dementia syndrome is useful for the management of patients. However, recognition of a vascular component in a dementia syndrome is useful for the management of patients. Many questions remain unanswered about the mechanisms of dementia in stroke patients. Should stroke patients with dementia be treated differently? Is it possible to select a subgroup of stroke patients at higher risk of dementia to be followed up over time? Does the treatment of risk factors for stroke delay the clinical expression of dementia in patients with associated Alzheimer pathology? Finally, does early recognition of post-stroke dementia improve life expectancy and quality of life of the patients and decrease the cost for society? Prospective studies are still necessary to address these important questions.

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