KNOW TO PREVENT: RISK FACTORS OF THE VASCULAR DEMENTIA

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[Conoscere per prevenire: i fattori di rischio della demenza vascolare]

ABSTRACT

The importance of identifying risk factors for vascular dementia (VaD) is derived from the concrete possibility to implement an effective prevention, unlike what happens with degenerative dementias. The aim of this work is to review current knowledge regarding risk factors for vascular dementia.

Key words: *Dementia, vascular dementia, degenerative dementia, risk factors, prevention.*

***Received** January 11, 2013; **Accepted** January 22, 2013*

VaD is the second cause of dementia in Europe and United States, after Alzheimer's disease (AD). Imputable to it are 10-20% of all cases[1] against the 50-60% of cases of AD[2] . In Asia AD and VaD incidence and prevalence almost overlap[3] , probably due to an increased risk of stroke that characterizes the Asian continent.

The mechanisms by which vascular risk factors affect cognitive functions are only partially understood. Almost certainly are involved aging, various co-morbidities, lifestyle and genetic[4] .

Risk factors can be divided into two main groups: modifiable factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, cigarette smoking, physical inactivity, obesity, excessive alcohol consumption) and non-modifiable factors (advanced age, male gender, ethnicity, previous stroke or myocardial infarction). All above mentioned are primary risk factors for stroke - 90% of the stroke risk is attributable to them[5] - but none of them seem to be able to determine brain damage, and therefore cognitive impairment, in a straightforward manner. If the onset of dementia after repeated ischemic events is an established fact, it is not entirely clear whether risk factors listed above are able to determine a cognitive deficit through a secondary mechanism, independent from stroke. This hypothesis, though valid, is difficult to prove because the time required for risk factors exert their deleterious effects is not well known, so it is not easy to perform longitudinal studies.

Doubtless, stroke is itself a risk factor for development of dementia, increasing nine times the risk of onset[6] . In a study conducted on hospitalized patients, risk of developing dementia was 8.4/100 in those who had had a stroke, and 1.3/100 in controls[7] . The risk changes depending on the location, extent and number of cerebral infarcts. For all these reasons, it seems clear that prevention of ischemic events could have some positive effects on the incidence of vascular dementia[8].

Let us see in detail the individual risk factors:

Hypertension

Hypertension exposes cerebral microcirculation to a pulse pressure greater and an abnormal flow which damages the endothelium and mediates

the muscle cells, causing lipohyalinosis and fibrinoid necrosis[9].

A well established element is that hypertension might cause a reduced cerebral blood flow and an increased risk of lesions of periventricular white matter[10,11]. It can cause both damage to wall and critical stenosis of vessels. In the first case occurs arteriolosclerosis and consequent occlusion of vascular lumen, ischemia and lacunar infarction; in the second, it will have a complete cerebral infarct (Binswanger's disease). These two events constitute the context of Subcortical Ischemic Vascular Dementia (SIVD)[12] . Neuroradiological alterations so will be respectively lacunae and white matter lesions (WML). Multiple longitudinal studies confirm that untreated hypertension in middle age (especially systolic), is associated with dementia in old age, more frequently to VaD rather than AD[13,14,15]. In these studies, subjects who developed dementia had higher systolic pressure in middle age. Cognitive decline was proportional to severity of systolic hypertension (for each 10 mm Hg increase in systolic rises by 7% the risk of "average" impairment of cognitive function and 5% that of "high" impairment).

Hypertension in old age seems less related to dementia development. On the contrary, it would seem mainly hypotension (resulting in hypoperfusion) the mechanism which comes into play in aging, even if hypoperfusion may be a secondary mechanism[5]. In support of this, Rotterdam Study of 1993 demonstrated how higher values of blood pressure were able to maintain better cerebral blood flow in elderly patients with atherosclerotic plaques [16].

Rotterdam study demonstrated how people with hypertension in antihypertensive therapy should develop less frequently cognitive impairment compared to subjects who had never taken antihypertensive therapy. This positive effect was greater for individuals over 75 years (risk reduction of 8% compared to 4% under the age of 75). It is not clear, however, if the effect is due to lowering of pressure or to the use of a specific antihypertensive drug[5].

Similar results have been provided by other studies. SYST-EUR study demonstrated how treatment of hypertension through nitrendipine, with possible addition of enalapril or hydrochlorothiazide, is associated with a reduced incidence of dementia of about 50% (from 7.7 to 3.8 for 1000 patients/year)[17].

PROGRESS study (Perindopril Protection Against Recurrent Stroke)[18], based on use of perindopril and indapamide in patients with stroke or TIA, showed that combination therapy reduces risk of developing Vascular Cognitive Impairment (VCI), in contrast to treatment with perindopril alone. HOPE study (Heart Outcomes Prevention Evaluation)[19] showed a significant reduction in relative risk of cognitive decline through the use of Ramipril.

Diabetes Mellitus

Data from Rotterdam study[20] and Haas study[21] support that diabetes mellitus (DM) double the risk of AD and VCI, in all its subtypes, and appears to exert influence independently of its role as vascular risk factor. Metabolic stress caused by hyperglycemic states (through the formation of Advanced glycation end-product, AGE) or hypoglycemia (acute or subacute recurrent events cause neuronal necrosis) and effects of hyperinsulinemia (already in preclinical stage) are considered as potential causes[5].

Diabetics often have more hippocampal[22,23] and cortical atrophy, white matter lesions, lacunar infarcts[24] and typical lesions of AD. Interesting the detection of AGE in context of neuritic plaques and neurofibrillary tangles (even in the early stages of AD[25]) and the increased presence of tangles in diabetics[13].

In contrast to what was seen for hypertension, it appears that diabetics treated (regardless of achievement of target blood glucose) do not enjoy a reduced risk of dementia[5].

Dyslipidemia

Certainly high cholesterol levels are a risk factor for formation of atherosclerotic plaques; however, the role of lipids in increasing risk of dementia is controversial. Evidence from long-term longitudinal studies suggest that increased cholesterol's levels in middle age increase the risk of developing AD and VCI in old age[26,27].

Rotterdam study demonstrates that treatment of hypercholesterolemia with statins appears to reduce incidence of dementia, while this does not happen for other drugs[28]. The authors argue that the effect depends more on anti-inflammatory properties of statins that those hemorheologic.

Atrial fibrillation

It is known as chronic atrial fibrillation is associated with an increased incidence of stroke and heart failure and also, regardless of these conditions, with an increased mortality and morbidity. It is an independent risk factor for development of AD and VCI. This increase cannot be explained with enhanced risk of stroke.

The mechanism by which atrial fibrillation increases risk of cognitive impairment, independently from stroke, is unclear. The hypothesis contemplates hypoperfusion from low cardiac output (in patients with rapid ventricular response), clinically silent stroke or microembolic stroke[5].

Currently there is no evidence of any therapeutic benefit on the risk of dementia neither with drugs for rhythm control nor with anticoagulation therapy.

Smoking and Alcohol

Many evidences assert that smoking is associated with an increased risk of both AD and VCI[29,30,31]. Subjects who smoke more than two packs a day would have a doubled risk for dementia (both types). Smokers also have an increased risk of death for dementia[32].

Zutphen Elderly Study[33] has monitored the effect of smoking and alcohol on cognition, demonstrating a positive correlation between consumption and medium-high incidence of cognitive disorders. Risks and benefits of alcohol consumption are discussed since many years. To date, the only certainty appear to be an increased risk of cognitive decline in people who consume large amounts of alcohol.

Hyperhomocysteinemia

Increased levels of homocysteine has been linked with heart disease[34], carotid stenosis[35], stroke[36,37] and, most recently, with cognitive impairment. Homocysteine levels appear to increase with age[38], probably due to vitamin deficiencies (B6, B12, folate).

Though several studies guarantee a correlation between hyperhomocysteinemia and dementia, it is also true that many deny it. Studies that have tried to correct hyperhomocysteinemia by vitamin supplementation have yielded conflicting results[39,40].

Apolipoprotein E

ApoE is a glycoprotein responsible for lipid transport in brain and other organs. There are three isoforms (E2, E3 and E4) encoded by three alleles (ε2, ε3, ε4). ApoE polymorphism, already known as risk factor for AD, it is considered, by some authors, as a possible risk factor for VaD: the ε4 allele of the APO-E is, in fact, associated with hypercholesterolemia, increase of low-density lipoprotein (LDL) and apo-lipoproteinemia with obvious atherogenic repercussions. ε4 allele is significantly present in patients affected by degenerative dementias compared to healthy ones of the same age that have not ε4[41,42].

Obesity

Obesity, or body fat, is an emerging risk factor for dementia that is attracting ever more attentions, due to the marked effects on metabolism[43]. Some studies suggest that an increase in weight, an high body mass index and an excessive thickness of skin folds increase the risk of dementia, especially if these findings are present in average age[44]. Body Mass Index (BMI) in old age, instead, seems to have a negative correlation with VCI[45].

Education

Low levels of education appear to be associated with an increased risk of VaD. Remains to understand, however, whether this data should refer to a lower socioeconomic status, less healthy lifestyles or to a lower cognitive reserve[46,47].

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