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Hypotension in Subcortical Vascular Dementia, a New Risk Factor – Wasn't It Hypertension?

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1. Introduction

The identification of additional genetic susceptibility genes in the etiology of AD and the metabolic mechanisms leading to differences in age of onset and disease pathogenesis are active areas of current susceptibility. Although all the contributing factors may never be known, scientists have identified several common threads. They include: age (more than 65 years old), sex (women are more likely than men are to develop the disease, in part because they live longer), toxicity (such as overexposure to certain trace metals, such as aluminum), head injury (serious traumatic injury to the head, for example, a concussion with a prolonged loss of consciousness) may be a risk factor for Alzheimer's), hormone replacement therapy (the exact role hormone replacement therapy may play in the development of dementia isn't yet clear; throughout the 1980s and '90s, evidence seemed to show that estrogen supplements given after menopause could reduce the risk of dementia; results from the large-scale Women's Health Initiative Memory Study indicated an increased risk of dementia for women taking estrogen after age 65: the verdict is not yet in on whether estrogen affects the risk of dementia if given at an earlier age), lifestyle (the same factors that put you at risk of heart disease, such as high blood pressure and high cholesterol, may also increase the likelihood that you'll develop Alzheimer's disease, poorly controlled diabetes is another risk factor). Atrial fibrillation, systolic hypertension, and angina have been associated with more rapid decline in cognition, while history of coronary artery bypass graft surgery, diabetes, and antihypertensive medications were associated with a slower rate of decline, and may represent modifiable risk factors for secondary prevention in Alzheimer disease. There was an age interaction such that systolic hypertension, angina, and myocardial infarction were associated with greater decline with increasing baseline age. The attenuated decline for diabetes and coronary artery bypass graft surgery may be due to selective survival. Some of these effects appear to vary with age (Mielke et al., 2007). There is an overlap of risk factors between VaD and AD, so much so that it raises some serious questions about vascular contributions to AD. Recognition that cerebrovascular disease causing dementia may be modified by treatment of cerebrovascular risk factors serves as an important tool for investigating various treatments aimed at secondary prevention of

vascular cognitive impairment (Moretti et al., 2008). Some individuals presenting cerebrovascular pathology probably have some component of Alzheimer's Disease (AD) pathology as part of their dementia; this relationship supports the possible interaction between cerebrovascular disease, aging and the degenerative process (see data and Literature in: Brookmeyer et al., 1998). Various factors may influence the nature and severity of brain degeneration. The degree of cerebral grey matter damage, neuronal death, and survival will be dictated by the multiplicity, size, and laterality of the tissue injury or the extent of vascular disease (Kalaria, 1996; Kalaria, 2010). Anatomical features of the circulation, including the size of vessels and vascular wall cellular elements, e.g., arterioles versus capillaries, are important factors in defining the pathology. The distribution territories of the anterior, posterior, and middle cerebral and the lenticulo-striate arteries affect different structures, including the angular gyrus, the caudate nucleus and medial thalamus in the dominant hemisphere, the amygdala, and the hippocampus, all structures implicated in forms of cognitive impairment (Kalaria, 2010; Ferrer et al, 2008). The origin and degree of vascular occlusion or injury and whether this results in ischemic or hemorrhagic lesions are further factors that define the extent and severity of damage. Alterations in specific genes associated with systemic disease or brain-specific proteins and environmental or lifestyle factors may further modify the course of degeneration. On the other hand, vascular dementia is defined simply as the syndrome of dementia due to brain vascular disease (Hebert et al., 2003). Numerous epidemiological studies show a high prevalence of vascular brain injury amongst the elderly (Wolf et al., 1991; Wu et al., 2002) and recent evidence supports a strong association between vascular risk factors and dementia (Vermeer et al, 2003; Chui, 1989). Overall in the Western world, vascular disease is the second most common cause of dementia (Skoog et al., 1993). However in the very elderly, aged 85 years and older, there is a high risk of both stroke and Alzheimer's disease, and the prevalence of VaD is reported to be slightly higher than that of Alzheimer's disease (46.9% and 43.5%, respectively, with some patients possibly having mixed forms of dementia) (Skoog et al., 1993). Vascular dementia is a heterogeneous syndrome, grouping together a broad category of patients in whom various manifestations of cognitive decline are attributed to cerebral- or cardio-vascular disease. The National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al, 1993) elaborated a clinical and diagnostic tool, the so- called NINDS-AIREN criterium. It lists different pathologies, in order to identify patients with different subtypes of VaD: multi-infarct dementia (multiple large and complete infarcts); post-hemorrhage dementia, and subcortical VaD (small-vessel disease). According to NINDS-AIREN, the subcortical VaD (sVaD) is mainly due to lacunar infarct, occurring in distribution of small arteriole, usually in the white matter, basal ganglia, thalamus and pons, or to microinfarct - not seen on macroscopic examination, small area of cystic or non-cystic necrosis surrounded by astrocytes. Incomplete infarct may also be present, due to a selective loss of neurons, myelin, and oligodendrocytes, without cystic necrosis, occurring in the periphery of major artery distribution infarcts (e.g., penumbra) or in deep white matter. Incomplete white matter infarcts are associated with myelin pallor, astrocytosis, and a variable degree of axonal loss. Subcortical VaD now incorporates the old entities 'lacunar state' and 'Binswanger disease' and relates to small vessel disease and hypoperfusion resulting in focal and diffuse ischaemic white matter lesions and incomplete ischaemic injury (Erkinjuntti et al 1997; Pantoni et al., 2000). Assaying cerebrovascular risk

factors probably can't be used for diagnosis of microvascular VaD, but the more risk factors there are might have some predictive value. There is an uncanny overlap of risk factors between VaD and AD, so much so that it raises some serious questions about vascular contributions to AD. Hypertension has often been observed to be a risk factor for VaD (Brookmeyer et al., 1998; Hebert et al., 2000) and sometimes for AD (Posner et al., 2002; LAuner et al., 1995; Morris et al. 2001) although not always (van Dijck et al., 2004). Hypertension leads to changes in arterioles and eventually to arteriolar occlusive disease and then on to infarction. Hypertension's effects on the brain in VaD or AD could also be related to changes in blood flow or blood-brain-barrier integrity. In fact, a number of epidemiological studies show strong associations between elevations in middle-life blood pressure and the prevalence of later life cognitive impairment and dementia. Increase in systolic blood pressure levels has been associated with more severe periventricular and subcortical white matter lesions (van Dijck et al., 2004). People with poorly controlled hypertension had a higher risk of severe white matter lesions than those without hypertension. But, it clearly merged that a potential negative effect of decreasing diastolic blood pressure level on the occurrence of severe periventricular white matter lesions should be taken into account. Recent large observational studies have suggested that high blood pressure may also play a role in Alzheimer's disease and in the so-called mixed forms of dementia, also defined as overlapping syndromes (vascular/degenerative dementia). The mechanisms linking hypertension to Alzheimer's disease remain to be elucidated, but white matter lesions seen on cerebral magnetic resonance imaging appear to be a good marker of this association (Brookmeyer et al., 1998; Ferrer et al., 2008; Tzourio, 2007). Hypertension leads to changes in arterioles and eventually to arteriolar occlusive disease and then on to infarction, and consequent brain parenchima degeneration (Skoog et al., 1993; 1Hebert et al., 2000; Posner et al., 2002). A large number of epidemiological studies show strong associations between elevations in middle-life blood pressure and the prevalence of later life cognitive impairment and dementia. Early evidence suggest that treatment hypertension in the elderly may be quite successful in reducing incident dementia. In the Syst-Eur trial (Forette et al., 1998), given the high percentage of elderly suffering with untreated hypertension, are that secondary prevention treatment trials such as Syst-Eur might have a substantial impact on cognitive impairment. Indeed, high blood pressure may accelerate cerebral white matter lesions (Yamamoto et al., 1998; Schmidt et al., 1999), but white matter lesions have been found to be facilitated also by excessive fall in blood pressure, (Kario et al., 1996; Nakamura et al., 1995; Watanabe et al., 1996; Chamorro et al., 1997), including orthostatic dysregulation (Matsubayashi et al., 1997) and postprandial hypotension (Kohara et al., 1999). The traditional general practice teaches that "the lower the blood pressure is, the better is the prognosis"; nevertheless, low blood pressure as a predictor of increased mortality has been described in a 5-year prospective study in Finland (Mattila et al. 1988) as well as paradoxical survival of elderly men with high blood pressure (Brookmeyer et al., 1988; 33Langer et al., 1989). Notwithstanding all of this, interpretations of these so-called J-shaped curves between blood pressure, and mortality have always been viewed with caution and skepticism by epidemiologists and statisticians (Fletcher & Bulpitt, 1992; Glynn et al., 1995). Chronic low blood pressure has been positively associated with a number of clinical symptoms and psychosomatic distress—including unexplained fatigue, depression, and anxiety—and with minor psychiatric morbidity (de Buyzere et al., 1998). A causal relationship between low blood pressure and low mood remains uncertain, but a vicious

circle should not be excluded (de Buyzere et al., 1998). Zhu et al. (1998) observed that there was a correlation between systolic pressure reduction and cognitive decline in women, which was not accounted for by other factors. Baseline blood pressure level was not significantly related to cognitive decline in that sample with initial good cognition. The Authors speculated that blood pressure reduction might be an early change of the dementing process (see also literature in Gorelick, 1997), even if no clear statement merges on this point (Ferrer et al., 2008). Ruitenberg et al. (2001) found out that lower systolic and diastolic blood pressures at baseline were associated with a higher risk of dementia at follow-up. This association was observed across all age strata, in men as well in woman and both in Alzheimer's disease and vascular dementia. Subjects with incident dementia also decreased more in blood pressure level than in persons without dementia, even if not significantly (Ruitenberg et al., 2001). This may reflect that low blood pressure causes or contributes to dementia or that incipient dementia leads a drop in blood pressure (Ruitenberg et al., 2001). The authors suggested that for the first part of the proposition, they observed an inverse association between blood pressure and dementia mainly in subjects, who used antihypertensive medication (Ruitenberg et al., 2001). This may indicate that their hypertension was longer lasting, and perhaps that these patients were more susceptible to pressure drops, causing inadequate cerebral blood flow. That would be particularly important in vulnerable areas, such as watershed zones and white matter. A second explanation given by the authors (Ruitenberg et al., 2001) was that low pressure might be a consequence of an incipient dementia. The Authors found that blood pressure was lower in subjects with manifest dementia, and those with dementia, who presented lower pressure, declined more rapidly. The possible explanation given by these Authors (Ruitenberg et al., 2001) is that several areas are involved in pressure regulation; Burke et al. (1994) reported a strong correlation between the decrease of the number of C1 neurones in the medulla oblongata and blood pressure dysregulation in Alzheimer patients. Guo et al. (1999) examined whether initially low blood pressure is related to the incidence of dementia and showed that individuals with baseline systolic pressure of 140 mmHg or less had a significantly higher risk of dementia and Alzheimer's disease. That was the first study that has reported clearly an association between relatively low systolic pressure and increased incidence of dementia with a particular presumable sufferance of brain parenchima, generally hypoperfused in dementia patients (Brown & Frackowiak, 1991), related to an impairment of the cerebral autoregulation, secondary to the degenerative disorder. The direct consequence would be a sequential ulterior reduction of blood pressure, due to dysregulation, which might accelerate the lowering of blood perfusion, altered regulation flow capacity, and therefore the underlying degenerative process (Forette et al., 1998 Bolster et al., 2001; Nilsson et al., 2007). Starting from these studies, we would like to prove if hypotension is a key point in vascular dementia patients, and if this aspect reflects its importance in the daily living assistance.

2. Subjects and methods

2.1 Patients

Study subjects were men and women aged 68–94 years, entering in Cognitive Disorder Unit Evaluation of the University of Trieste, with Mini-Mental State Examination (MMSE) scores of at least 14 (Folstein et al., 1975) and satisfying the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (APA, 2000) for dementia, recruited from June 1st

2007 to December 31st 2010. We have examined 2657 patients, who have been diagnosed as suffering from Mild Cognitive Impairment, Alzheimer's Disease, Frontal Lobe Dementia, Lewy Body Dementia and Parkinson – dementia complex. 1047 patients suffered from vascular dementia: 183 have been diagnosed as Multi-Infarct Dementia. 864 patients suffered from subcortical vascular dementia: these study subjects satisfied the criteria for probable VaD in accordance with the NINDS-AIREN criteria (Roman et al., 1993). A patient was diagnosed as having subcortical VaD (sVaD) when the CT/MRI scan showed moderate to severe ischemic white matter changes (Erkinjunnti et al., 2000) and at least one lacunar infarct. Brain CT-scans or MRI images were randomized and assessed independently, after the radiologist's opinion, by neurologists (RM, PT). Patients were not included in the study if they showed signs of normal pressure hydrocephalus, previous brain tumors, previous diagnosis of major stroke or brain hemorrhage. We did not include patients with white matter lesions, caused by specific etiologies, such as multiple sclerosis, brain irradiation, collagen vascular disease, and genetic forms of vascular dementia (such as CADASIL or CARASIL). Patients with previous major psychiatric illness (i.e. schizophrenia, bipolar disorders, psychosis, compulsive-obsessive disorders, etc) or central nervous system disorders and alcoholism were excluded too.

2.2 Study design

This was a prospective cohort study, designed to investigate gait (balance and equilibrium) disorders, behavioral alterations, drug intake of a subcortical dementia population. Study subjects were 646 men and women, diagnosed as previously stated as subcortical vascular dementia (sVaD), not bedridden, aged 68-94 years outpatients, recruited from June, 1st 2007 to December, 31st 2010, who underwent a standardized baseline assessment that included a detailed history, a physical examination, laboratory tests and psychiatric evaluations. The physical examination included evaluations of pulse rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessel and carotid artery evaluation, electrocardiographic evaluation, and chest X-ray. The physical examination was repeated at every visit; electrocardiographic evaluation and laboratory tests were repeated every 3 months. Caregivers have been instructed to measure blood pressure 3 times/week, baseline and after two minutes in hortostatism and write the evaluation in a diary, which we checked at each visit. Patients in both groups were allowed to continue any previous therapy (e.g. cholinesterase inhibitors, antihypertensive, antidyslipidemic, antidiabetic drugs). (Table 1). Patients were divided in two groups: those with hypertension history and at baseline, who progressively registered low blood pressure (415 patients) and those with hypertension history, who maintained elevated values of systolic/diastolic pressure (398 patients). From this point, the former will be defined as group A, the latter as group B. All patients were followed with periodical neurological and neuropsychological examinations. Visits were scheduled to take place every four months. A complete neuropsychological examination was conducted at baseline, and every 6 months; every 12 months' results were compared. The trial was conducted in accordance with the Declaration of Helsinki and with the Ethics Guidelines of the Institute.

2.3 Outcome measures

Global performance was assessed using the Ten Point Clock test (Manos, 1997) at every visit. Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI)

(Cummings et al., 1994) at every visit. In particular, we have examined sub-item "apathy", from the complex of NPI evaluation system. The Complex activities of daily living were evaluated by the Instrumental activity of Daily living (IADL) (Lawton & Brody, 1969). Frontal Battery has been evaluated every three months (Dubois et al., 1997). Mobility problems were assessed by the Tinetti scale for equilibrium/balance and gait (Tinetti, 1986) at every visit. Hachinski Ischemic score (HIS) was done (Hachinski et al., 1973). Patients were registered for their medical intake and for their blood pressure diaries.

2.4 Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0). Within- and between -group changes from baseline to 12, 24 and 36 months were tested using the Wilcoxon Signed Ranks test. This was done for the overall scores for each efficacy variable. Spearman's rank correlation analyses were performed between behavioral outcome measures (NPI), Tinetti scale, Ten Point Clock Test (TPCT), FAB assessment score, Apathy, and BI. Results are presented as mean changes from baseline with standard deviations, and P-values are presented where appropriate.

3. Results

We have examined 2657 patients, who have been diagnosed as suffering from Mild Cognitive Impairment, Alzheimer's Disease, Frontal Lobe Dementia, Lewy Body Dementia and Parkinson – dementia complex. 1047 patients suffered from vascular dementia: 183 have been diagnosed as Multi-Infarct Dementia. 864 patients suffered from subcortical vascular dementia. These patients, 415 men and 449 women, were included in the study (Table 1).

Age in years (mean ± SD)	72.4 ± 5.8
Gender (male/female)	401/412
Education level in years (mean ± SD)	10.4 ± 2.3
Concomitant illnesses (N.+ % patients)	
Essential hypertension	794 (97.6%)
Diabetes mellitus, type 2	236 (29.1%)
Ischaemic cardiopathy/valvular failure/arrythmias	413 (50.8%)
Chronic obstructive bronchopathy	205 (25.2%)
Neoplasia	36 (4.4%)

Table 1. Baseline characteristics of patients.

Their mean age was 72.4 + 5.8 years, and they had a mean education level of 10.4 + 2.3 years. The diagnosis was based on historical information and neuropsychological assessment and supported by findings on structural (CT or magnetic resonance) imaging. Subsequent follow-up of subjects has reinforced the clinical diagnoses in all cases. Brain CT-scans or MRI images were available for all the 864 selected patients; all the patients attended CT scans, 246 patients did, moreover, MRI studies. These 246 patients were requested by us to complete their diagnostic route with MRI sequences, in case of not adequate imaging acquisition, or not convincing data. Thirty one patients died during follow-up; twenty patients did not have a caregiver, who could guarantee adequate compliance, and therefore have been excluded, after the first year from the study. All the other 813 patients (401 men

and 412 women) completed the full 36-month study. Patients were allowed to continue any previous therapy (e.g. antihypertensive, antidyslipidemic, antidiabetic drugs) (Table 2).

Drug utilization mg/day	baseline	12 months	24 months	36 months
ACE inhibitor	**412 patients**	**292 patients**	**203 patients**	173 patients
Sartan	**283 patients**	**169 patients**	**179 patients**	143 patients
Calcium antagonists	**345 patients**	**172 patients**	**167 patients**	158 patients
Two or more (Antihypertensive) drugs together	**246 patients**	**0**	**0**	**0**
Antidiabetic medication	**186 patients**	**251 patients**	**198 patients**	105 patients
Antiplatetelet drugs	**321 patients**	**349 patients**	**430 patients**	349 patients
ASA	**247 patients**	**344 patients**	**376 patients**	389 patients
Digoxin	**223 patients**	**215 patients**	**175 patients**	125 patients
Diuretics	**153 patients**	**187 patients**	**178 patients**	196 patients
Thiazide diuretics	**165 patients**	**143 patients**	**189 patients**	110 patients
Lipid lowering drugs	**156 patients**	**189 patients**	**265 patients**	311 patients
Nitroglycerine or analogue	**234 patients**	**254 patients**	**209 patients**	148 patients
Bronchodilators	**121 patients**	**87 patients**	**97 patients**	104 patients
A combination of the above therapies	**512 patients**	**683 patients**	**545 patients**	**631patients**

Table 2. A synopsis of the drugs employed by the two groups of patients at baseline

During the follow-up, the patients were prescribed neuroleptics and/or benzodiazepines (Table 3).

Drug utilization	baseline	12 months	24 months	36 months
Benzodiazepines	**144 patients**	**289 patients**	**276 patients**	314 patients
Typical neurolpetics	**78 patients**	**356 patients**	**498 patients**	577 patients
Atypical neurolpetics	**24 patients**	**115 patients**	**167 patients**	345 patients
Two or more drugs	203 patients	345 patients	406 patients	567 patients

Table 3. A synopsis of the SNC drugs employed by the patients

The patients were homogeneously recruited and no demographical/social/ cultural/clinical difference distinguish from each other. Patients were divided in two groups: those with hypertension history and at baseline, who progressively registered low blood pressure (415 patients), and those with hypertension history, who maintained elevated values of systolic/diastolic pressure (398 patients). From this point, the former will be defined as group A, the latter as group B. Two neurologists of the group revised all the imaging, employing the Blennow et al. (1991) scale for CT scans and the Scheltens et al. (1993) scale for MRI imaging. There was 94.2% inter-rater agreement for the independent assessment of the scans (kappa=0.76). Considering the global health conditions, there was an obvious deterioration in the patients as evidenced by the increase of the daily drug uptake (Table 3). Main scores obtained by the patients, during the follow-up have been reported in table 4 as mean and SD . Particularly, the results obtained in the FAB scale, Tinetti Scale, apathy (as sub-score of NPI) have been reported in table 4a which reports the differences within Group A, in the follow-up; in table b, it has been reported the differences within Group B during follow-up; in table 4c it has been reported the differences between the two groups in the follow-up. According to a Wilcoxon Signed Ranks test, there was a general worsening of the cognitive, behavioral and instrumental capacities of the patients observed in the 36 months of follow-up within the two groups (table 4a and 4b). It has been showed that there was an evident difference between groups, as evidenced in table 4c: no significant difference has been registered between the two groups at baseline, a part from the performance obtained at the FAB test ($p<0.05$). At twelve, twenty four and thirty six months, the differences between the two groups were significant ($p<0.01$) as demonstrated by table 4c.

Tests	Baseline		12 months		24 months		36 months	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
TPCT	7.7 ± 0.2	7.4 ± 0.5	6.1 ± 0.1	6.8 ± 0.3	5.4 ± 0.2	6.1 ± 0.5	4.1 ± 0.1	5.9 ± 0.6
NPI	24.5 ± 3.2	23.5 ± 2.4	41.4 ± 2.1	34.5 ± 3.2	66.4 ± 1.1	64.5 ± 2.7	86.3 ± 9.1	74.5 ± 3.2
Apathy (NPI)	6.6± 0.2	6.2 ± 0.4	8.3 ± 0.1	6.8 ± 0.6	9.2 ± 0.5	7.9 ± 0.7	11.1± 0.2	9.6± 0.1
FAB	13.3 ± 1.2	14.1 ± 1.1	10.3 ± 0.5	11.1 ± 1.1	9.3 ± 0.9	10.8 ± 1.3	8.4 ± 0.2	10.1 ± 0.9
Barthel Index	89.1 ± 5.3	87.1 ± 6.2	81.1 ± 1.2	83.1 ± 2.4	76.8 ± 6.1	81.1 ± 4.1	61.1 ± 7.3	69.1 ± 4.3
Tinetti score	21.8 ± 1.8	22.1 ± 1.1	18.3 ± 1.4	21.4 ± 1.4	17.7 ± 1.5	21.1 ± 0.5	15.7 ± 1.6	19.1± 1.1
Hachinski Ischemic Score	7.6 ± 0.1	8.1 ± 0.3	6.4 ± 0.11	7.9 ± 0.1	6.2 ± 0.3	7.3 ± 0.1	6.2 ± 0.1	6.9 ± 0.3

Table 4. Tests results in the patients observed during follow-up

Tests	12 months vs baseline	24 months vs baseline	36 months vs baseline
TPCT	0.9 ± 0.3 p<0.01	5.4 ± 0.1 p<0.01	3.6 ± 0.2 p<0.01
NPI	-16.9 ± 1.3 p<0.01	-41.9 ± 4.3 p<0.01	-61.8 ± 2.1 p<0.01
Apathy (NPI)	-1.7 ± 0.4 p<0.01	-2.6 ± 0.3 p<0.01	-4.5 ± 0.1 p<0.01
FAB	3.2 ± 0.7 p<0.01	4.3 ± 0.3 p<0.01	4.9 ±1.0 p<0.01
Barthel Index	8± 9.3 p<0.01	12.3 ± 5.1 p<0.01	28 ± 4 p<0.01
Tinetti score	3.5 ± 0.4 p<0.01	4.1 ± 1.3 p<0.01	6.1 ± 0.2 p<0.01
Hachinski Ischemic Score	0.8 ± 0.3 p<0.01	1.4 ± 0.2 p<0.01	1.4 ± 0.1 p<0.01

Table 4 a. Tests results in the patients observed during follow-up in Group A

Tests	12 months vs baseline	24 months vs baseline	36 months vs baseline
TPCT	0.6 ± 0.1 p<0.05	1.3 ± 0.1 p<0.05	1.5 ± 0.2 p<0.01
NPI	-11 ± 1.2 p<0.05	-41 ± 0.3 p<0.05	-51 ± 2.1 p<0.01
Apathy (NPI)	-0.6 ± 0.2 p<0.05	-1.3 ± 0.2 p<0.05	-3.4 ± 0.3 p<0.01
FAB	3 ± 0.1 p<0.05	3.3 ± 0.2 p<0.05	4 ±0.2 p<0.01
Barthel Index	4 ± 2.8 p<0.05	6 ± 2.1 p<0.05	26 ± 1.5 p<0.01
Tinetti score	0.7 ± 0.2 p<0.05	1.1 ± 0.6 p<0.05	6.4 ± 1.4 p<0.01
Hachinski Ischemic Score	0.2 ± 0.2 p<0.05	1 ± 0.2 p<0.05	1.2 ± 0.3 p<0.01

Table 4 b. Tests results in the patients observed during follow-up in Group B

Tests	baseline	12 months vs baseline	24 months vs baseline	36 months vs baseline
TPCT	-0.3 ±0.2 ns	-0.8 ±0.2 p<0.05	0.6 ±0.3 p <0.01	1.8 ±0.5 p<0.01
NPI	-1 ±0.8 ns	6.9 ±1.1 p <0.05	1.9 ±1.6 p <0.01	-11.38 ±5.9 p <0.01
Apathy (NPI)	-0.4 ±0.2 ns	1.5 ±0.5 p <0.01	2.7 ±0.2 p <0.01	-1.5 ±0.1 p <0.01
FAB	-0.8 ±0.2 p<0.05	-1.2 ±0.6 p <0.05	-1.5 ±0.4 p <0.01	1.7 ±0.5 p <0.01
Barthel Index	-2 ±1.7 ns	-2.1 ±1.2 p <0.05	-4.3 ± 2 p <0.01	8.0 ±3.0 p <0.01
Tinetti score	-0.3 ±0.7 ns	-3.1 ±0.1 p <0.05	3.4 ± 1 p <0.01	4.6 ±0.5 p <0.01
Hachinski Ischemic Score	-0.5 ±0.2 ns	-1.5 ±0.1 p <0.05	-1.1 ±0.2 p <0.01	0.37 ±0.2 p <0.01

Table 4 c. Tests results in the patients observed during follow-up B vs A

In group A, blood pressure mean values are 130/80 ± 6.5 mm Hg at baseline, and then a decrease of 10.4 ± 7.5 mm Hg at twelve months, 15.6 ± 6.7 mm Hg at twenty four months, and

18.7 ± 5.3 mm Hg at thirty six months. In group B, blood pressure mean values are 150/85 ± 10.2 mm Hg at baseline, and then a decrease of 8.4 ± 3.5 mm Hg at twelve months, 7.6 ± 3.5 mm Hg at twenty four months, and 11. 2 ± 5.3 mm Hg at thirty six months. In group A, there was a dramatic decrease of anti-hypertensive drugs prescriptions. In group B, patients maintained their original prescriptions, though under strict medical follow-up. Spearman's rank correlation analyses indicated that there was a significant correlation between NPI scores and Tinetti score over 24 months (NPI= 56.84 ±12.11, $r=0.81$, $p<0.01$), over 36 months (NPI= 66.03 ±8.81, $r=0.87$, $p<0.01$), in both group. Though it has been evidenced a significant decrease of Tinetti score in Group A, with low blood pressure than in Group B (see table 4, 4 1, b and c). We have found a correlation between benzodiazepines and neuroleptics intake and Tinetti score at 12, 24 and 36 months (respectively $r=0.77$, $p<0.05$; $r=0.78$, $p<0.05$; $r=0.67$, $p<0.05$ at 12 months; $r=0.81$, $p<0.01$; $r=0.77$, $p<0.05$; $r=0.84$, $p<0.01$ at 24 months; $r=0.81$, $p<0.01$; $r=0.82$, $p<0.01$; $r=0.89$, $p<0.01$ at 36 months) in both Groups. We have observed a positive correlation between apathy and NPI total scores in both the groups over 12, 24 and 36 months (respectively $r=0.78$, $p<0.05$; $r=0.8$, $p<0.05$ at baseline; $r=0.82$, $p<0.01$; $r=0.67$, $p<0.05$; at 12 months; $r=0.86$, $p<0.01$; $r=0.77$, $p<0.05$ at 24 months; $r=0.91$, $p<0.01$; $r=0.82$, $p<0.01$ at 36 months). Finally, we did observe a positive correlation between apathy scores and FAB scores only in Group A at every session; in Group B at 24 and at 36 months (respectively $r=0.78$, $p<0.05$ at baseline; $r=0.82$, $p<0.01$ at 12 months, only for Group A; $r=0.86$, $p<0.01$; $r=0.77$, $p<0.05$ at 24 months; $r=0.91$, $p<0.01$; $r=0.82$, $p<0.01$ at 36 months, respectively).

4. Discussion

We have studied well selected 864 patients, for three years, suffering from subcortical vascular dementia. Our aim has been to prove if hypotension is a key point in vascular dementia patients, and if this aspect reflects its importance in the daily living assistance. What we have observed are different points. Subcortical vascular dementia is related somehow to hypertension, mainly because) all the patients recruited have been diagnosed hypertension, during their life. Curiously, some of them (n=415; group A), during the follow-up, registered a dramatic decrease of their blood pressure values, constantly during the entire follow-up, even if the anti-hypertensive drugs have been interrupted; some other (n=398; group B), who had a hypertension history, but maintained elevated values of systolic/diastolic pressure during the entire follow-up. These patients have been studied, and what merged is that the two groups did not differ from a neurological, behavioral, and general drug intake at baseline; there was only a significant difference in cognition performance, as far as group A frontal functions (implementation of strategies, executive function, judgment capability, abstract reasoning, go/no go strategies and auto-inhibition) appear significantly worse ($p<0.05$) than those of Group B. During follow-up, both patients did worse, in their life functions, as far as cognition, behavior, gait, functional independence; but, during the entire follow-up, Group A did worse in all the items when compared to Group B. In particular, these patients were referred as more apathic, abulic, with less frontal performances, with major walking impairment and with lower independence. In other words, it seems that given a selected population, in which hypertension has been correctly established and treated, it might have led to a well-defined white-matter deterioration (the previously called Binswanger' disease); then, when dementia has been diagnosed, the sudden modification

of blood pressure regulation, changed in hypotension, led to a poorer life expectance, due to a worse performance in cognition (as above mentioned), behavior (more apathy and abulia), walking strategies. All these aspects reflect a functional sufference of frontal subcortical neural pathways: it is not known the reason, but frontal lobes have a metabolism rate under basal condition that is 20% more than that of the other brain areas (Moretti, 2006). And it is also well known that age cognitive modifications are related to frontal dysfunctions (Levine et al., 1997; Esposito, 1999; Kramer et al., 1999), due to a reduction of brain reserve capacity. This brings an aged individual closer to the level of insufficiency where only minor additional lesions may be required to precipitate dementia. The degenerative aging changes, though milder, repeat much of the pathology of Alzheimer's disease. In vascular dementia, especially in subcortical vascular type, there is an accentuate expression of what is found in old age (Moretti, 2006). The complete and incomplete white matter infarction, frequently coexisting, would, by virtue of their high prevalence, be the underlying substrate in the recognition of white matter disease (Capizzano Aristides et al., 2007), leuko-encephalopathy or leuko-araiosis (Hachinski, 1994). Having this point stated, it should be consider another question: why are these patients so sensitive to hypotension? And another major problem is: why do these patients change their historical profile and suddenly have low blood pressure, having a positive history of hypertension and not clear signs of new concomitant pathologies, which can determine, *per se*, low blood pressure? The hypothesis here are suggestive, but not at all conclusive. The small artery vessels of an hypertensive patient show a degeneration of the smooth muscle layer, which is replaced by collagen in a hyaline fibrosis, leading to a subtotal luminal occlusion. These arterioles share traits with non-hypertensive lipohyalinosis (Zhang et al, 1994), as well as with hypertensive arteriolosclerosis, and may concur with hypertensive changes. Anatomically, the smaller resistance blood vessels undergo degenerative changes consisting of thickening and fibrosis of the media (in muscular arteries) and intima, and patchy degeneration of smooth muscle cells producing luminal narrowing and increased vascular resistance. Although the resting CBF is the same in normotensive and hypertensive individuals, these structural changes limit the capacity of the resistance vessels for maximal vasodilatation and impair tolerance of lower blood pressures, while improving tolerance to hypertension through vasoconstriction of these same vessels. Long-term antihypertensive treatment can reverse these adaptive changes and shift the auto-regulation curve back to its normal range, although only limited reversibility occurs in elderly hypertensive patients (Moretti et al., 2008). Moreover, it has been observed that there is another possible explanation which might be related to the sudden dys-regulation observed in these patients. Relatively low blood pressure seems to be correlated with dementia even in a preclinical stage. Different Authors (Guo et al., 1991) started from the speculation that cerebral blood flow is reduced in dementia patients (Brown & Frackowiak, 1991). That was generally thought to be related with reduced metabolic activity of the brain or with a major vascular lesion. The authors hypothesized that the reduction of cerebral blood flow might be related to the impairment of the cerebral autoregulation, secondary to the degenerative disorder. The direct consequence would be a sequential ulterior reduction of blood pressure, due to dys-regulation, which might accelerate the lowering of blood perfusion and therefore the underlying degenerative

process (Yamamoto et al., 1998; Bolster et al., 2001; Nilsson et al., 2007; Mehagnoul-Schipper et al., 2002). Moreover, the authors interpreted these results as a potential expression of the frailty and deteriorated vitality of the oldest old, in keeping constantly the auto-regulation capabilities of the normal brain, and expressed their concern, due to this frailty, on the real impact of lowering pressure in oldest age (Nilsson et al., 2007). An age-related impairment of the vascular auto-regulation due to impaired functioning of the autonomic nervous system can lead to symptoms derived from blood pressure altered dysregulation in the elderly. Additionally, age-related arteriolar changes, including endothelial changes, have been suggested to reduce the baroreflex activity and thereby predispose for deleterious blood pressure falls (Salloway, 2003). The prevalence of orthostatic and non-orthostatic hypotension reached 50% in clinically evaluated VaD cases (Salloway et al., 2003; Mirski, 2005). The possible *liaison* that relates lower blood pressure, dysregulation of cerebral blood flow, vascular dementia, (and eventual AD dementia) might be the pivotal role of acetylcholine (Ach). Ach regulates the cerebral blood flow through the parasympathetic innervation of the circle of Willis and of the pial vessels (Vasquez & Purve, 1979), and it causes significant arterial relaxation by promoting the synthesis of vasodilator agents (Vanhoutte, 1989). Preclinical research using the spontaneously hypertensive stroke-prone rat model of VaD has shown a significant reduction in the levels of acetylcholine (ACh) and choline in the cortex, hippocampus and cerebrospinal fluid compared with normal rats (Kimura et al., 2000). When compared with normal rats, spontaneously hypertensive stroke-prone rats have significantly lower levels of acetylcholine in the cerebrospinal fluid (CSF) (Togashi et al., 1994). In the latter study, the differences in CSF levels between normal rats and stroke prone rats increased with age, suggesting progressive deterioration of central cholinergic function in hypertensive stroke prone rats. The cholinesterase inhibitor epistigmine has been shown to improve blood flow in the Sprague-Dawley rat with tandem occlusion of left middle cerebral and common carotid arteries. Epistigmine also enhanced the ischaemia-induced rostral shift of cerebral blood flow maximum in the contralateral hemisphere and the redistribution of cerebral blood flow, a phenomenon possibly related to recovery of function (Scremin et al., 1997). Very recently, to prove the role of acetylcholine in vessel regulation muscarinic receptors, M5, have been studied. The M5 muscarinic receptor is the most recent member of the muscarinic acetylcholine receptor family (M1-M5) to be cloned. Because M5 receptor mRNA has been detected in several blood vessels, Yamada et al. (2001) investigated whether the lack of M5 receptors led to changes in vascular tone by using several in vivo and in vitro vascular preparations in knockout mice. Strikingly, acetylcholine, a powerful dilator of most vascular beds, virtually lost the ability to dilate cerebral arteries and arterioles in M5R_/_ mice. This effect was specific for cerebral blood vessels, because acetylcholine-mediated dilation of extra-cerebral arteries remained fully intact in M5R_/_ mice. Therefore, as often happens in neurological studies, the more hypotheses, the more questions: why should patients with the same pathology (subcortical vascular dementia) respond so differently to blood pressure regulation? What is the role of blood pressure dysregulation in sVAD patients, without a previous history of hypertension? Should we consider the possibility to treat differently patients with dementia and hypertension? More studies should consider these fundamental points, in order to implement knowledge and eventfully ameliorate treatment options for vascular dementia.

5. Conclusions

In conclusion, we could state:

1. low flow states are critical to the pathogenesis of ischemic leuko-encephalopathy; in particular this is particularly true in subcortical vascular dementia, where the cerebral frontal subcortical regions are particularly sensitive to hypo-perfusion
2. We do not know several points: is hypotension a primary event in vascular dementia or is it secondary to the degeneration of brain structure? What is the role of acetylcholine in blood flow dys-regulation? Why do patients with dementia have such different response to blood pressure control?
3. Taking into considerations all these points, we strictly recommend to the clinicians who face every day these patients that they should check strictly blood pressure, and that they should taper anti-hypertensive medications according to aging-associated declines in BP and tendency toward orthostasis? The neurological concept of "tailored therapy" should begin with the most huge and wide-spread diffused drugs, such as hypertensive drugs
4. In frail patients, such as the old patients with dementia, clinicians should consider the concept of the minimization of ancillary drugs, e.g. anti-diabetes, bronchodilators, diuretics, anty-arythmics, and so on. The entire drug set should be reconsidered at every visit, taking into account the real state of the patients, updated at the moment
5. Benzodiazepines and other meds that could lower BP in the elderly should be prescribed when necessary, without doubts, but the prescriptions should be followed during the time course of the life span of the demented patients.

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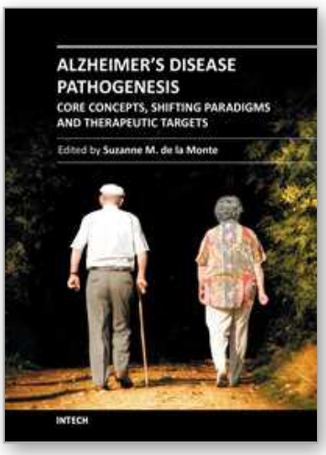

Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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