ejpmr, 2019,6(12), 91-97

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review article

ISSN 2394-3211

EJPMR

CEREBROVASCULAR DISEASE AND DEMENTIA

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Article Received on 02/10/2019 **Article Revised on 23/10/2019** **Article Accepted on 13/11/2019**

ABSTRACT

Cerebrovascular disease is a major contributor to later-life dementia, accounting for up to 20% of cases of dementia. Atherosclerotic and arteriolosclerotic mechanisms account for most of the burden of disease. Cerebrovascular disease may take several forms. Macrovascular disease in the form of large vessel and larger arteriole infarcts produce a wide spectrum of clinical syndromes. Single strategic infarctions, multiple bilateral infarctions and multiple lacunar infarctions can lead to cognitive dysfunction that spans a large range of both severity and type of cognitive deficits. Microvascular disease almost certainly plays a role in the pathogenesis of dementia. Small vessel disease, which is not evident radiographically, often coexists with macrovascular disease and also with Alzheimer's disease. Amyloid angiopathy is relevant in cognitive disorders in the elderly and causes micro-haemorrhages and large haemorrhages. Other much less common aetiologies include vasculitides and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Neuroimaging plays a critical role in the diagnosis of vascular dementia. There is no framework for rating the extent of cerebrovascular pathology that is validated against increasing cognitive impairment. Although advances in imaging have increased our recognition of cerebrovascular disease in the elderly, vascular dementia is still inadequately recognized in clinical practice.

KEYWORDS: Macrovascular, radiographically, arteriopathy.

INTRODUCTION

Stroke is very common in the elderly[1], and cerebrovascular disease is a major contributor to late life dementia even though it has proven to be somewhat elusive to diagnose. This review discusses the diagnosis and clinical spectrum of cerebrovascular disease and cognitive impairment. For consistency throughout this article, a ''stroke'' refers to a clinically recognized instance of a cerebrovascular event, and an ''infarct''refers to a vascular brain lesion recognized by imaging or neuropathology. The label ''vascular cognitive impairment''(VCI) is used to refer to both cognitive disorders without dementia and those with dementia of cerebrovascular origin, i.e. vascular dementia (VaD). The acronym VaD will be used specifically when the syndrome of dementia is being considered. There are two major patho-anatomic variants of VCI. One disease group is caused by ''macrovascular'' impairments, including instances of large vessel infarctions and other infarcts that are visible on imaging or to the naked eye at neuropathological examination. The other disease group is associated with ''microvascular'' impairments[2,3], whose importance is inferred by their associations with imaging features such as white matter hyperintensities and lacunar infarcts, and from associations with vascular risk factors. Macrovascular disease is what is diagnosed clinically and radiographically.

The burden of microvascular disease has been more difficult to gauge on clinical and radiographic grounds.

Cognitive disorders that are associated with cerebrovascular disease may vary from ''focal'' deficits, such as aphasia, visual agnosia or neglect, to more pervasive impairment, ranging from mild disorders below the threshold for dementia to severe dementia. The cognitive symptoms are highly variable, sometimes looking very much like the pattern seen in Alzheimer's disease (AD) and sometimes appearing quite distinct.[4,5] In contrast to neurodegenerative diseases such as AD, there is no single cognitive profile that characterizes VaD. The most common appearance of VaD, however, is a dementia in which mental slowing is prominent while short-term memory impairment is somewhat less prominent.[4, 5]

Imaging features of cerebrovascular disease associated with VCI

The appearance of VCI and VaD seen by neuroimaging is remarkably diverse. Single infarcts can produce pervasive cognitive impairment in a dementia-like

picture when located in the hippocampus, medial thalamus[6], caudate nuclei[7, 8] and right parietal locations. Infarcts involving the right parietal lobe can produce a delirium acutely[9], and then might evolve into a cognitive disorder characterized by profound apathy, spatial disorientation, and impaired attention and concentration. Multiple lacunar infarctions can also cause dementia.[10] While the spectrum of cognitive deficits caused by cerebrovascular disease can vary considerably, apathy, impaired executive function and psychomotor slowing predominate over anterograde amnesia. A large minority of the elderly have clinically silent lacunar infarctions[11–13], increasingly so with advancing age. In initially non-demented individuals, the presence of silent infarcts is associated with an increased risk of cognitive decline and dementia.[14]

Extensive white matter hyperintensities have a strong but not invariant relationship to VCI. Binswanger's disease is the eponym associated with extensive ischaemic change in white matter and lacunar infarcts.[15] Clinically, there is no specific cognitive or behavioural syndrome that is invariably associated with extensive white matter changes on imaging. Some have speculated that the white matter lesions could be a marker for microvascular disease.[16] Persons with more extensive white matter hyperintensities (WMH) are more likely to have cerebrovascular risk factors[17–19], to have cognitive impairment[20,21], and to experience cognitive decline.[22] WMH are seen in patients with AD[23–27] but when WMH on MRI include confluent, ''diffuse and extensive'' hyperintensities on T2 weighted images and the presence of vascular-like lesions on T1 weighted images[25,28,29], a substantial vascular aetiology to cognitive impairment should be suspected.

Amyloid angiopathy produces a variety of imaging lesions. Small hemorrhages may occur clinically silently in patients with dementia[30], whereas larger hemorrhages may present with stroke-like events.[31,32]

Amyloid angiopathy may rarely produce an inflammatory lesion that is most evident in the white matter, mimicking the appearance of a glioma.[33,34] It is not yet possible to distinguish definitively between amyloidogenic and atherosclerotic aetiologies of lobar haemorrhages.[35] However, clinical criteria that include multiple cortical or cortico-subcortical haemorrhages in the absence of another cause in persons over age 55 have excellent specificity in a small series.[36] The use of gradient echo MRI has enhanced the detection of clinically covert haemorrhages.[30]

Because of the pleomorphic nature of the vascular lesions that produce VCI, it is very difficult to define a minimum vascular burden, either radiographically or neuropathologically, for VCI or VaD. An expert panel[28] considered ''relevant cerebrovascular disease'' to include instances in which there were multiple infarcts and extensive white matter disease.

Diagnostic importance of CVD on imaging to VaD

There are two features of cerebrovascular disease that strongly suggest relevance to cognitive impairment.These are: (1) the onset of, or marked worsening of, cognitive impairment following a stroke (within 3 months), and (2) the presence on brain imaging of bilateral grey or white matter infarcts in the frontal, temporal or parietal cortices, basal ganglia or thalamus.

These features are the core elements of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) diagnostic criteria for probable vascular dementia[28], which have been used in clinical trials in VaD. In a patient with cognitive impairment, the presence of only one of these features falls under the diagnostic category of possible vascular dementia.

The presence of a third feature, ''focal'' neurological signs, increases confidence in the diagnosis of clinically relevant cerebrovascular disease. However, ''focal'' neurological signs, such as a unilateral Babinski sign or hyper-reflexia, are non-specific. The presence of two such features, by contrast, is stronger evidence for relevant cerebrovascular disease.

Unfortunately, the NINDS-AIREN criteria lack sensitivity.

Autopsy studies show that important cerebrovascular disease is often under recognized by ante-mortem clinical diagnoses using these criteria.[37–39] The presumed reasons for the lack of sensitivity are the practical inability to perform serial imaging in patients with cognitive impairment and the reality that some cerebral macrovascular disease and all microvascular disease are not accompanied by obvious clinical stroke events.

It is possible to tabulate the extent of historical linkages between stroke and dementia, the extent and specificity of focal neurological signs and the extent of imaging evidence of relevant cerebrovascular disease[40] (Table 1). The purpose of this tabulation is to provide clinicians with a metric for describing the burden of cerebrovascular disease on the basis of clinical and imaging features. It should be clear, however, that such a scheme has not been validated pathologically.

Table 1: An index of cerebrovascular disease in cognitive impairment.

Not supportive – low probability of CVD	Supportive – moderate probability of CVD	Most strongly supportive – high probability of CVD
No history of stroke	Any stroke above midbrain by history, without subsequent impact on cognition	Stroke temporally related to onset of dementia or worsening of cognition
None or one focal sign (e.g. an extensor toe sign or a reflex asymmetry)	2 or 3 neurologic signs suggestive of cerebrovascular origin in the absence of history of stroke	Multiple (.3) neurologic signs strongly suggestive of cerebrovascular origin in the absence of history of stroke
None or minimal white matter hyperintensities	White matter hyperintensities – mild to moderate	White matter hyperintensities – severe
None or one lacune	2 to 3 lacunes	4 or more lacunes
No cortical infarcts or only one small (single gyrus) infarct	Cortical infarct, moderate, single not in critical region	Cortical infarcts, large, multiple
No infarcts in critical regions (hippocampus, caudate, thalamus, parietal cortex)	Lacune or small infarct only in critical regions	Hippocampal, caudate, thalamic, parietal cortex infarct larger than lacune

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Epidemiology of VaD

In population-based studies, VaD, by definition the macrovascular type, is about one-fifth as common as AD.[41] In a series of European studies, the pooled prevalence of VaD was 1.6% in the over-65-year-old population (compared with an AD prevalence of 4.4% in the same studies).[42] North American studies yield similar estimates averaged together.[43–46] Prevalence and incidence of VaD rises steadily with advancing age.

The prevalence estimates for VaD from population-based studies are much higher than those reported from memory disorder clinics[47,48], suggesting that patients with cerebrovascular disease differ from AD patients with respect to their interactions with the medical care system. Dementia in patients with cerebrovascular disease is almost certainly under-recognized in clinical practice, both by primary care physicians and by neurologists.

Dementia following stroke is common; after stroke, there is a high risk for subsequent dementia compared to controls without new strokes.[49–53] The consistency of the increased risk of dementia following stroke, a period during which cognitive impairment is explicitly sought and documented, demonstrates that VaD is more common than data from memory disorder clinics would indicate.

Individuals with clinically important cerebrovascular disease have reduced survival, and this relationship is true for patients with VaD.[54] In autopsy series, the proportion of vascular dementia ranges from quite low[47, 55] to as high as 20%.[38, 39] The lower numbers almost certainly reflect referral bias, whereas the higher numbers from studies that are population derived may be more representative.

Risk factors for VaD

Diabetes mellitus is a strong risk factor for both VaD[56] and clinically diagnosed AD.[57–59] Similarly, hypertension has often been observed to be a risk factor for VaD[60,61] and sometimes for AD.[62–64] The APOE e4 genotype is also a risk factor for VaD, just as itis for AD.[65] APOE genotype may modulate the effects of vascular risk factors on AD.[66–68] Because of difficulties in case definition in epidemiological studies, the specifics of the link between diabetes, hypertension and the APOE e4 genotype and underlying pathology are unclear. These vascular risk factors have direct effects on blood vessels, vascular endothelium and vascular functions, but the unresolved question is whether these mechanisms promote AD type pathology or whether their role is primarily vascular. In the latter capacity, they could increase risk of dementia by causing atherosclerotic or arteriolosclerotic vascular disease, which would lower the threshold at which AD-type changes cause cognitive impairment.

Pathological basis of VaD

On the macrovascular level, infarcts in supratentorial grey and white matter structures may impair cognitive functioning. As mentioned for imaging, a logical scheme that accounts for all ischaemic infarcts — their locations and sizes, as well as their interactions — is simply not available to the field at this time. Simply measuring total infarct volume and establishing a quantitative threshold is not sufficient to accommodate the impact of small but strategically located lesions, e.g. in the thalamus or hippocampus. Thus, neuropathologists find themselves in the position of making subjective judgments about the aetiological importance of the ischaemic infarct burden. Despite nearly 50 years of attention to this problem, there is no systematic way to grade cerebrovascular pathology in a quantitative way that reflects increasing burden of disease.

In an autopsy series carried out by the author that included 12 cases who were considered to represent ‘‘pure’’ VaD (based on the profusion of infarctions and the low level of AD-type pathology), there were no instances of single strategic infarctions, several instances

of multiple large vessel distribution infarcts and several instances of pure lacunar infarctions.[39] One individual had infarctions primarily in the white matter. Had the clinical case definition included VCI without dementia, instances of single infarcts would have been much more common. An autopsy series from Vienna, Austria, found that cystic infarcts accounted for 30% of VaD, lacunar infarction for 48% and microinfarcts for 18%.[3]

Microvascular damage[2,10,69–71] cannot be directly appreciated clinically or on neuroimaging. Microvascular pathology consists of ''foci of pallor, neuronal loss, and gliosis found on microscopic examination[2]''. Microvascular pathology has been cited as being pivotal in the production of dementia, even more important than macro-infarcts.[2] In the Honolulu-Asia Aging Study, high levels of microvascular lesions were as common as high levels of AD pathology in individuals with dementia, regardless of clinical diagnosis.

Microvascular pathology was associated with dementia with an odds ratio of 4.96 (confidence interval 2.1–10.2) compared to those with little or no microvascular pathology.[2] The odds ratio for a high level of neurofibrillary tangle pathology was comparable, 4.27.

A careful study of dementia patients with lacunar infarcts showed that the lacunes themselves were correlated more strongly with the degree of hippocampal and cortical cerebral atrophy than with the dementia itself.[72] The intriguing implication was that microvascular changes were responsible for both the grey matter losses and the cognitive disorder. The role of microvascular ischaemic disease of the white matter is another area whose contribution to dementia is surmised but not proved.[16]

Alzheimer-type pathology often coexists with cerebrovascular disease. The presence of infarcts, neither on imaging nor at autopsy, precludes concurrent AD pathology. In patients with coexistent AD pathology, there is much evidence that VaD pathology and AD pathology are additive.[73–75] Patients with combined AD and VaD had more severe dementia than those with AD alone. In one study, lacunar infarctions appeared to be more important than large vessel infarcts in this additive effect.[75] Some have taken this finding to suggest that because lacunar infarcts may be more tightly linked to microvascular disease than large vessel infarcts, the additive effects on AD by vascular disease may also be through microvascular lesions.

Amyloid angiopathy, which becomes more common with advancing age[76], represents deposition of amyloid-*b* peptide in the media and adventitia of cortical and leptomeningeal vessels. Amyloid angiopathy with haemorrhages is uncommon (about 5% prevalence) inpatients dying with AD[31], whereas AD occurs in about half of patients with cerebral haemorrhages due to amyloid angiopathy.[77] In AD, amyloid angiopathy itself becomes more abundant with advancing parenchymal disease.[78] Whether amyloid angiopathy contributes to microvascular disease is not well understood at this time.

There are several other pathophysiological mechanisms for VaD. Survivors of episodes of anoxic encephalopathy may often be profoundly demented. On rare occasions, vasculitides could cause a dementia[79], but in general, vasculitis is a fulminant condition that is more likely to lead to acute encephalopathies than to a more chronic condition, although survivors of cerebral vasculitis could be left with a dementia. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) should also be mentioned for completeness as it produces a dementia, but it is quite rare.[80, 81] Mutations in the NOTCH3 gene located on chromosome 19 are responsible for this syndrome.[82]

Treatment of VaD

The cholinesterase inhibitors galantamine[83] and donepezil[84] have been shown to be modestly beneficial in patients with VaD diagnosed according to NINDS-AIREN criteria.[28] The magnitude of treatment effect appears to be nearly identical to that seen in AD patients. The drug memantine, approved for the treatment of moderate to severe AD, also has shown modest benefits in VaD patients.[85,86] None of these agents have received US FDA approval for a vascular dementia indication however.

Antihypertensive therapy in cognitively intact individuals appears to reduce the rate of incident dementia.[87] A review[87] of the large-scale randomized trials of antihypertensives showed that in five of six, treatment had a beneficial effect on cognitive function or dementia.[88–92] It is unclear if the type of antihypertensive drug makes a difference or not.

CONCLUSIONS

Cerebrovascular disease is common in the elderly, and it makes a major contribution to late-life dementia. Neuroimaging has substantially improved our ability to document cerebral infarctions. It has also made us aware of the extent of white matter disease that is likely to have an underlying vascular basis. It is possible that the introduction of amyloid imaging techniques[93] may be as helpful in defining VaD as they are for AD. Advances in understanding the neuropathological basis of cognitive impairment in cerebrovascular disease are needed to enable clinicians to diagnose VCI more effectively. Only then will better treatment strategies for symptomatic VCI become more accessible.

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