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Demonstration of Subclinical Organ Damage to the Central Nervous System in Essential Hypertension

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1. Introduction

Hypertension is a common condition, which affects approximately 25% of the adult population, with a higher prevalence in black (African origin) people. Presently it is considered to affect 1 billion people worldwide. Essential or primary hypertension, also known as hypertension of unknown cause, constitutes approximately 90-95% of cases of hypertension. It is a major risk factor for cardiovascular and cerebrovascular diseases and is responsible for most deaths worldwide. Risk factors for hypertension include family history, ageing, lifestyle (e.g. stress, diet, alcohol), and obesity.

The prevalence of hypertension in Cuba according to the 2010 statistics of the Ministry of Health is 202.7/1000 (http://files.sld.cu/hta/files/2011/09/prevalencia-de-hta.pdf), but it is considered to be underestimated. An epidemiological study conducted in 1995 in urban areas had revealed a prevalence of 30.6%.

As the population ages, the prevalence of hypertension is expected to increase even further, making it very important to establish more effective preventive measures. The Framingham Heart Study has implied that individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension. It has been well established that the relationship between blood pressure (BP) and risk of cardiovascular events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance to suffer from heart attack, heart failure, stroke, and kidney disease (Chobanian et al, 2003).

Primary hypertension results from the interplay of internal derangements (primarily in the kidney) and the external environment. Sodium, the main extracellular cation, has long been considered the pivotal environmental factor in the disorder. Many pathophysiologic factors have been implicated in the genesis of essential hypertension: increased sympathetic nervous system activity, perhaps related to heightened exposure or response to psychosocial stress; overproduction of sodium-retaining hormones and vasoconstrictors; long-term high

sodium intake; inadequate dietary intake of potassium and calcium; increased or inappropriate renin secretion with resultant increased production of angiotensin II and aldosterone; deficiencies of vasodilators, such as prostacyclin, nitric oxide, and the natriuretic peptides; alterations in expression of the kallikrein–kinin system that affect vascular tone and renal salt handling; abnormalities of resistance vessels, including selective lesions in the renal microvasculature; diabetes mellitus; insulin resistance; obesity; increased activity of vascular growth factors; alterations in adrenergic receptors that influence heart rate, iontropic properties of the heart, and vascular tone; and altered cellular ion transport. The concept that structural and functional abnormalities in the vasculature, including endothelial dysfunction, increased oxidative stress, vascular remodeling, and decreased compliance, may antedate hypertension and contribute to its pathogenesis has gained support in recent years (Adrogue & Madias, 2007; Oparil et al, 2003).

Hypertension has been extensively recognized as a highly prevalent risk factor for cardiovascular disease, becoming an increasingly common health problem worldwide because of increasing longevity and prevalence of contributing factors such as obesity, physical inactivity and an unhealthy diet. The current prevalence in many developing countries, particularly in urban societies, is already as high as those seen in developed countries. It also plays a major etiologic role in the development of cerebrovascular disease and renal failure.

In the 2007 European Guidelines for the management of arterial hypertension, it is recognized that although cardiovascular morbidity and mortality bear a continuous relationship with both systolic and diastolic blood pressures; the relationship has been reported to be less steep for coronary events than for stroke, which has been labelled as the most important ''hypertension related'' complication. The fact that hypertension is considered a major risk factor for an array of cardiovascular and related diseases, and the wide prevalence of high BP in the population, led to the World Health Organization (WHO) listing high BP as the first cause of death worldwide (Mancia et al, 2007).

Taking into account the very high prevalence of hypertension in the general population and its deleterious consequences, signs of organ involvement are sought carefully, and a large body of evidence is now available on the crucial role of subclinical organ damage. For cardiovascular and renal diseases this has been well established, as the techniques applied are widely available; but the detection of initial brain deterioration, requires the use of imaging techniques, whose availability and costs do not allow indiscriminate use by general medical practitioners.

In this chapter we present an update on the current status of markers employed for the early detection of brain damage in essential hypertension, and our experience in relation to the use of serum biochemical markers of brain injury.

2. Target organ damage in hypertension

The consequences of hypertension have been in constant debate since the mid 20th century. The most renowned consequences are probably those related with its role as a risk factor for myocardial infarction, heart failure, stroke and kidney disease, although it has also been involved in the development of vascular cognitive impairment and vascular dementia [Mancia et al, 2007; Chobanian et al, 2003; Henskens et al, 2009]. Chronic hypertension affects the cardiac and vascular systems, and various organs, especially the brain, kidney, and retina.

Table 1 shows the Position Statement of the 2007 European Guidelines for the Management of Arterial Hypertension concerning the detection of subclinical organ damage in hypertensive patients.

Organ damage	Techniques for detection
Heart •Left ventricular hypertrophy •Angina or prior myocardial infarction •Prior coronary revascularization •Heart failure	Electrocardiography should be part of all routine assessment of subjects with high BP in order to detect left ventricular hypertrophy, patterns of ''strain'', ischemia and arrhythmias. Echocardiography is recommended when a more sensitive detection of left ventricular hypertrophy is considered useful. Geometric patterns can be defined echocardio-graphically, of which concentric hypertrophy carries the worse prognosis. Diastolic dysfunction can be evaluated by transmitral Doppler.
Brain •Stroke or transient ischemic attack •White matter hyperintensities (WMH)	Silent brain infarcts, lacunar infarctions, microbleeds and white matter lesions are not infrequent in hypertensives, and can be detected by MRI or CT. Availability and costs do not allow indiscriminate use of these techniques. In elderly hypertensives, cognitive tests may help to detect initial brain deterioration.
Chronic kidney disease GFR below 60 ml/min per 1.73 m2 (corresponding approximately to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women), 20 or (2) the presence of albuminuria (>300 mg/day or 200 mg albumin/g creatinine)	Diagnosis of hypertension-related renal damage is based on a reduced renal function or an elevated urinary excretion of albumin. Estimation from serum creatinine of glomerular filtration rate (MDRD formula, requiring age, gender, race) or creatinine clearance (Cockroft–Gault formula, requiring also body weight) should be routine procedure. Urinary protein should be sought in all hypertensives by dipstick. In dipstick negative patients low grade albuminuria (microalbuminuria) should be determined in spot urine and related to urinary creatinine excretion.
Peripheral arterial disease	Ultrasound scanning of carotid arteries is recommended when detection of vascular hypertrophy or asymptomatic atherosclerosis is deemed useful. Large artery stiffening (leading to isolated systolic hypertension in the elderly) can be measured by pulse wave velocity. It might be more widely recommended if its availability were greater. A low ankle-brachial BP index signals advanced peripheral artery disease.
Retinopathy	Fundoscopy – Examination of eye grounds is recommended in severe hypertensives only. Mild retinal changes are largely non-specific except in young patients. Hemorrhages, exudates and papilloedema, only present in severe hypertension, are associated with increased CV risk.

Table 1. Detection of subclinical organ damage in hypertensive patients

The brain is an early target for organ damage due to high BP, which is the major modifiable risk factor in men and women for ischemic and hemorrhagic stroke, as well as small vessel disease predisposing to lacunar infarction, white matter lesions (WML), and cerebral microbleeds, which are frequently silent. Arterial hypertension has been related to the development of brain damage, dementia, other CNS dysfunctions and even to milder forms of brain injury (Al-Sarraf and Philip, 2003; Amenta et al, 2003). The mechanisms underlying brain damage are thought to be a consequence of oxidative stress, inflammation and a defect in blood-brain barrier permeability (Al-Sarraf & Philip, 2003, Ishida et al, 2006; Poulet et al, 2006; Ueno et al, 2004).

Currently, hypertension guidelines mainly recognize the heart and kidneys as the crucial target organs affected by high blood pressure. Nevertheless, recently Henskens et al (2009) showed that silent cerebrovascular disease (identified with brain MRI) is a more frequent finding in hypertensive patients than cardiorenal damage. On the other hand, cardiovascular risk in these patients equaled that of patients with cardiorenal involvement and was significantly higher than that observed in patients without any hypertensive target-organ damage. This work suggested that the addition of silent cerebrovascular disease as a marker of hypertensive target-organ damage, apart from measures of cardiorenal involvement, refined the identification of patients at increased risk of cardiovascular and cerebrovascular complications. Thus, extending the search for hypertensive target-organ damage to other organs such as the brain might not only refine risk stratification, but might also optimize antihypertensive therapy. According to the results obtained by Henskens et al, 35% of the patients free of organ damage had actually silent brain damage. If we take into account that in the current guidelines for the management of arterial hypertension, the decision of drug intervention depends largely on the presence of target-organ involvement, these patients would be receiving suboptimal treatment.

The Reappraisal of the European Guidelines on hypertension management (Mancia et al, 2009) reports that, in a group of 192 untreated hypertensive patients (aged 18–90 years) without overt cardiovascular disease, silent cerebrovascular lesions (WML, lacunar infarcts, cerebral microbleeds) were more prevalent (44%) than cardiac (21%) and renal (26%) subclinical damage and frequently occur in the absence of other signs of organ damage. On the other hand, 58% of patients with demonstrable cardiac or renal damage or both had silent cerebrovascular lesions.

Stroke is the main neurological cause of mortality and the third most common cause of death worldwide, and hypertension is still it´s most important risk factor. In clinical trials, antihypertensive therapy has been associated with 35–40 percent reductions in stroke incidence [Chobanian et al, 2003].

Ohira et al (2006) studied a cohort of more than 14 000 men and women aged 45 to 64 years (free of clinical stroke) from the ARIC study (Atherosclerosis Risk in Communities), who were followed during an average of 13.4 years. They found that during the follow-up period, 531 incident ischemic strokes occurred (105 lacunar, 326 nonlacunar, and 100 cardioembolic strokes), and hypertension was the most powerful predictor for all ischemic stroke subtypes.

The evaluation of the consequences of hypertension on the heart and kidney has become a mainstay in routine clinical practice for years. Nevertheless, target organ damage to the brain

is currently a research issue, and little has been accomplished in relation to introducing effective and low cost evaluation methods to be used by the medical practitioner.

3. Biomarkers for brain damage in hypertension

During the last decade research efforts have increased trying to demonstrate subclinical organ damage to the central nervous system as a consequence of essential hypertension. The most important evidence has been obtained employing imaging techniques (MRI, CT and positron emission tomography), as microvascular disease results in chronic ischemic changes affecting mainly the white matter.

Neuropsychological methods have demonstrated impairment of different cognitive domains (attention, memory, executive function) in hypertensive patients. Although the effect of anti-hypertensive treatment on cognitive function and dementia onset is controversial, a meta-analysis of randomized clinical trials suggested that anti-hypertensive treatment is beneficial for the prevention of cognitive decline, particularly in elderly high risk patients (O'Sullivan et al, 2003).

Another line of investigation has been brain electrical activity in hypertension. A recent study in neurologically asymptomatic hypertensive patients showed that quantitative EEG revealed altered spontaneous brain activity, mainly in the frontal and midline regions of the left hemisphere, which they infer as probably associated with brain hypoperfusion (De Quesada, 2010).

There is ongoing research into the association of blood pressure variability over the daytime and night-time periods (e.g.dipping status, early morning surge) with early brain deterioration in hypertension. To date it remains unknown whether and to what extent monitoring ambulatory blood pressure could prove useful for detecting subclinical damage of the central nervous system in hypertensive patients (Sierra, 2011).

There are many published reports indicating that serum molecular markers for neuronal damage are useful for estimating the timing and extent of cerebral injury, as well as for long term clinical outcome in several conditions, such as cardiopulmonary bypass, cardiac arrest, stroke, traumatic brain injury and others. For many years research has been directed toward the identification of biomarkers for establishing the differential diagnosis, aetiology and prognosis, which have gone from the application of clinical scores to more complex imaging techniques. In between these two methods, blood based biomarkers have received an important attention, especially during the last decade.

3.1 Imaging techniques

There is strong evidence that cerebral white matter hyperintensities (WMH) in hypertensive patients should be considered a silent early marker of brain damage. MRI and positron emission tomography (PET) techniques have shown signs of hypertensive target organ damage in the brain of asymptomatic hypertensive patients. WMHs or leukoaraiosis have been extensively documented in hypertensive patients, but silent lacunar infarcts and microbleeds can also be found, and recently dilated Virchow-Robin spaces have been considered as indicative of vascular damage (Angelini et al, 2009; Kitagawa, 2010; Lindgren et al, 1997; Mancia et al, 2007).

Hypertension is associated with the risk of subclinical brain damage noticed on cerebral MRI, particularly in elderly individuals. The most common types of brain lesions are WMH,

which can be seen in almost all elderly individuals with hypertension and silent infarcts, the frequency of which varies between 10% and 30% according to different studies. Both lesions are characterized by high signal on T2-weighted images. Another type of lesion, more recently identified, are microbleeds, which are seen in about 5% of individuals on MRI Gradient echo (GRE) T2* images (Tzourio et al, 2010).

Several studies have suggested that sustained or uncontrolled hypertension is associated with a greater WMH load. The level of blood pressure also seems to play a role, higher blood pressure values being associated with higher grades of WMH. These dose-dependent effects provide strong support for a causal relationship between high BP and WMH.

Older age and hypertension are constantly reported to be the main risk factors for cerebral WMH. Hypertensive patients have a higher rate and extension of cerebral WMHs compared with normotensives (Sierra et al, 2011).

In humans, long term hypertension has been associated with the presence of periventricular and subcortical white matter lesions, and a subsequent cognitive decline has been demonstrated in certain settings (De Leeuw et al, 2002; Lindgren et al, 1997). Henskens et al (2009) described a continuous relationship between the volume of WMHs and ambulatory BP levels, while successfully controlled hypertension had a lower risk of WMHs (De Leeuw et al, 2002; Kuller et al, 2010). White matter lesions may arise from factors associated with brain hypoperfusion and breakdown of the blood-brain barrier, leading to decreased cerebral blood flow and consequent cerebral ischemia (De Leeuw et al, 2002; Henskens et al, 2009).

The clinical significance and pathological substrate of WMH are incompletely understood. It is known that they are an important prognostic factor for stroke, cognitive impairment, dementia and death. Cerebral WMH are more common and extensive in patients with cardiovascular risk factors, such as hypertension and diabetes mellitus, heart disease, and symptomatic cerebrovascular disease (Sierra el al, 2011).

Kitagawa (2010) studied the association between cerebral blood flow (CBF) and cognitive decline in hypertensive patients. They enrolled 27 cognitively intact patients with lacunar infarction or cerebral white matter lesions in MRI and measured CBF and cerebral vascular reactivity (CVR) with PET. Their results strongly suggest that cerebral hypoperfusion is associated with later cognitive decline in hypertensive patients with cerebral small vessel disease.

The pathogenesis of WMH remains unclear, but the main current hypothesis concerning the association between high BP and WMH is that long-standing hypertension causes lipohyalinosis of the media and thickening of the vessel walls, with narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep white matter. On the other hand, low BP has also been reported to be a risk factor for WMH (Sierra, 2011).

3.2 Retinal microvascular abnormalities

The retina offers a unique, noninvasive, and easily accessible window to study the microvascular etiology of cerebrovascular disease. Retinal and cerebral small vessels share similar embryological origins, anatomical features, and physiological properties. The hypertensive retinal changes defined qualitatively from a fundus examination have been traditionally classified into four grades of retinopathy (Scheie, 1953); nevertheless, most hypertensive patients today present early in the process of their illness, and hemorrhages

and exudates (grade 3), not to mention papilloedema (grade 4), are observed very rarely. The milder degrees of retinopathy appear to be largely non-specific arteriolar alterations (Grades 1 and 2) and their usefulness for prognosis has been questioned (Mancia et al, 2007), except for young patients. Thus, more selective methods for objectively investigating ocular damage in hypertension have been developed and studied. Digitized retinal photographs can be analyzed by a semiautomated program to quantify geometric and topological properties of arteriolar and venular trees. This method has identified hypertension-related topological alterations of retinal vasculature and showed that retinal arteriolar and venular narrowing may precede the development of hypertension (Grassi & Schmieder, 2011).

Cheung et al (2011) provided interesting data on the quantitative and qualitative assessment of retinal microvascular abnormalities in a general population and their relationships with blood pressure values. These authors developed new quantitative parameters which describe the retinal branching pattern (retinal vascular branching angle, the retinal vascular branching asymmetry ratio and the retinal vascular fractal dimension), as well as qualitative parameters (focal arteriolar narrowing, arteriovenous nicking, opacification of the arteriolar wall and retinopathy signs). These innovative parameters allow the investigators to improve the sensitivity and specificity of the approach in detecting retinal microcirculatory alterations.

Recently the presence of WMHs was said to be related not only to elevated brachial systolic BP, pulse pressure and arterial stiffness, but also to retinal arterial narrowing (Scuteri et al, 2011).

Studies have shown that retinal microvascular flow is reduced in persons with WMH and lacunar infarction. In a cohort of 1684 asymptomatic people aged 51–72 years from the ARIC study, individuals with WMH were more likely to have retinal microvascular abnormalities (Sierra et al, 2011). Retinal microvascular abnormalities measured at baseline were prospectively associated with a long-term risk of subclinical cerebrovascular disease on MRI, independent of conventional risk factors in this population-based cohort of middle-aged persons without clinical stroke. The authors suggested that retinal microvascular abnormalities are early and, possibly, more sensitive markers of subclinical cerebral small-vessel disease before radiological and clinical manifestations become apparent.

3.3 Cognitive tests

The role of hypertension as a risk factor for cognitive impairment is known from cross-sectional and longitudinal studies. The outcome of chronic microvascular damage is a continuous progression from mild cognitive alterations to overt vascular dementia. Semplicini et al (2011) reported the time course of cognitive changes in a cohort of long-term treated hypertensives, who never met the clinical criteria for dementia. At basal observation, the executive functions (the most affected cognitive domains) correlated with attention and cerebrovascular damage, but not with BP. They found that attention was positively correlated to BP (the higher the BP, the better attention performance). After 6-year follow-up, attention and executive functions improved, in spite of the minor BP changes, memory decline and progression of cerebrovascular damage. Based on these findings they suggested that short-term BP lowering negatively affected executive performance through unfavorable effects on attention. During long-term treatment, attention improved, probably because of adaptation of the cerebral circulation to lower BP, and this would also account for

improvement of executive functions, in spite of the similar BP control and greater cerebrovascular damage.

Cognitive tests may help to detect initial brain deterioration in hypertension. It has been established that microvascular brain damage electively and predominantly affects executive function, with a slower information processing, impairments in the ability to shift from one task to another, and deficits in the ability to hold and manipulate information (i.e., working memory). Ideally, neuropsychological evaluation should include tests exploring multiple cognitive domains (executive function and activation, language, visuospatial ability, memory), in addition to neurobehavioral symptoms and mood. It has been put forward that future clinical guidelines should make clear that cognitive impairment has to be considered as target-organ damage in hypertensive patients, although it has been mentioned in the 2007 Guidelines from European Society of Hypertension (Scuteri et al, 2011).

The mechanisms underlying hypertension-related cognitive changes are complex and are not yet fully understood. It has been suggested that increased BP may explain the deterioration in cognitive functions in hypertensive individuals involving small vessel disease, white-matter lesions and endothelial dysfunction. An association was encountered between the presence of WMH and poorer performance on neuropsychological tests in middle-aged, asymptomatic, never-treated essential hypertensive patients (Sierra, 2011).

3.4 Physiological and neurophysiological methods

3.4.1 Ambulatory blood pressure monitoring

There is ongoing research into the association of blood pressure variability over the daytime and night-time periods (e.g. dipping status, early morning surge) with early brain deterioration in hypertension. To date it remains unknown whether and to what extent ambulatory blood pressure monitoring (ABPM) could prove useful for detecting subclinical damage of the central nervous system in hypertensive patients.

In essential hypertension, the presence of WMH has been associated with an exaggerated decline in nocturnal BP; however, this finding has not been replicated in subsequent studies. Steady and pulsatile components of daytime, night time and 24-h BP have gained increased interest in the prediction of WMH, lacunar infarctions and stroke. Van Boxtel et al (2006) reported no association between night time dipping of BP and WMH load, whereas daytime and 24-h pulse pressure averages were associated with pWMH, and systolic BP and mean arterial pressure for all periods were higher in patients with lacunar infarctions. They concluded that there was no relationship between diurnal BP rhythm and evidence of structural or functional cerebral damage in a population of newly diagnosed hypertensive individuals, but that the ABP profile may predict lesion type in early asymptomatic cerebral abnormalities.

Although in the Japanese population, nondipping and extreme dipping have repeatedly been associated with silent cerebrovascular disease (WMH and lacunar infarctions), the consequences of diurnal BP variations on the brain remain to be elucidated in Caucasian populations. Several reasons have been adduced: limitations in study size; different considerations for lesion description; classification of dipping (no consensus on what BP variable to use: systolic BP, diastolic BP or mean arterial pressure); optimal cutoff values; presentation of data (relative dipping or dipping status); duration of hypertension and treatment history (Van Boxtel et al, 2006). In advanced old age, hypertension was found to

be associated with evidence of target-organ damage; ABPM was positively associated with cerebral periventricular hyperintensities on MRI, and was more effective than conventional BP measurement in predicting HT target-organ damage (O'Sullivan et al, 2003).

Very recently Sierra (2011) extensively reviewed the association between ABP parameters and WMH, and concluded that although ABPM 24-hour values are related to the presence and severity of cerebral WMH, the direction of this association still remains speculative and that larger, longitudinal studies will be required to establish causality.

3.4.2 Brain electrical activity

Another line of investigation has been brain electrical activity in hypertension. A study conducted in neurologically asymptomatic hypertensive patients showed that quantitative EEG revealed altered spontaneous brain activity, mainly in the frontal and midline regions of the left hemisphere, which they infer as probably associated with brain hypoperfusion (De Quesada et al, 2005). More recently De Quesada-Martínez & Reyes Moreno (2010) investigated the localization of paroxysmal activity employing Low Resolution Electromagnetic Tomography (LORETA) in 84 patients with high BP and no history of neurological diseases. They found that the generators for the paroxysmal activity were mainly localized on the right Brodmannn´s 17 and 37 areas, and on the left Brodmannn´s 6, 39 and 10 areas. These regions are very sensitive to hypoperfusion caused by arterial hypertension.

3.5 Blood biomarkers

There are many published reports indicating that serum molecular markers for neuronal damage are useful for estimating the timing and extent of cerebral injury, as well as for long term clinical outcome in several conditions, such as cardiopulmonary bypass, cardiac arrest, stroke, traumatic brain injury and others (Dassan et al, 2009; Gottesman & Wityk, 2006; Marchi et al, 2006; Selakovic et al, 2005; Shinozaki et al, 2009).

Nevertheless, to our best knowledge attempts to demonstrate silent brain damage in hypertension employing serum biochemical markers have only been made in two settings:

1. Schmidt et al. in 2004 provided preliminary evidence demonstrating that increased S100B was associated with eclampsia, but not with preeclampsia or chronic hypertension in pregnant women, conditions very dissimilar to essential hypertension. They hypothesized that increased S100B could be secondary to cerebral vascular changes leading to overperfusion, edema, and ischemia, as well as to seizures themselves, although they deemed the latter less plausible.
2. Al-Rawi and Atiyah (2009) measured salivary and serum levels of neuron specific enolase (NSE) in 25 hypertensive patients. Although they did not attain statistical significance, they observed higher mean serum NSE levels in hypertensive patients than in healthy controls, with values ranging between those obtained in ischemic stroke patients and healthy controls. The object of their study was not hypertension, and no associations were made with clinical variables related to the severity of hypertension.

For decades, researchers have sought for clinically useful blood biomarkers of nervous system injury, and these efforts have intensified in the past few years. Although the ideal biomarker remains elusive, several molecules have received attention (CK-BB, glial fibrillary acidic protein, S100B, NSE, among others) (Laskowitz et al, 2009; Mayer & Linares, 2009). Of

these, NSE and S100B are the ones which have been studied most often in clinical settings (Dassan et al, 2009; Kleine et al, 2003; Konstantinou et al, 2008; Selakovic et al, 2005; Van Munster et al, 2009). NSE has been recognized in the guidelines developed by the American Academy of Neurology as a useful prognostic indicator in comatose patients with global hypoxic-ischemic brain injury.

Following we present our experience in relation to the serum biochemical markers (NSE and S100B) as early predictors of brain damage in essential hypertension (González-Quevedo et al, 2011).

Fifty patients with essential arterial hypertension, who had been referred by the general practitioner to the Department of Ophthalmology for evaluation of retinopathy were recruited. The hypertension status of the study sample was assessed using standard criteria formulated by Joint National Committee VII (Chobanian et al, 2003). The mean (±SD) age was 57.6±11.6 years, and 38% were males. Ninety six % of the patients had a diagnosis of essential hypertension that dated back from over 5 years (5 to 35 years); only 2 of them had less than five years of disease duration. All patients completed an interview aimed to ascertain their personal pathological history and medication used. Forty seven patients (94%) were receiving antihypertensive drugs. Those with clinical evidence of known neurological disease, malignancies, chronic degenerative or inflammatory diseases, recent infection or trauma were not included.

The control group was comprised of 42 apparently healthy subjects who volunteered to be included in this study - mean (±SD) age was 52.4±12.5 years, and 42.9% were males. Hypertension was excluded by clinical history and blood pressure (BP) measurement taken before blood extraction, no retinopathy was detected at fundoscopic examination, and no known history of neurological, cardiovascular, liver, renal, inflammatory or malignant diseases was reported. Those referring recent infection or trauma were not included.

Before blood extraction, BP was measured in patients and controls in the right arm and in the seated position after a 5-min rest period, following the recommendations of Perloff et al (1993). Hypertensive patients were classified in four groups according to BP measurements: <120/80; 120-139/80-89; 140-159/90-99 and > 160/100 (Chobanian et al, 2003). Fundoscopic examination to evaluate hypertensive retinopathy was carried out in all patients and controls and they were classified according to Scheie (1953).

Brain MRI scanning was conducted in 23 of the 50 hypertensive patients. Both groups of patients (with and without MRI) had a similar composition with respect to demographic and clinical variables. The degree of WMH severity was rated visually on axial FLAIR images using the Fazekas scale (Fazekas et al, 1987), and patients were classified in two groups:

- Group 0-I: Included Grade 0 (no hyperintense lesions) and Grade I (slight changes: only one lesion < 10 mm or grouped lesion areas < 20 mm for any diameter).
- Group II-III: Included Grade II (only one hyperintense lesion from 10 – 20 mm or grouped hyperintense areas > 20 mm for any diameter), and Grade III (severe changes: confluent hyperintense areas on both sides ≥ 20 mm for any diameter).

Lacunes were defined as hypointense foci of <3 mm on MPRAGE that were surrounded by white matter or subcortical gray matter and not located in areas with a high prevalence of widened perivascular spaces (eg, anterior commissure, vertex). The number of lacunes was recoded into none, few (1 to 3 lacunes), and many (4 lacunes or more).

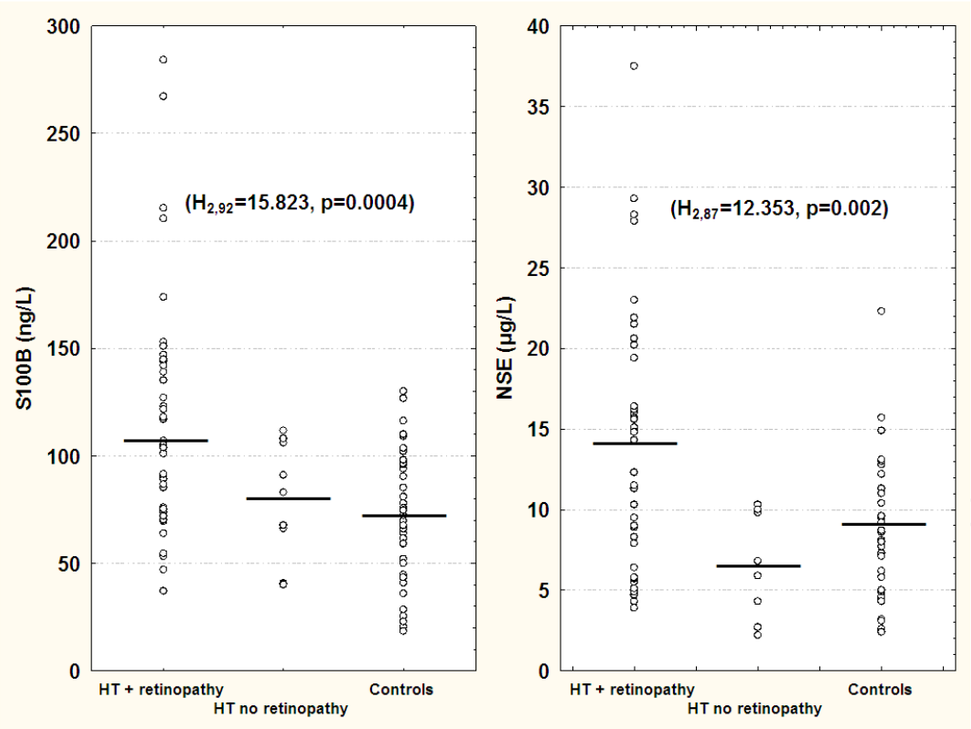
Dilated Virchow Robin spaces (> 2 mm) were identified and classified in 3 groups: None (no dilated Virchow spaces); Few (1 to 3); Many (4 or more).

Serum S100B and NSE were determined employing the immunoassay kits CanAg S100 EIA (708-10) and CanAg NSE EIA (420-10) from CanAg Diagnostics AB (Sweden).

Table 2 shows the mean serum concentrations for S-100B and NSE in hypertensive patients and controls. Both proteins displayed significantly higher levels in patients with respect to controls, while no differences were detected with gender and age. No correlation was observed between NSE and S-100B levels.

Serum proteins	Control n=42	Hypertension n=50	Student´s t- test	P
S-100B (ng/L)	72.3 ± 29.5	108.6 ± 53.1	t = 3.944	p = 0.0002
NSE (µg/L)	8.6 ± 4.2	12.5 ± 7.9	t = 2.749	p = 0.002

Table 2. Mean ± SD of serum S-100B and NSE levels in controls and hypertensive patients



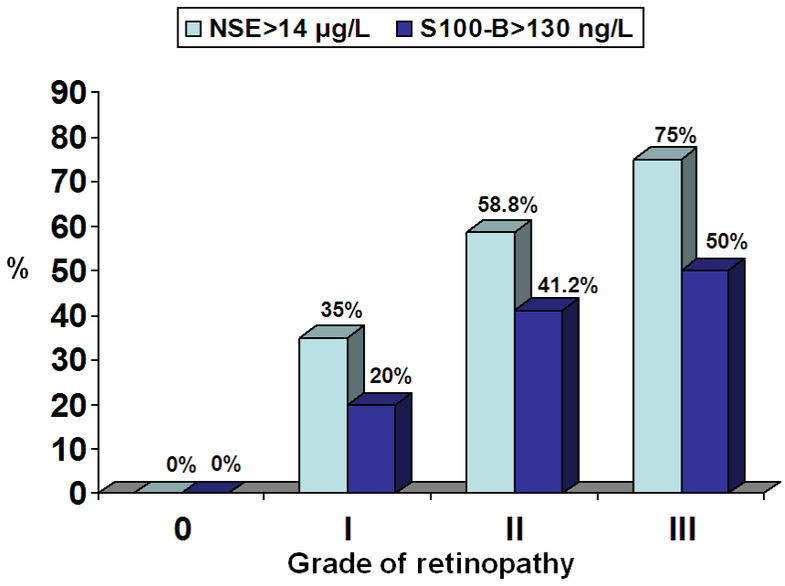
HT: hypertension
Results for Kruskal-Wallis test shown in the figure.
Pos hoc analysis for S-100B: HT + retinopathy *vs* control (p=0.0003)
Pos hoc analysis for NSE: HT + retinopathy *vs* HT no retinopathy (p=0.02)
HT + retinopathy *vs* control (p=0.01)

Fig. 1. Scatter plot of serum S-100B (A) and NSE (B) concentrations in controls and hypertensive patients with and without retinopathy.

Diastolic BP (DBP), but not systolic BP (SBP) taken immediately before blood extraction correlated with NSE levels (r=0.325, p = 0.023), while no correlation was found between S-100B concentration and SBP or DBP.

When patients were classified as having or not having retinopathy and compared with controls (Figure 1), higher NSE and S-100B levels were found to be associated with the presence of retinopathy (p=0.0004 and p=0.0022 respectively). For NSE a significant increase was demonstrated in patients exhibiting retinopathy with respect to those without retinopathy (p=0.029), while for S-100B, a similar tendency was observed, but it did not reach statistical significance. It should be pointed out that hypertensive patients without retinopathy displayed serum S-100B and NSE concentrations (means: 83 and 6.3 respectively) very similar to controls (means: 72.3 and 8.6 respectively).

The association with the grade of retinopathy could be further confirmed when patients were distributed according to NSE and S100B cut off levels. Figure 2 shows how the frequency of patients with NSE>14 µg/L and S100B>130 ng/L significantly increased with the grade of retinopathy. The X^2 test was conducted considering two groups of retinopathy: lower severity (0 – I) and higher severity (II – III) to avoid empty cells. It is noteworthy that NSE>14 µg/L and S100B>130 ng/L were not observed in hypertensive patients without retinopathy.



NSE: χ^2=6.766, p=0.009; S100B: χ^2=5.347, p=0.021

Fig. 2. Percentage of patients with increased serum NSE and S100B levels according to grade of retinopathy.

The independent variables included in the multivariate regression analysis (SBP, DBP, grade of retinopathy and years of hypertension), with NSE as the dependent variable, fitted the whole generalized regression model (multiple R=0.547; F=4.335, p=0.005). NSE was independently associated with diastolic blood pressure and grade of retinopathy, but not with systolic blood pressure and duration of hypertension; whereas no associations were observed for S-100B.

As brain MRI scans were performed in 23 of the hypertensive patients, the results were evaluated with respect to NSE and S-100B levels (Table 3). Distribution of the patients according to the Fazekas Scale revealed some degree of WMHs in 17 (73.9%), while only 6 patients displayed no hyperintense lesions (Grade 0). Eight patients classified as Grade I, seven as Grade II and 2 patients as grade III. Non parametric statistical analysis assembling Grades 0-I and Grades II-III, showed that patients with more severe WMHs had higher serum NSE levels than those with no hyperintensities or slight changes ($p < 0.05$), while S-100B levels did not differ. Hyperintensities were not associated with other risk factors (smoking, alcohol, diabetes).

Dilated Virchow Robin spaces and lacunes were detected in 11 and 5 patients respectively. No significant differences for S-100B or NSE levels were encountered when analyzing the presence of dilated Virchow spaces or of lacunes.

Brain MRI variables		n	S-100B (ng/L)	NSE (μg/L)
WMH (Fazekas scale)	Grades 0 - I	14	124.3 (53.2 – 210.4)	10.6 (3.9 – 16.4)
	Grades II - III	9	107.0 (53.6 – 215.3)	20.6 * (4.3 - 29.3)
Dilated Virchow Robin spaces	None	12	117.0 (53.2 – 151.0)	9.1 (4.3 – 20.2)
	Few	1	121.7	12.3
	Many	10	114.8 (63.7 – 241.3)	16.1 (4.6 – 28.8)
Presence of lacunes	None	18	131.1 (53.2 – 215.3)	13.3 (3.9 – 28.3)
	Few	5	103.8 (73.8 – 121.7)	12.3 (4.9 – 20.6)
	Many	0	-	-

WMH: white matter hyperintensities
Medians and 10-90 percentiles of NSE and S-100B are presented
* Mann-Whitney U test: $Z = 1.980$, $p = 0.049$ (Fazekas scale 0-I *vs* II-III)

Table 3. Brain MRI variables and serum concentrations of S-100B and NSE in hypertensive patients.

To rule out the effect of antihypertensive treatment on blood levels of S-100B and NSE, two analyses were carried out: 1) effect of one or two antihypertensive drugs *vs* joint administration of more than two drugs (polytherapy) and 2) effect of individual groups of antihypertensive drugs (ACE inhibitors, calcium channel blockers, β-blockers, diuretics). No significant differences were observed when patients treated with polytherapy were

compared with those receiving one or two drugs. None of the individual groups of antihypertensive drugs increased the serum concentrations of S-100B and NSE.

3.5.1 Discussion of blood markers in hypertension

In the present study we examined the status of serum NSE and S-100B in patients with essential arterial hypertension, and their possible implication as early markers of brain damage. We found that both markers were significantly higher in hypertensive patients than in controls and the multivariate analysis revealed that NSE was independently associated with two variables expressing severity of hypertension: diastolic blood pressure (but not systolic) and grade of retinopathy; while S-100B was not associated with any of the clinical variables analyzed. Furthermore, seeking for a neuroanatomical support to the serum concentration of these brain specific proteins, brain MRI studies performed in a group of hypertensive patients, denoted a relationship between increased serum NSE levels (but not S-100B) and more severe white matter lesions. This is the first study demonstrating raised NSE levels related to severity in essential hypertension, and suggesting that it may be a marker of early brain damage accompanying the hypertensive syndrome.

MRI and positron emission tomography (PET) techniques have shown signs of hypertensive target organ damage in the brain of asymptomatic hypertensive patients as we explained with more details in previous sections of this chapter. Although this study is limited by the fact that brain MRI could only be performed in half of the cohort, a relationship between increased serum NSE levels and severity of WMHs was observed.

The fact that NSE and S-100B are elevated in hypertensive patients with respect to controls does not necessarily denote early signs of brain damage. It is important to take into account that although S100B and NSE are highly specific for brain tissue, they are also expressed in other cell types under physiological and pathological conditions. S-100B is found in adipocytes, bladder and colon cells, and elevated serum levels have been reported in patients with bone fractures, thoracic contusions, burns and melanoma (Dassan et al, 2009; Kleine et al, 2003). NSE is also present in erythrocytes and platelets; while high serum levels have been reported with malignant tumors such as neuroblastomas, small cell carcinoma of the lung and seminomas (Kleine et al, 2003; Shinozaki et al, 2009). Although the issue of contamination of these serum proteins with extracerebral sources was strictly controlled in this study, it cannot be absolutely ruled out.

Our results indicate that NSE is independently associated with the severity of hypertension (specifically expressed through increased DBP and the grade of retinopathy) and the brain MRI studies suggest that NSE increase could be in relation to the severity of white matter lesions. The fact that non-nervous tissue NSE content is so low with respect to brain that it is not liable to increase serum levels - with the exception of malignancies of the neuroendocrine system and some other tumors (Kleine et al, 2003) -, could point to a certain degree of silent brain damage in a subset of hypertensive patients.

In the case of S-100B, the lack of association with variables related to the severity of hypertension after multivariate analysis, and with MRI findings, strongly suggests that this increase is probably not originating in the nervous system. Nevertheless, this issue remains an open question that should be addressed in the future.

An additional cause leading to elevation of S-100B and NSE could have been the antihypertensive treatment that more than 90% of the patients were receiving. Nevertheless, the analysis carried out indicates that no specific group of antihypertensive drugs was associated with increased serum S-100B or NSE in our study, nor did we find any reference in the literature in this respect.

Our results provide preliminary evidence suggesting that raised NSE and S100B could be the result of silent brain damage in a group of hypertensive patients; however, inflammation is an important coexisting factor that must be considered, especially in the case of S100B, where no clear association could be established with severity of hypertension or of WMHs. The possibility that increased NSE and/or S100B could be related to the systemic inflammatory process clearly demonstrated in hypertension cannot be ruled out, and will be the object of future work in our laboratory.

Since the observation made by Sesso et al in 2003 that increasing levels of C-reactive protein were associated with an increased risk of developing hypertension, scientists have been trying to unravel the mechanisms linking chronic low-grade systemic inflammation with high blood pressure. Independent associations between inflammatory biomarkers (C-reactive protein, interleukins 6 and 18, tumor necrosis factor-α) and measures of arterial stiffness and wave reflections (Schnabel et al, 2008; Vlachopoulos et al, 2010) and in essential hypertension (Bautista et al, 2005) have been established.

There are some reports linking S100B with inflammation. Depending on its concentration, S100B has two opposing effects, trophic and toxic. At nanomolar concentrations, S100B stimulates neurite outgrowth and enhances survival of neurons. However, at micromolar concentrations, S100B stimulates the expression of proinflammatory cytokines such as IL-6 and induces apoptosis (Steiner et al, 2011).

In experimental animals, overproduction of S100B in the astrocytes of stroke-prone spontaneously hypertensive rats has been demonstrated, while treatment with arundic acid prevented hypertension-induced stroke and inhibited the enlargement of the stroke lesion by preventing the inflammatory changes caused by overproduction of the S100B protein in the astrocytes (Higashino et al, 2009). On the other hand, in a clinical setting, the degree of systemic inflammation was found to be associated with S100B concentration in acute ischemic stroke, independent of the size of the ischemic lesion (Beer et al, 2010).

Very recently Steiner et al (2011) provided solid evidence showing that $CD3^+$ $CD8^+$ T cells and $CD3^-$ $CD56^+$ NK cells express S100B, and that stimulated $CD8^+$ T cells release S100B which could lead to activation of granulocytes and monocytes. This could indicate a novel regulatory mechanism of innate immune functions by S100B+ T cells distinct from cytokine- and chemokine-mediated pathways. Due to the emerging role of S100B as an interface with the immune system, the results provide the ground for a wide array of future studies in physiological and pathological conditions that have been associated with increased S100B levels (Steiner et al, 2011).

Thus, the association of raised S100B levels in hypertensive patients –where low level chronic inflammation has been well established- could gain new meaning in view of the above described and formerly unknown close interactions between S100B and the immune system. Overall, at this point all these considerations are hypothetical and require additional research.

In conclusion, in the present study we have shown that serum NSE and S-100B are elevated in hypertensive patients, and furthermore that NSE (but not S-100B) is associated with the severity of hypertension and white matter lesions. Our findings provide for the first time preliminary evidence suggesting that raised NSE could be the result of silent brain damage in a subset of hypertensive patients. Additional research is needed involving larger cohorts, more sensitive imaging techniques and the use of other biochemical, electrophysiological and neurocognitive methods in order to consistently confirm this hypothesis.

4. Conclusion

Contrary to the subclinical detection of cardiovascular and renal target organ damage, which is very well established in clinical practice for the management of hypertension, brain target organ damage to date has no readily available technique to be used by the medical practitioner. From the evidence previously presented, it is obvious that at this moment, the only method that can be reliably employed for this purpose is brain MRI. Nevertheless, MRI is not as widely accessible as it would be needed, to screen such a highly prevalent disease, and is furthermore, very costly. On the other hand, it should be taken into account that several studies have alerted on the high frequency of subclinical brain target organ damage, as compared to cardiorenal damage. Thus there is no doubt that the search for effective, less expensive and available methods is urgently required. In this respect blood biomarkers of brain damage are a promising and practically unexplored avenue that needs to be more deeply investigated.

What could be the clinical relevance of our preliminary findings? The use of serum S-100B and NSE as early and quantitative markers could prove important as a potential tool in the hands of clinicians for the detection and prevention of initial brain deterioration in hypertensive patients. On the other hand, the longitudinal study of this cohort could also offer important information on their usefulness as prognostic factors.

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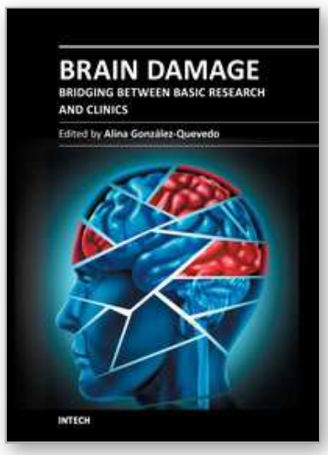

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"Brain Damage - Bridging Between Basic Research and Clinics" represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors' personal experiences with current knowledge in this field. In general, the necessary link between basic and clinical neurosciences is highlighted, as it is through this interaction that the theoretical understanding of the pathophysiological mechanisms can be successfully translated into better ways to diagnose, treat and prevent the catastrophic events that occur when the brain suffers from external or internal noxious events. The book spans different aspects of brain injury, starting from damage occurring in the fetal and child brain, followed by different neurodegenerative processes. Attention is also focused on the negative effects of drug addictions and sleep deprivation on the brain, as well as on the early assessment of brain injury for preventive strategies employing sensitive biomarkers.

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