VASCULAR COGNITIVE IMPAIRMENT – DEFINITION AND TERMS

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ABSTRACT

Vascular cognitive impairment (VCI) incorporates the complex interactions between vascular etiologies, risk factors and cellular changes within the brain and cognition. It includes the patients with vascular disease sufficient to cause a dementia syndrome . It may includes cases with cognitive impairment related to hypertension, silent infarcts, strategic infarcts, diabetes or atherosclerosis.

The spectrum of brain changes comprise both ischemic factors and cellular precesses such as demyelination, axonal damage, diaschisis and atrophy. The studies suggest the association between vascular factors predisposing to cerebrovascular diseases and Alzheimer disease (AD). The hypertension, atrial fibrillation, carotid thickening and diabetes can increase the relative risk for Alzheimer disease.

Studies of computed tomography (CT) and magnetic resonance imaging (MRI) showed that bilateral as opposed to unilateral ischemic lesions are critical. They showed the importance of deep infarcts in the frontal and limbic areas. Other studies indicated that the cortical lesions in the parietal and temporal areas are more important.

Focal clinical signs, neuroimaging and neuropsychological findings may be reliably used to predict the neuropathologic diagnosis of vascular dementia (VaD). (1)

Key words: vascular cognitive impairment, cerebrovascular disease, vascular dementia

INTRODUCTION

The term of VCI include the subjects affected with any degree of cognitive impairment resulting from CVD, ranging from mild cognitive impairment (MCI) to VaD.

VCI includes those patients with vascular disease sufficient to cause a dementia syndrome or VaD. Ischemic brain lesions are considered to be the primary cause of the cognitive impairment. (2)

In the term of VCI there are supposed interactions between vascular etiologies, risk factors, and cellular changes within the brain and cognition. VaD is caused by infarcts of varying sizes including the lacunar infarcts and microinfarcts. (3) VCI cases that do not meet the criteria for dementia are considered as vascular cognitive impairment no dementia (vascular CIND). (4) The dementia resulting from CVD involves multiple causes, risk factors and clinical manifestations. AD and CVD coexist in a large proportion of patients. (5) These patients may present clinically either as AD with evidence of cerebrovascular lesions on imaging or with features of both AD and VCI.

CI may include the cognitive impairment related to diabetes or atherosclerosis, hypertension, transient ischemic attacks, multiple cortico-subcortical infarcts, silent infarcts, strategic infarcts, small vessel disease with lessions of white matter and lacunae. The two main factors to be defined in VCI are the severity of cognitive impairment and the pattern of affected cognitive domains. (6)

VaD, as the subset of VCI patients who fulfill dementia criteria, is the second most common cause of dementia (10%-50% of the patients). The prevalence of VaD had been reported to range from 1,2% -4,2% in persons aged 65 years and older[7]. Prevalence can be viewed as a function of incidence multiplied by the average duration of the disease. In the case of VaD, the disease duration is limited only by death. The incidence data are preferable to prevalence, because prevalence may be confounded by

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the varying duration of survival.The incidence of VaD increases with increasing age. There are not significant difference between prevalence of VaD in men and women. (8)

Risk factors of VCI

- Vascular: arterial hypertension, coronary heart disease, atrial fibrillation, diabetes, myocardial infarction, lipid abnormalities, atherosclerosis, smoking
- Stroke-related factors: transient ischemic attacks (TIA)
- Genetic factors: family history, pathogenic mutations
- Site and size of infarcts
- Specific gene polymorphisms
- Demographic factors

Histopathology

Large infarcts, can involve either vascular territories in whole or in part, or the watershed areas. Lacunes are grossly visible, usually cavitated, infarcts with ragged margins, with the major diameter ranging from 0,5 to 15 mm. (9,10) Lacunes and enlarged perivascular spaces are located especially in the basal ganglia and white matter, mostly in the frontal areas. If the lacunes or the large infarcts there are in the critical areas, they can give rise to dementia. Other critical locations are: medial thalamus, head of caudate nucleus, angular gyrus, frontal and cingulate cortex. Lesions in the hippocampus are common in the VaD. Bilateral hippocampal sclerosis has been identified as a substrate of dementia in the old patients. (11) The microinfarcts and the pseudolaminar necrosis are also two of the most important tissue lesions.

The white matter lesions is important in understanding of cognitive and motor decline in most of patients with VaD. Leukoaraiosis is often attributed to ischemia. Severe and moderate degrees of leukoaraiosis may be associated with only subtle neurological symptoms, but the patients may present with marked cognitive impairments despite the mild leukoaraiosis. Several large population based studies indicated a relation between CVD risk factors and leukoaraiosis (10). Leukoaraiosis has been associated with cognitive dysfunction of variable degree as well as with neurological impairment. Censori et al investigated clinical features associated with dementia after stroke and this study revealed that leukoaraiosis was present in 1/3 of patients with post stroke dementia as opposed to 1/6 of those without dementia. Patients who presented post stroke dementia had more frequent diabetes mellitus, atrial fibrillation, large middle cerebral artery infarction and more severe neurological deficits at entry and at the three months than the non-demented patients. (12)

Marked dilation of Virchow-Robin spaces has may be the mechanism of dementia in several cases. (10) Prior extravasation of plasma in the parenchyma of the brain, followed by a chronic inflammatory reaction resulting in loss of consistency of the tissue leads to the dilation of perivascular spaces. (13)

There are in vascular in VaD the alterations beyond classical histopathology, which are evident only by immunohistochemical techniques. Thus, in addition to the classical changes, focal and global ischemia in experimental animals induces upregulation of β amiloid precursor RNA and protein in neurons and glia. (10) Global ischemia induces accumulation of β amiloid precursor protein in the hippocampus, especially in the areas surrounding those destined to die. β amiloid is expressed in reactive astrocytes between 3 and 60 days post stroke, but not after this time. Apolipoprotein E expression is also increased. (14,15)

Infarcts are associated with widespread activation of microglia, characterized by the expression of major histocompatibility complex class I and II antigens, and complement receptor , as well as the synthesis of β amiloid precursor protein. (10)

Cortical vascular dementia

In the case of cor tical vascular dementia, the onset consisted of days to weeks, there is a stepwise deterioration and a fluctuating course of cognitive state. (16,17)

This syndrome is characterized by predominantly cortical and sub-cortical infarcts.The memory impairment appear early. These patients present agnosia, apraxia, aphasia and also some degree of the dysexecutive functions.

Strategic infarct dementia

Strategic infarct dementia is characterized by focal ischemic lesions involving specific sites that are critical for higher cortical functions. The mechanism of the strategic infarct dementia is not very well known, yet. The cortical sites involved are as follows: the hippocampal area, angular gyrus and cyngulate gyrus. The subcortical sites are: fornix, thalamus, basal forebrain, globus pallidus, the genu of the internal capsule. (18,19)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and hereditary small vessel dementia (CADASIL)

It is caused by a mutation of the Notch 3 gene, which codes for a large transmembrane receptor. Genetic analysis has shown multiple mutation, with the ckuster in the first 2 exons encoding epidermal growth factor-like repeats. In the case of CDASIL, most of the damage is ischaemic, with multiple lacunar infarcts and other areas of leukoaraiosis, but haemorrhage has been also reported. It begins with migraine, usually with aura, as the first symptom. The migraine may begin even before the age of 10 years, but usually during the third decade. This may be preceded by a decade by psychiatric manifestation. CADASIL patients present motor deficits, ataxic hemiparesis, hemianopsia, dysarthria. Epilepsy, pseudobulbar palsy and coma may occurs but is uncommon. The pathology is dominated by widespread lacunes in white matter, basal ganglia, and brain stem. The vessel walls show marked concentric thickening due to deposition of PAS + granular material. This material appears in electron mycroscopy as compact deposits of osmophilic granular material (GOM) apposed to the basal lamina of smooth muscle cells. This is patognomonic of the disease. (10)

CADASIL patients presents hyperintense signals on T2 weighted images located in the white matter, predominantly periventricular and deep, basal ganglia, brainstem. These aspects associated with a positive family history and the presence of GOM in skin or nerve-muscle biopsies, put the clinical diagnosis. (20)

Subcortical vascular dementia

Subcortical vascular dementia incorporates two clinical entities: Binswanger′s disease and the lacunar state. (21)

A history of hypertension is present in 80% of patients. A history of stroke at some stage is almost universal. Diabetes is also often present as risk factor for vascular disease in these patients. There is often a clinical history of prolonged transient ischemic attack. Dementia is intermittently progresive but may become gradually progresive. (22)

Memory loss is lesser than in AD. Behavioural changes are early and proeminent. Also, depression is common in these patients. Clinically, we meet subcortical cognitive syndrome and bulbar signs, gait disorders, dysarthria, motor hemiparesis. At these patients we also meet the dysexecutive syndrom including the impairment in goal formulation, initiation, planning, organizing. Incontinence develops later, but may occur while cognition is still intact. Fluctuating mood with irritability, dizziness and epilepsy were also reported. (23)

The essential changes includes extensive ischemic white matter lesions and lacunar infarcts in the deep gray and white matter structures.The patients having predominantly white matter lesions are included in the Binswanger type. The patients with predominantly lacunar infarcts are included in the lacunar state.

Cerebral amyloid angiopathy (CAA)

It is also known as congophilic angiopathy. In these patients there are the deposit in leptomeningeal and cerebral small blood vessels of material with the psysicochemical properties of amyloid. The main involved protein constituent is β- amyloid. Aβ protein – associated CAA that also contains cystatin C is the predominant type of CAA at old age. CAA extends to the walls of vessels in the leptomeninges, perforating arteries, intraparenchymal arterioles. Very rarely there are vascular deposits in the large cranial arteries.

The clinical features are spasticity, ataxia, facial paralysis, cognitive impairment and sometimes the seizures. The clinical symptoms depend on the distribution of the accumulated protein within the brain and the related hemorrhages. Severe CAA is a high risk for hemorrhagic strokes.

CAA was also found in patients with ischemic cerebral infarction. Severity of CAA was associated with an increased frequency of cerebral infarction in patients with AD. (24)

The hereditary form of CAA is due to mutations in at least two different cordons in the β – amyloid precursor protein gene. (24)

Sporadic form of CAA is common, the prevalence increasing with the age. CAA contribute to dementia through mechanism like hemorrhages, cortical microinfarcts and white matter lesions. Multiple hemorrhages are considered the main involved in the substrate of dementia in these patients. (25)

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