NEUROPSYCHOLOGICAL AND STRUCTURAL BRAIN CORRELATES OF LACUNAR INFARCTS

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to obtain the Degree of Doctor in Neurosciences.

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Present work contains four studies that have been carried out in the Neuropsychology Research Group of the Psychiatry and Clinical Psychobiology Department at the Faculty of Medicine, University of Barcelona. This group, lead by Prof. Carme Junqué, belongs to the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). The following studies have been funded by a Mapfre Medicine and Catalan Society of Neurology grants, as well as with grants from the University of Barcelona to M. Grau Olivares.

'Imposible es el adjetivo de los necios'

Napoleón Bonaparte

'Primer principio: no dejarse vencer nunca ni por las personas ni por los acontecimientos'

Marie Curie

'Genius is simple patience carried to extreme'

Buffon

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Foreword

The present thesis to obtain the degree of Doctor through the Neuroscience Program PhD, offered by the University of Barcelona is the result of four different studies that have been carried out at the Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine. During the first two years of this work I obtained the DEA (Diploma d'Estudis Avançats).

Those four studies will be presented hereunder, two of which are published and two have been submitted for their publication into international journals.

Grau-Olivares M, Arboix A, Bartrés-Faz D, Junqué C. Neuropsychological abnormalities associated with lacunar infarction. *J Neurol Sci* 2007;257:160-165.

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GLOSSARY OF ABBREVIATIONS

AD	Alzheimer's Disease
ADL	Activities of daily living
AH	Ataxic hemiparesis
ALS	Atypical lacunar syndrome
BJLOT	Benton Judgement of Line Orientation Test
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computarized tomography
DCHS	Dysarthria-clumsy hand syndrome
ERC	Enthorinal cortex
HACP	Homolateral ataxia and crural paresis
HDL	High density level
HTA	Hypertension
IH	Intracerebral haemorrhage
LI	Lacunar infarct
MCI	Mild cognitive impairment
MCI-V	Mild cognitive impairment of the vascular type
MID	Multi-infarct dementia
MLI	Multiple lacunar infarct
MMSE	Mini Mental State Examination
MRI	Magnetic resonance image
NIHSS	National Institute of Health Stroke Scale
OR	Odds ratio
PMH	Pure motor hemiplegia

PSD	Post-stroke dementia
PSS	Pure sensory stroke
ROI	Region of interest
SIVD	Subcortical ischaemic vascular disease
SMS	Sensorimotor stroke
SMP2	Statistical Parametric Mapping
SPS3	Secondary Prevention of Small Subcortical Strokes
SVD	Subcortical vascular dementia
TIA	Transient ischemic attack
VaD	Vascular Dementia
TMT-A/B	Trail Making Test A y B
VCI	Vascular Cognitive Impairment
WMH	White matter hyperintensities
WML	White matter lesions

1- INTRODUCTION

Stroke is the second leading cause of death worldwide and is a major determinant of adult disability (Di Carlo *et al*.,2000). It has many sequelae, including cognitive impairment and dementia. Hospital-based studies show that up to a third of stroke patients have dementia within three months of stroke (Pohjasvaara *et al*.,1998). Stroke is characterized by sudden onset of focal neurological symptoms in the appropriate clinical setting and the exclusion of other conditions that can present in a similar way. The ratio of cerebral infarcts to intracerebral hemorrhages is usually 5:1 or 6:1.

Vascular dementia (VaD) has historically been based on stroke and the multi-infarct model (Erkinjuntti *et al*.,2002), although recognition is increasing that several vascular pathologies (eg, subcortical ischaemic small-vessel disease or lacunar infarcts), as well as cortical infarcts, can lead to dementia (Hachinski *et al*.,1974; Esiri *et al*.,1997; Rockwood *et al*.,1999; Erkinjuntti *et al*.,1999; Pohjasvaara *et al*.,2000; Ballard *et al*.,2000). The term 'vascular cognitive impairment' (VCI) was proposed by Sachdev (Sachdev,1999) to define vascular cognitive deficits of sufficient severity to meet criteria for a diagnosable disorder. It was intended as an umbrella term to include the spectrum of impairment from mild 'vascular cognitive impairment' (VCI) to VaD (Roman *et al*.,2004). This term includes vascular cognitive impairment without dementia and vascular mild cognitive impairment, that is, mild cognitive impairments that have a presumed primary vascular basis, as well as vascular dementia.

Vascular cognitive impairment covers subjects who have cognitive impairment related to stroke, multiple cortical infarcts, multiple subcortical infarcts, small-vessel disease with white matter hyperintensities and lacunae. In the present work we have been working with the two latest entities white matter hyperintensities and lacunar infarcts, also called small-vessel disease.

Compared with other stroke subtypes, the prognosis after lacunar infarction is usually a non-severe vascular lesion with favourable recovery of neurological dysfunction, almost no acute mortality and low risk of recurrence (Clavier *et al*.,1994). Even though mild neuropsychological disturbances mainly executive disorders are not infrequent in those patients, in clinical studies, the proportion of vascular dementia caused by small-vessel disease ranges from 36% to 67% depending of the studies (Chui, 2001). On the other hand, it has been recently reported that brain changes other than those directly related to subcortical cerebrovascular damage (white matter hyperintensities and lacunes) such as global or regional gray-matter shrinkage (i.e. hippocampal atrophy) (Laakso *et al*.,1996; Fein *et al*.,2000; Mungas *et al*.,2001), may also account for cognitive deficits in cerebral vascular lesions.

2- REVIEW OF THE LITERATURE

2.1- Lacunar infarcts

The **lacunes or lacunar infarcts** (LI) are described like small ischemic infarcts (no more than 15 mm) in the territory of the perforant arterioles (Fisher,1982). Lacunes predominate in the basal ganglia, especially the putamen, the thalamus, the white matter of internal capsule and pons, and in centrum semiovale (Combarros, 1991). The vascular territories involved are usually the lenticulostriate branches of the anterior and middle cerebral arteries, the thalamoperforating branches of the posterior cerebral arteries, and the paramedian branches of the basilar artery (Martí-Vilalta,2004). Most autopsy-documeted LI are small, ranging from 0.2 to 15 mm in size (Mohr et al,1998).

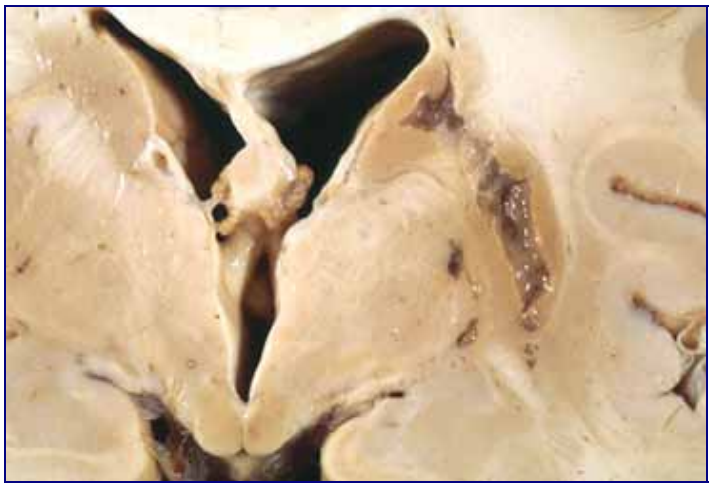

Fig. 1. Lacunar infarcts in the basal ganglia (Source: www.neuropathologyweb.org)

There are different arteriopaties underlying lacunar infarcts, such is microatheroma which is believed to be the most common mechanism of arterial stenosis underlying symptomatic lacunes (Fisher,1969; Fisher,1977; Fisher,1979). These kind of atheromatous deposits are commonly encountered in patients with chronic hypertension.

Other arterial disorders that may cause lacunes are the *lipohyalinosis and the fibrinoid necroses.* These are considered to be the most frequent causes of lacunes and affect the penetrating arteries in a segmental fashion in subjects with chronic hypertension (Gautier,1978). The smaller penetrating arteries are more frequently affected for the smaller lacunes, especially those that are clinically asymptomatic. It is thought that lipohyalinosis represents an intermediate stage between the fibrinoid necrosis characteristic of severe hypertension and the microatheroma associated with long-standing hypertension (Fisher,1969; Heptinstall,1974; Chester,1978). The *Charcot-Bouchard aneurysms* is another common arteriopathy seen in chronic hypertensive subjects (Ross Russell,1963; Cole,1967; Fisher,1969; Fisher,1971).

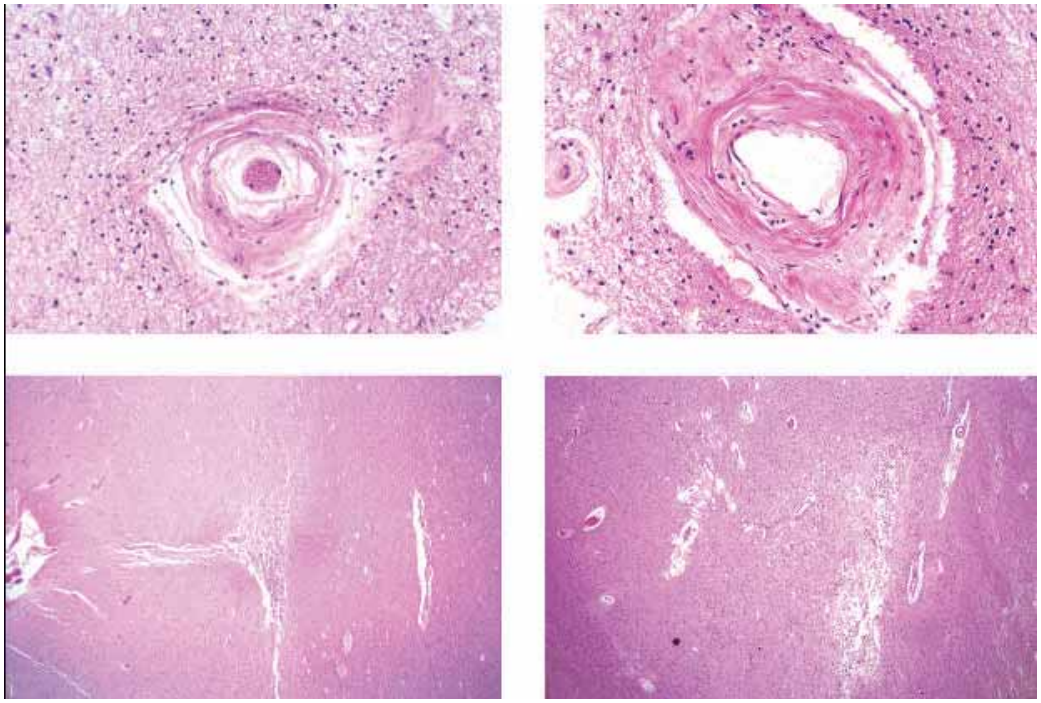

Fig. 2 Microscopic appearance of brain lesions commonly seen in the brains of patients with small vessel disease
(Source: www.nature.com/clinicalpractice/neuro)

In general, patients presenting with lacunar infarction have a good prognosis, compared with other vascular processes (ischemic or hemorrhagic stroke), although it is not always as good as 'classically' accepted. The prognosis of lacunes is influenced by several factors. Generally, when the sensory or motor deficit is complete the prognosis is worse than when associated with an incomplete deficit. Likewise, when the size of the infarct is large the prognosis is worse.

2.2- Epidemiology, etiology, and risk factors

The LI suppose about 20–25% of all ischemic strokes (Fisher,1982; Wardlaw,2005) and affect mostly adults between 55 and 75 years of age, with the incidence increasing with age. In the Barcelona Stroke Registry, 399 (11%) of the 3,577 acute stroke patients had a LI (Martí-Vilalta and Arboix, 1999).

The main etiologic risk factor of the LI is *hypertension* (Fisher,1982; Wolf, 1985; Baumgartner *et al*.,2003). Microembolism was suggested as a cause of LI when in pathological studies identified a normal arteriole underlying a lacunar infarct (Fisher,1979).

LI of unusual etiology are infrequent so cardioembolism constitutes a rare cause for LI (Mast,1994; Boiten,1996) as well as haematological diseases, carotid plaque embolism or embolism associated with severe stenosis of a perforated arteriole (Waterson,1990) and amyloid angiopathy (Loes,1990).

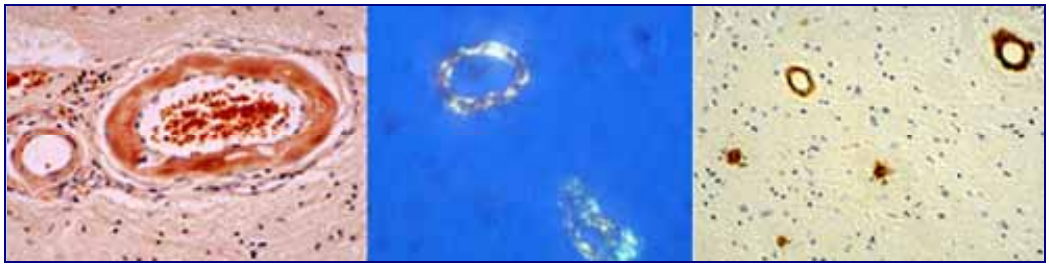

Fig.3 Cerebral Amyloid angiopathy (Source: www.neuropathologyweb.org)

Lacunar infarcts have a unique pathophysiological mechanism but the vascular risk factor profile is not unique. The known risk factors account only for part of the risk of lacunar stroke because some patients have none of the known risk factors. Is important to identify persons who are at high risk for lacunar infarcts because some of them can be treated. There are a number of unmodifiable and modifiable vascular risk factors.

a) *Unmodifiable risk factors*

The most important are the age and the gender.

- *Age:* is the most important risk factor for stroke in general and also for lacunar infarcts. There is evidence that the incidence of LI increases with age (Bamford *et al*.,1987; Sacco *et al*.,1991; Norrving and Staf, 1991). The mean age of patients suffering a LI is quite wide and range from 58 to 72 in various studies (Gross *et al*.,1984; Bamford *et al*.,1987; Gandolfo *et al*.,1988; Norrving and Cronqvist,1989; Arboix *et al*.,1990; Boiten and Lodder,1991; Norrving and Staaf,1991; Sacco *et al*.,1991).

- *Gender:* in many studies men present more often LI than women (Donnan *et al*.,1982; Gandolfo *et al*.,1988; Anzalone and Landi ,1989; Norrving and Cronqvist ,1989; Arboix *et al*.,1990; Boiten and Lodder,1991; Norrving and Staaf,1991).

- *Others:* genetic susceptibility as well as ethnicity.

b) Modifiable risk factors

Modifiable risk factors for lacunar stroke include hypertension, diabetes mellitus, cigarette smoking, ischaemic heart disease, and transient ischemic attack (TIA). Other possible risk factors that are less well documented include hypercholesterolaemia, hyperhomocysteinaemia, alcohol abuse, obesity, physical inactivity, elevated haematocrit and elevated fibrinogen.

- *Hypertension (HTA):* is the most important modifiable risk factor for stroke (Helgason and Wolf,1997; Whishnant,1997; Arboix *et al*.,2001a) and specially for lacunar infarcts (Arboix *et al*.,2004a; Jackson and Sudlow, 2005) although the latter is controversial. This controversy originated from the different frequencies of HTA in both clinical and pathological studies. HTA may aggravate atherosclerosis and induce complex pathological changes in arteries and arterioles. As a consequence, HTA is a precursor of large-artery disease (Strandgaard,1996) and hypertensive small-vessel disease, such as lipohyalinosis, which is one of the most common causes of lacunar infarction (Henriques *et al*.,1996; Mohr and Martí-Vilalta,1998; Besson *et al*.,2000).

  There are many clinical studies providing data about HTA in lacunar patients. The frequency of hypertension in these studies ranges from 44% (Lodder *et al*.,1990) to 75% (Mohr *et al*.,1978; Loeb *et al*.,1986; Foulkes *et al*.,1988) and reached almost 76% in one study (Arboix *et al*.,2004a). These differences may be explained by differences in the definition of HTA. In some studies HTA is defined as systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 95 mm Hg but in other studies high blood pressure is defined as ≥ 140/90 mm Hg.

Case-control studies showed that the risk of lacunar infarction was increased 5- to 9-fold by hypertension (Gandolfo *et al*.,1988; You *et al*.,1995; Boiten *et al*.,1996), thus demonstrating that HTA is an important risk factor for lacunar infarcts. However, many lacunar patients do not have hypertension.

- *Diabetes mellitus:* is also a major risk factor for stroke. The relative risk of stroke is increased independently 2- to 3- fold in patients with diabetes mellitus (Sacco *et al*.,1997). Diabetes can cause a small vessel arteriolopathy, and might therefore be a risk factor for small vessel disease causing lacunar stroke. Several case-control studies showed that diabetic patients have an independent relative risk of lacunar infarction from 2 to 3.6 (Gandolfo *et al*.,1988; You *et al*.,1995; Boiten *et al*.,1996), which is similar to the risk of ischaemic stroke in general. The frequency of diabetes in clinical studies ranges from 2% to 37% in lacunar patients (Pullicino *et al*.,1980; Ghika *et al*.,1989). All clinical studies showed that the frequency of diabetes mellitus did not differ between patients with lacunar and those with non-lacunar infarction. These studies reported that diabetes mellitus was an equally important risk factor for lacunar infarction as it is for cerebral infarction, however it is not a unique risk factor for cerebral small vessel disease and resultant lacunar stroke. Nevertheless some studies have demonstrated that diabetes is more common among patients with lacunar compared with non-lacunar infarction (Jackson and Sudlow,2005) and that is an important risk factor for patients with multiple lacunar infarcts (Arauz *et al*.,2003). Diabetes mellitus is commonly associated with other risk factors, most frequently hypertension (Dyken,1991; Sacco *et al*.,1997).

- *Cigarette smoking:* is an independent risk factor for stroke, especially brain infarction (Wolf *et al*.,1988; Shinton and Beevers,1989). In two case-control studies, smoking increased the risk of lacunar infarction 2.3 and 6.6 times respectively (Gandolfo *et al*.,1988; You *et al*.,1995). In these studies, the definition of smoking differed (especially concerning current and ex-smokers) as well as controlling for confounding variables,

which may have caused the different relative risks. In clinical studies of lacunar infarcts, 28%-68% smoked cigarettes (Norrving and Staaf,1991; Lodder *et al*.,1990). In some studies, the frequency of smoking was similar in patients with lacunar infarct to those with non-lacunar infarction [68 vs 69%; odds ratio (OR) 0.94; 95% confidence interval (CI) 0.57-1.58] (Lodder *et al*.,1990), indicating that cigarette smoking is a non-specific risk factor for lacunar infarction. Nevertheless other studies showed stronger association between cigarette smoking and lacunar stroke than non-lacunar stroke (Sacco *et al*.,2006). Once other study carried out by Mannami *et al*.,2004 demonstrated that smoking increased the risk of stroke and subarachnoid hemorrhage for men and women and the risk of ischemic stroke, either lacunar or large-artery occlusive infarction, for men.

- *Heart disease:* Heart disease in general, including ischaemic or coronary heart disease, is a known risk factor for stroke (Dyken,1991; Norris and Hachinski, 1991; Sacco *et al*.,1997), as well as the major cause of death among stroke survivors (Dyken, 1991). Case-control studies, showed that heart disease was not a risk factor for lacunar infarction (You *et al*.,1995), but specifically the presence of ischaemic heart disease increased the risk of lacunar infarction from 2,6 to 4,3 times (Gandolfo *et al*.,1988; Boiten *et al*.,1996). Clinical studies showed that between 8-39% of lacunar infarct patients had a history of ischaemic heart disease (Norrving and Cronqvist, 1989; Lodder *et al*.,1990). The frequency of coronary heart disease did not differ between patients with lacunar and non-lacunar infarcts (Lodder *et al*.,1990; Boiten and Lodder, 1991). A recent study reported that ischemic heart disease was significantly associated with atypical lacunar syndrome (Arboix *et al*.,2006).

- *Transient ischemic attacks:* It is questionable whether TIAs are considered a risk factor or just another form of stroke (Dyken, 1991). TIAs can identify patients with a high risk of stroke, and could therefore be considered as a risk factor (Dyken, 1991; Sacco *et al*.,1997). Clinical

studies showed that between 7 to 34% of lacunar patients had a previous TIA (Tegeler *et al*.,1991; Gandolfo *et al*.,1988). Therefore, the presence of previous TIAs might also be considered as a risk factor for lacunar infarction.

c) *Other possible risk factors*

Other less well documented risk factors associated with a lacunar infarction have been described (Sacco *et al*.,1997).

- *Hypercholesterolaemia:* There is still a debate as to weather hypercholesterolaemia is a risk factor for stroke. In some case-control studies hypercholesterolaemia was not shown to be a risk factor for lacunar stroke (Gandolfo *et al*.,1988; You *et al*.,1995). However, in a recent study (Amarenco *et al*.,2006) the authors reported that the risk of brain infarction was increased concomitantly with lipid levels in both atherothrombotic and lacunar stroke.

- *Alcohol consumption:* Is well known that heavy drinking increases the risk of stroke whereas light to moderate drinking probably decreases it. From a prospective cohort study (Physicians' Health Study) it was reported that light to moderate alcohol consumption reduced the risk of ischaemic stroke in men (Berger *et al*.,1999). One case-control study demonstrated that alcohol consumption did not increase the risk of lacunar infarct (You *et al*.,1995). Iso *et al* (2004) showed there was no excess risk of total stroke among drinkers of 1 to 149 g ethanol per week compared with occasional drinkers, and there was a lower risk of ischemic stroke, specifically lacunar infarction.

2.3- Clinical features and diagnoses

Although pathological and radiological studies have shown that up to 80% of lacunes (or radiological small, deep infarcts) are clinically 'silent' there are some well known classical clinical syndromes associated with lacunar infarcts. Classical lacunar syndromes were described by CM. Fisher and colleagues in the 1960s. They described pure motor hemiplegia (PMH) (Fisher and Curry, 1965), pure sensory stroke (PSS) (Fisher, 1965), sensorimotor stroke (Fisher, 1965), dysarthria-clumsy hand syndrome (DCHS) (Fisher, 1967), and homolateral ataxia and crural paresis (HACP) (Fisher and Cole, 1965).

a) ***Pure motor hemiplegia (PMH):*** is the most common syndrome (Orgogozo and Bogousslavsky, 1989). It was the first lacunar syndrome recognized clinically (Fisher and Curry, 1965) and is also known as pure motor hemiparesis. The frequency of PMH in Sagrat Cor Hospital stroke registry was about 12.7% of cases and constituted 50% of lacunar syndromes (Arboix *et al*.,2001b). The original definition of PMH was 'a paralysis complete or incomplete of the face, arm and leg on one side unaccompanied by sensory signs, visual field defect, dysphasia, or apractagnosia', but the complete syndrome is uncommon. This clinical syndrome has been reported from autopsied cases with focal infarction involving the corona radiata (De Reuck and van der Eecken, 1976), internal capsule (Fisher and Curry, 1965; Chokroverty *et al*.,1975; Leestma and Noronha, 1976), pons (Fisher, 1971), and medullary pyramid (Fisher and Curry, 1965; Chokroverty *et al*.,1975; Leestma and Noronha, 1976).

   The most common correlations have been with capsular locations, mostly the posterior limb. Posterior limb capsular lacunes usually involve the globus pallidus and posterior limb of the capsule, which are supplied by the lenticuloestriate branches of the middle cerebral artery (Rascol *et al*.,1982).

   Although the main elements of the pure motor stroke syndromes are motor, these patients may present with other complaints, especially sensory disturbances (42% of cases) (Donnan *et al*.,1982). These

complaints usually present as numbness, heaviness, and loss of feeling. Improvement is seen in a high percentage of patients when the syndrome is partial hemiparesis.

b) ***Pure sensory stroke (PSS):*** this is the sensory equivalent of PMH, but most studies suggest that it is less frequent, for example 6% of all lacunar syndromes (Bamford *et al*.,1987) and 7% in the Stroke Data Bank (Chamorro *et al*.,1991). In a prospective hospital-based study was found that PSS accounted for 5.4% of acute ischemic stroke and 17.4% of lacunar syndromes (Arboix *et al*.,2005). In the original paper, Fisher (1965) suggested that there should be objective sensory loss, but in a later paper (Fisher, 1982) he recognized that there would be cases with persistent sensory symptoms in the absence of objective signs. It is assumed that this syndrome is related with infarction of the sensory pathway of the brainstem, thalamus or thalamocortical projections. The thalamus is supplied by very small arteries susceptible to the effects of chronic hypertension (Percherson, 1976). The most common location of the infarct is the thalamus (Fisher, 1965; Fisher, 1978; Mohr *et al*.,1977), mostly in the ventral posterior nuclei, the main sensory relay nuclei to the cerebrum (Fisher, 1965). Other sites associated with pure sensory stroke have been caused by a lacune in the centrum semiovale, presumably with involvement of the thalamocortical projection area (Rosenberg, 1981). The Stroke Data Bank also reported a lesion in the anterior limb of the internal capsule. Lesions in this area could arise by disruption of the anterior thalamic radiation (Chamorro *et al*.,1991). Variants in the topography of pure sensory stroke have been reported that involve less than the entire side of the body. The complaints in other cases have involved the face, arm, and leg; head, cheek, lips, and hand; unilateral intraoral and perioral sites and fingers, the so called ‘cheiro-oral syndrome’; face, fingers and foot; shoulder tip and lower jaw; distal forearm alone; fingers alone; and leg alone (Combarros *et al*;1991; Fisher, 1965). The clinical course of these patients is good and improvement appears to be the rule, often returning to normal within weeks (Fisher, 1982; Arboix et al.,2005). Partial improvement in the trunk

with persistence of deficit in the distal extremities, a pattern common in hemispheral disease, is not very common.

c) ***Sensorimotor Stroke (SMS):*** it was not one of the original lacunar syndromes described by Fisher and colleagues. For many years, it was considered that this syndrome could not occur from occlusion of a single perforating artery because of the different vascular supply of the internal capsule and the thalamus. The inclusion of SMS as a classical lacunar syndrome was based on a single case with autopsy (Mohr *et al*.,1977). This case was the result of a lacune in the ventro-posterior nucleus of the thalamus but there was also pallor of the adjacent capsule. The sensory symptoms preceded the motor symptoms, although there were marked sensory and motor signs that both persisted. In a Magnetic Resonance Image (MRI) study (Hommel *et al*.,1990), the infarcts in cases of SMS were larger than for other lacunar syndromes although still thought to equate with lacunes. In the Stroke Data Bank (Chamorro *et al*.,1991) the SMS was the most frequent lacunar syndrome after PMH. 31 per cent of these patients had a lesion in the posterior limb of the internal capsule, 22 per cent had a lesion in the corona radiata, 7 per cent in the genu of the capsule, 6 per cent in the anterior limb of the capsule, and only 9 per cent in the thalamus. In an other prospective hospital-based study SMS accounted for 3.3% of all acute stroke patients, 3.6% of ischemic stroke patients and 13% of lacunar syndromes (Arboix *et al*.,2003). There are three anatomical arguments that could justify those symptoms: 1) The motor and sensory disturbance occurs from a lacune that is primarily in the thalamus but extends into the posterior limb of the internal capsule. 2) A lacune that is primarily in the capsule may interrupt thalamo-cortical sensory fibres. 3) The close anatomical and vascular relationship between the motor and sensory rolandic cortices may actually make the possibility of a pure SMS from cortical infarction more likely than a cortical PMH (Orgogozo and Bogousslavsky, 1989).

d) ***Homolateral ataxia and crural paresis (HACP) and Ataxic hemiparesis (AH):*** the original cases of HACP were described as exhibiting weakness of the lower limb, especially the ankle and toes, a Babinski sign, and 'striking dysmetria of the arm and leg on the same side' (Fisher and Cole, 1965). Bogousslavsky *et al*., 1992 suggested that true HACP may be seen most frequently from partial anterior cerebral artery infarcts. The syndrome of ataxic hemiparesis has both cerebellar and pyramidal elements (Fisher, 1978). In his later paper, Fisher reported three cases who had prominent vertical nystagmus as well as pyramidal weakness and cerebellar signs. He drew the cases together under the new term 'ataxic hemiparesis' (Fisher, 1978). He makes the point that many other cases reported with CT evidence of corona radiata lacunes of similar size have had much more extensive deficits. Some sensory variants of AH have been reported but there is no evidence that the anatomical and clinical issues raised are significantly different from those concerning PMH and SMS (Orgogozo and Bogousslavsky, 1989). The usual form manifests as a mild to moderate weakness of the leg, especially the ankle, with little or no weakness of the upper limb and face, accompanied by an ataxia of the arm and leg on the same side. In a few cases, a mild and transient hemisensory deficit may initially accompany the motor findings (Fisher, 1982; Huang and Liu,1984). This syndrome commonly develops only gradually, requiring from hours to a day or more to reach its peak. There are a few instances of a chronic state, but some degree of improvement within days or months is usual. In some cases, the syndrome changes, the hemiparesis clearing and the ataxia remaining (Huang and Liu,1984).

e) ***Dysarthria-Clumsy Hand Syndrome (DCHS):*** the clinical deficit appears with dysarthria and ataxia of the upper limb, but they do not occur in isolation. The syndrome usually includes facial weakness, which at times may be profound, dysphagia, and some weakness of the hand and even of the leg. The reflexes usually are exaggerated on the affected side, and the plantar response is extensor. The clinical picture usually develops suddenly. The best-recognized association of this syndrome

has been with lacunes in the anterior limb of the internal capsule (Fisher, 1965). Other sites have been reported less often: in the genu of the internal capsule (Spertell and Ransom,1979), in the anterior internal capsule (Fisher, 1965) and in the basis pontis (Glass *et al*.,1990). This syndrome has also been reported following hemorrhage of the pons (Tjeerdsma *et al*.,1996). DCHS is the most uncommon and poorly studied of the classic lacunar syndromes (Fisher, 1967; Fisher, 1991). In a prospective hospital-based stroke registry accounted for 1.9% of acute ischaemic stroke and 6.1% of lacunar syndromes (Arboix *et al*.,2004b). Usually the outcome is good and patients with this syndrome improve within days/months.

f) ***Atypical lacunar syndrome (ALS):*** in contrast to well defined classic or typical lacunar syndromes, there is little information on atypical lacunar syndrome (Besson *et al*.,2000; Bamford, 2002; Martí-Vilalta *et al*.,2004). ALS includes dysarthria-facial paresis, isolated dysarthria, isolated hemiataxia, pure motor hemiparesis with transient internuclear ophtalmoplegia, pure motor hemiparesis with transient subcortical aphasia, unilateral or bilateral paramedian thalamic infarct syndrome and hemichorea hemiballismus. In a prospective hospital-based stroke registry ALS accounted for 2.1% of ischaemic stroke and 6.8% of lacunar syndromes (Arboix *et al*.,2006). Isolated dysarthria or dysarthria facial paresis followed by isolated hemiataxia were the most frequent ALS. Both are related to selective involvement of the motor fibre along the course of the pyramidal tract secondary to a small cerebral lacunar infarct that disrupts the corticospinal fibres independently of the sites of the lesion (internal capsule, pons or corona radiate) (Arboix and Martí-Vilalta, 1990; Urban *et al*.,1996; Kim *et al*.,2003). The outcome of ALS is favourable the same as the other lacunar syndromes.

2.4- Neuropsychology of lacunar infarcts and white matter hyperintensities

Single and multiple lacunar infarcts

Compared with other stroke subtypes, the prognosis after lacunar infarction is much better with almost no acute mortality, a generally excellent recovery, a low risk of recurrence and little or no effect on long-term survival (Clavier *et al*.,1994). Data regarding the prognosis of lacunar stroke in relation to the risk of developing cognitive decline, dementia and other behavioural dysfunction is based on small series of patients or single case reports. For example, capsular genu infarcts have been associated with severe verbal memory loss and cognitive deficits consistent with dementia (Tatemichi *et al*.,1992), contextual amnesia (Schnider *et al*.,1996), and recurrent memory loss (Chukwudelunzu *et al*.,2001). A persistent hemiespatial neglect developed in a patient following a small infarction of the posterior limb of the right internal capsule (Ferro *et al*.,1984), and atypical aphasia syndromes were associated with circumscribed non-hemorrhagic infarctions of the anterior limb of the internal capsule and of the striatum, in the dominant hemisphere (Damasio *et al*.,1982). A relationship between lacunar infarcts in the basal ganglia and thalamus and cognitive function in lacunar infarct patients has been reported previously (Tatemichi *et al*.,1992; Gold *et al*.,2005). These findings were challenged by a report by Appelros (Appelros *et al*.,2005), who observed a lack of correlation between basal ganglia lacunes and cognitive decline. These impairments probably resulted from the interruption of prefrontal-subcortical loops by the lacunar infarction in the striatum, globus pallidus or thalamus, or by white matter lesions interrupting the prefrontal or anterior cingulate cortices from their basal ganglia or thalamocortical connections (Cummings, 1993; Mega and Cummings, 1994). Interruption of the dorsolateral prefrontal-subcortical loop results in executive dysfunction (Boyle *et al*.,2002).

Therefore, although these reports suggest a relationship between brain lesions caused by lacunar infarction and a specific neuropsychological

impairment, little is known regarding the frequency and type of neuropsychological dysfunction in acute lacunar stroke patients.

Other studies about lacunar infarcts (van Zandvoort *et al*.,2000; van Zandvoort *et al*.,2001) reported that in general, recovery of the neurological deficit is quite good, although several patients reported subjective problems in regard to their premorbid level of functioning. Subtle but persistent cognitive deficits have been suggested to cause these difficulties for example problems with sustained attention and speed of cognitive performance. According to these authors these cognitive disturbances could explain the decrease in quality of life often observed in patients with these lesions.

Although all those studies suggest a neuroanatomical correspondence between the vascular brain lesion and specific cognitive impairment, further studies are needed with larger samples and longer follow-up periods to establish this issue.

Single lacunes are known to produce relatively well-circunscribed neurologic deficits (Fisher, 1982; Brust,1983) but the cognitive consequences of multiple lacunes are different. Multiple lacunes have been more specifically associated with signs of frontal lobe dysfunction (Fisher, 1965; Fisher, 1982; Ishii *et al*.,1986; Wolfe *et al*.,1990; Wolfe *et al*.,1994; Corbett *et al*.,1994; Leskelä *et al*.,1999).

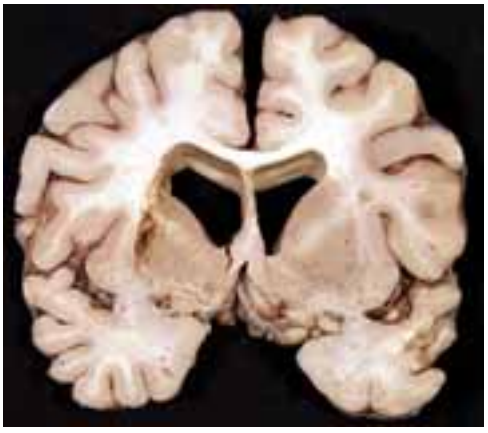

Fig.4. Single lacunar infarction (Source: www.neuropathology.com)

Is well known that multiple subcortical infarctions can produce neuropsychological signs of frontal system dysfunction, even in the absence of a clinical diagnosis of dementia. It has been shown that these patients had difficulty shifting set, have impaired executive functions on a verbal learning task, decreased verbal fluency, and apathy in behavioural observation (Wolfe *et al*.,1990). The authors concluded that these deficits corresponded with the dorsolateral frontal syndrome. Rosvold (1972) suggested that the dorsolateral prefrontal cortex was part of a dorsal functional system including anterodorsal caudate, lateral pallidum, subthalamic nucleus and hippocampus. Corbett and coworkers (Corbett *et al*.,1994) reported that the lesions related to frontal cognitive impairment were predominantly located in the anterior periventricular white matter and in the basal ganglia. They also reported a relationship between the number of infarcts and ventricular enlargement with the severity of neuropsychological dysfunction but not with the volume of the lesion. These data suggest that multiple diffusely located small lesions are likely to result in greater functional disruption of frontal systems than a single lesion of the equivalent volume. It is probable that subcortical lesions have a multiplicative effect in disrupting pathways and producing frontal dysfunction rather than a simple additive effect (Tatemichi *et al*.,1990). Takashima *et al* (2003) studied 119 patients with frontal lobe dysfunction caused by multiple lacunar infarction and concluded that the frontal lobe function was related to advanced age, multiple lacunar infarcts and the presence of lower high density level (HDL) cholesterol values.

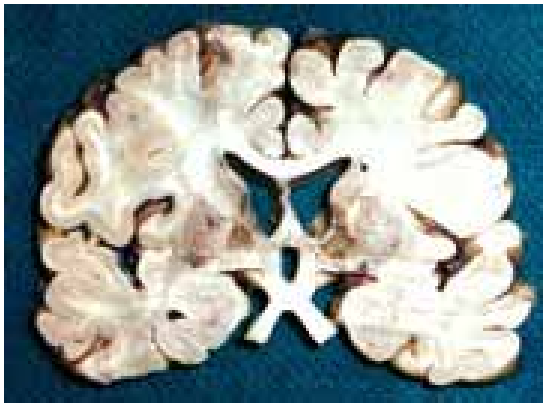

Fig.5. Multiple lacunar infarct (Source: www.neuropathology.com)

White matter hyperintensities (WMH)

White matter changes, also named white matter lesions (WML) or white matter hyperintensities (WMH) are detected with high frequency by neuroimaging techniques (Computed Tomography and Magnetic Ressonance Imaging) in aged subjects with cerebrovascular risk factors or diseases and in cognitively impaired subjects. WMH are believed to be caused by incomplete white matter infarction associated with small vessel disease affecting the deep penetrating arteries (Roman *et al*.,2002).

Their direct role in causing cognitive deterioration has not been established, although their frequency is higher in demented subjects than in normal controls, and they are associated with specific cognitive deficits, particularly those related to impairment of frontal lobe functions, especially executive functions (Pantoni *et al*.,1999; Bartrés-Faz *et al*., 2001). Executive functions are those involved in complex cognitions, including solving new problems, conceptual reasoning, inhibiting of overlearned patterns of behaviour, and modifying behaviour when have new information. Deficits in this domain are directly related to behavioural disorganization and functional decline.

WMH probably contributes to further disruption of predominantly frontal neuronal systems in addition to the disruption that results from focal infarction increasing the extent of cortical disconnection.

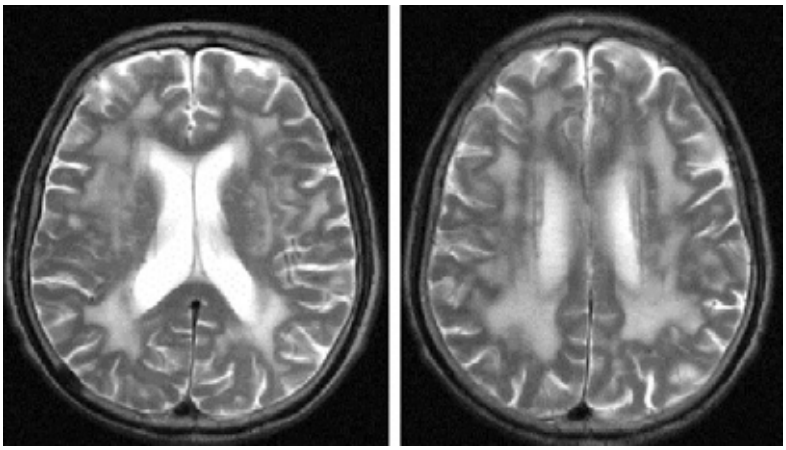

Fig.6. Periventricular white matter hyperintensities in T2 weighted MRI (Source: www.neuropathology.com)

A number of studies have also shown a relationship between white matter hyperintensities and lacunar infarction (Pantoni and Garcia,1997). Some authors have suggested that patients with lacunar infarcts have more severe WMH than patients with nonlacunar infarcts among patients with ischemic stroke (Mantyla *et al*.,1999). WMH has been also related to hypertension (Pantoni and Garcia,1995).

The presence of leukoaraiosis has been associated with cognitive dysfunction, mainly of the frontal lobe affecting speed procession measures, executive functions and verbal fluency (Steingart *et al*.,1987, Bartrés-Faz *et al*.,2001). It is not known whether WMH and the associated cognitive impairment progress gradually or stepwise in an event-like manner. Some authors have suggested that at least a threshold area of white matter lesions must be present before cognitive deficits become apparent (Takashima *et al*.,2003; Wen *et al*.,2004). In contrast, other studies did not find a relationship between white matter lesions and frontal lobe function (Schmidt *et al*.,1993; Breteler *et al*.,1994a). Schmidt and colleagues (1993) suggested that only complex mental processes were affected by WML's, leaving simple tasks

unaltered. In other studies (Koga *et al*.,2002) the authors suggested that among elderly subjects WMH are independently related to cognitive impairment and cognitive decline. This inconsistency may be caused by the differences in study designs, inclusion/exclusion criteria, or the method in rating WMH or cognition.

The white matter of the subcortical structures can be divided into the area just under the cortex and the area surrounding the ventricles. The subcortical region has a high density of short looped U-fibers, which connect adjacent cortical areas, whereas the periventricular region contains many long association fibers that connect the cortex with subcortical nuclei such as the striatum and more distant cortical areas (Brodal, 1998; Filley, 1998). Reserve mechanisms might explain why lesions affecting connectivity between neighboring brain regions have less influence on cognitive functions than lesions affecting connectivity between distant brain areas.

Some authors has suggested that white matter lesions in these separate regions might affect cognition in different ways (Ylikoski *et al*.,1993; Fukui *et al*.,1994; de Groot *et al*.,1998; de Groot *et al*.,2000a). In this vein, de Groot and colleagues (1998, 2000a), examined the relationship between periventricular and subcortical WML and cognitive functioning in 1.077 elderly subjects, and found that mainly periventricular WML's, rather than subortical WML's, were associated with cognitive impairment, in particular those that involved a speed component. The authors suggested that, the accelerated rate of cognitive decline found in the presence of severe periventricular WMLs was a prelude to the development of dementia. In contrast, Baum and colleagues (1996) reported the contrary and Garde *et al*.(2000) reported a relationship between WML severity at both locations and cognitive decline. Periventricular, but not subcortical WMLs, have been related to atherosclerosis *(De Leeuw et al.,2000)*. De Groot *et al*.(2000b), also reported that subcortical WMLs symptoms were associated with depressive symptoms. The mechanisms underlying these differences were not clear, but it is possible that the vascular architecture of the periventricular area is more vulnerable to damage than other white matter areas (Pantoni and García, 1997).

2.4.1- The concept of Vascular Cognitive Impairment (VCI)

Cognitive impairment is part of the clinical presentation of several conditions associated to cerebrovascular disease, but the precise frequency of vascular cognitive disorders is difficult to ascertain. Clinicopathological studies have shown a remarkable heterogeneity of vascular and brain parenchymal lesions (Fernando and Ince, 2004; Chui, 2005), and classification schemes based on clinical (O'Brien *et al*.,2003), radiological (Rockwood *et al*.,2005) and neuropathologic criteria (Vinters *et al*.,2000) have been proposed.

Concepts of vascular dementia (VaD) have historically been based on stroke and the multi-infarct model (Erkinjuntti *et al*.,2002). However, recognition is increasing that several vascular pathologies (eg, subcortical ischaemic small-vessel disease), as well as cortical infarcts, can lead to dementia (Hachinski *et al*.,1974; Esiri *et al*.,1997; Erkinjuntti *et al*.,1999; Rockwood *et al*.,1999a; Ballard *et al*.,2000; Pohasvaara *et al*.,2000a). Some investigators suggested that VaD might account for only 2-3% of dementias (Hansen and Crain,1995), while others demonstrated that 'pure' VaD was almost nonexistent in large dementia series studies, even when careful necropsies are performed (Nolan *et al*.,1998).

Clinically important cognitive impairments associated with vascular disease frequently do not fulfil traditional criteria for dementia, since these criteria are based on the concept of Alzheimer Disease (AD) and require the presence of prominent memory impairment, which is not a prime symptom in vascular dementia. VaD patients are likely to have a better preservation of long-term memory and greater deficits in frontal executive functioning (planning, organization, abstraction, category fluency initiation, reasoning, mental flexibility, sequencing, fine motor performance, the allocation of attentional sources) than AD patients (Mendez and Ashla-Mendez, 1991; Villardita *et al*.,1992; Almkvist, 1993; Padovani *et al*.,1995; Lafosse *et al*.,1997). In an effort to avoid scientifically constricting definitions, and to avoid artificial distinctions between different severities of cognitive impairment, we use the term vascular cognitive impairment.

As reported above, the term 'Vascular Cognitive Impairment' (VCI) was proposed by Sachdev (Sachdev, 1999) to define vascular cognitive deficits of sufficient severity to meet criteria for a diagnosable disorder. It was intended as an umbrella term to include the spectrum of impairment from mild 'vascular cognitive impairment' to VaD (Roman *et al*.,2004). Vascular cognitive impairment covers individuals who have cognitive impairment related to stroke, multiple cortical infarcts, multiple subcortical infarcts, or both, silent infarcts, strategic infarcts, small-vessel disease with white matter lesions, and lacunae. Vascular Cognitive impairment also plays an important role in patients with AD pathology who have coexisting vascular lesions.

There are several studies that have attempted to examine the frequency of patients with VCI. Prevalence rates varying from 15 to 20% in clinical settings (Rockwood *et al*.,2000; Szatmari *et al*.,1999). The relative prevalence of mild but potentially significant VCI varied enormously depending upon the criteria and concept used, and which cognitive domain was assessed.

Criteria based upon abnormalities of processing speed identify a much larger proportion of patients than criteria focusing upon memory. This is important in highlighting the different profile of early cognitive impairments in stroke patients compared to those typically reported in the context of Alzheimer's disease. Patients with VaD or who have experienced strokes indicate that attention, processing speed and executive function are the most frequently and most severely impaired aspects of cognition.

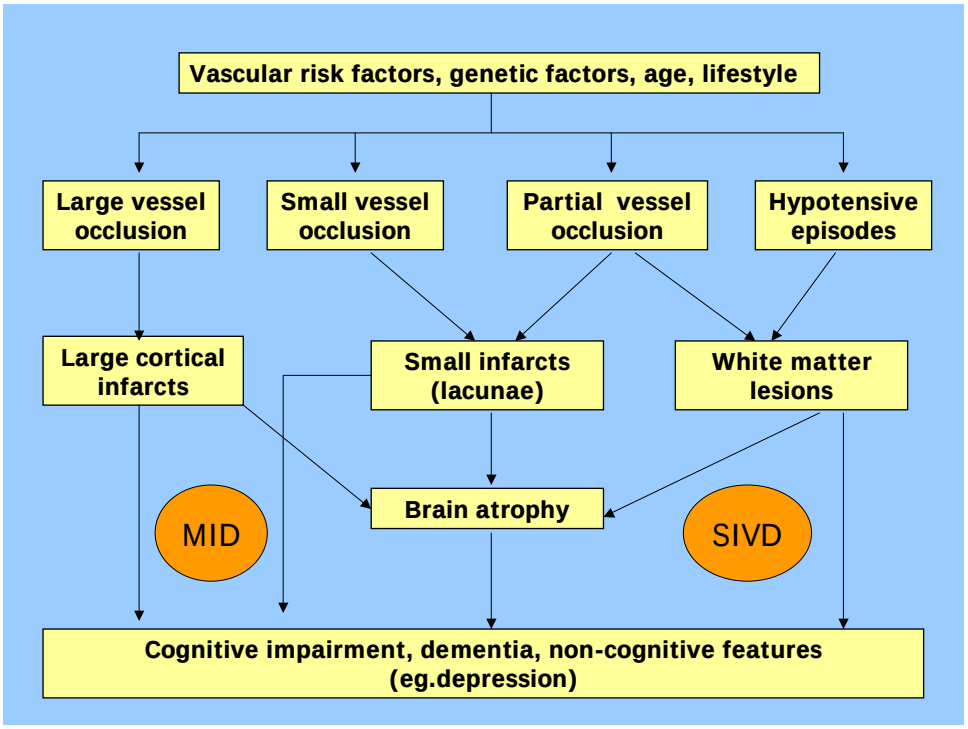

Fig.7 .The main pathology mechanisms in VCI.
MID= multi-infarct dementia; SIVD= subcortical ischaemic vascular disease.
(Source:The Lancet Neurology 2003;2:89-98)

Subtypes of vascular cognitive impairment:

a) Post-stroke dementia (PSD)

PSD includes multi-infarct dementia (MID) and haemorrhage-associated dementia. Is defined as dementia occurring in close temporal relation to a thromboembolic or haemorrhagic stroke. The prognosis for recovery of cognitive symptoms after an initial stroke is generally favourable, but some patients do not show the expected recovery, and instead develop persistent or progressive cognitive decline (Leys *et al*.,2005). Post-stroke dementia develops in up to a third of patients within a year of stroke (Esiri *et al*.,1999). PSD has long been considered the prototypical subtype of VaD, and it might therefore be expected that all patients with PSD would meet the criteria for VaD. The most important demographic predictor of PSD is age. The association with stroke risk factors is less robust, according to some authors (Leys *et al*.,2005). Evidence suggests heterogeneity of the underlying pathology, with many cases resulting

from different vascular causes and changes in the brain, as well as degenerative pathology.

The degree of pre-existing white matter disease, infarct volume, and global and medial temporal lobe atrophy, have been identified as some of the relevant imaging determinants of post-stroke dementia (Pohjasvaara *et al*.,2000b). A greater degree of severity of cognitive impairment after stroke has been associated with increased risk of PSD (Henon *et al*.,2001, Lin JH *et al*.,2003).

b) Strategic infarct dementia

Smaller infarcts in particular regions, for example in the deep central gray matter, may have an important role in causing dementia (Chui H, 2005). Lacunar infarcts involving the thalamus, internal capsule and basal ganglia are sometimes associated with widespread cognitive deficits, including confusion and memory impairment (Vermeer *et al*.,2003). Infarcts involving the dorsomedial and anterior thalamus might also produce significant executive symptoms and important amnesia, which can persist in some cases (Perren *et al*.,2005). Cognitive symptoms associated with strategic infarcts are often reversible by 12 months and they are therefore not a common cause of persistent dementia (Madureira *et al*.,1999).

c) Multi-infarct dementia (MID)

Multi-infarct dementia reflects the traditional view that multiple large cortical infarcts are required for dementia to develop. Coexisting subcortical infarcts, lacunes and white matter changes may be found (Hachinski *et al*.,1974). MID is related to atherothrombotic strokes, cardiac embolic strokes and major haemodynamic events. Typical clinical features of MID are focal neurological signs, such as hemiparesis, lateralized sensory changes and stepwise deterioration with cognitive impairment and aphasia. However, this type of vascular dementia is only one of several and is not the most common type in elderly people, who are more likely to have mixed AD and vascular dementia (MRC/CFAS 2001).

d) Intracerebral haemorrhage (IH)

IH, usually multiple, might cause widespread brain injury leading to dementia. The patients have usually chronic hypertension. The clinical syndrome usually comprises headache, nausea, reduced consciousness and, depending on the site of the haemorrhage different neurological symptoms such as contralateral hemiparesis and sensory loss, cranial nerve palsies, eye movement abnormalities or weakness (Wallin *et al*.,2002). In some cases, subarachnoidal haemorrhage leads to normal pressure hydrocephalus, which is a potentially treatable secondary dementia disorder. Another pathogenetic basis of post-haemorrhagic dementia is amyloid angiopathy (Vinters,1987), which makes the vessel wall liable to rupture and haemorrhage.

e) Alzheimer's disease with cerebrovascular disease

Evidence is accumulating that AD is commonly associated with vascular risk factors, including diabetes (Ott *et al*.,1999), hypertension and smoking (Luchsinger *et al*.,2005). Vascular and degenerative pathologies interact in terms of clinical expression of cognitive impairment (Snowdon *et al*.,1997; Esiri *et al*.,1999), and VaD and AD share common pathogenetic mechanisms (Meyer *et al*.,1999).

Many individuals with AD, especially those beyond 85 years of age, show significant vascular comorbidity, to the extent that they are more accurately characterized as having mixed vascular-AD dementia (Langa *et al*.,2004). Even though a mixed etiology is likely to be more common than either pure AD or VaD among older patients, there are no current clinical criteria for ante-mortem diagnosis of mixed dementia (O'Brien *et al*.,2003).

f) Subcortical vascular dementia (SVD)

In clinical studies, the proportion of vascular dementia caused by small-vessel disease ranges from 36% to 67% (Chui, 2001).

In SVD, the primary types of brain lesions are lacunar infarcts and ischaemic white matter lesions, whith demyelination and loss of axons, a

decreased number of oligodendrocytes, reactive astrocytosis, and the primary lesion site is the subcortical region (Wallin *et al*.,1991; Erkinjuntti *et al*.,2000a). This type of vascular dementia includes the old entities 'Lacunar state' and 'Binswanger's disease'. These are the two main pathophysiological pathways involved in SVD, and often coexist in the same patient (see Fig.8). In the first, occlusion of the arteriolar lumen due to arteriolosclerosis leads to the formation of lacunes, which results in a lacunar state (etat lacunaire). In the second, critical stenosis and hypoperfusion of multiple medullary arterioles causes widespread incomplete infarction of deep white matter (Englund *et al*.,1987), with a clinical picture of Binswanger's disease.

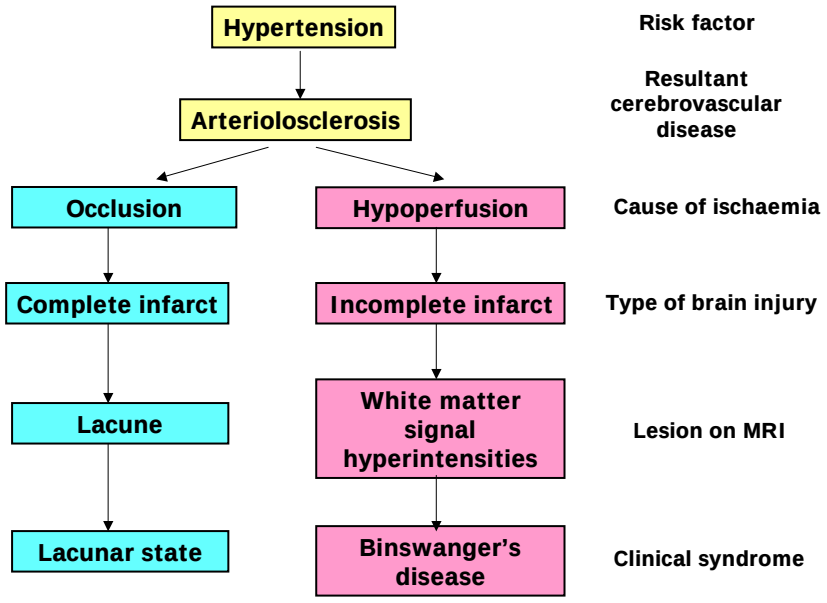

Fig. 8. Two pathophysiological pathways of SVD (Source: The Lancet Neurology 2002;1:426-436)

Patients with subcortical vascular dementia often have a history of multiple vascular disorders, including hypertension, diabetes and ischaemic heart disease. The onset of dementia is insidious in over half of the patients and the course is usually continuous and slowly progressive, seldom stepwise (Babikian and Ropper,1987; Pantoni *et al*.,1996).

The clinical symptoms are usually low mental speed, extrapyramidal symptoms (rigidity, hypokinesia), bilateral pyramidal symptoms (short steps, vivid reflex activity in the legs) and positive masseter reflex. Other neurological sign are imbalance and falls, urinary frequency and incontinence, dysarthria and dysphagia. Behavioural and psychiatric symptoms include depression, personality change, emotional lability, emotional bluntness and mental slowness. This syndrome is also called 'the subcortical syndrome' or 'frontosubcortical syndrome' (Coffey *et al*.,1989; Wallin *et al*.,1996; Wallin *et al*.,2000).

The typical cognitive syndrome in patients with subcortical vascular dementia is the 'dysexecutive syndrome'. It includes slowed information processing, memory deficits, behavioural and psychiatric symptoms (Erkinjuntti *et al*.,2000a) as well as impairment in goal formulation, initiation, planning, organizing, executing and abstracting (Cummings, 1994). The essential neuroimaging changes in subcortical vascular dementia include extensive ischaemic white matter lesions and lacunar infarcts in the deep grey and white matter structures.

These manifestations probably result from ischaemic interruption of parallel circuits from the prefrontal cortex to the basal ganglia and corresponding thalamocortical connections (Román *et al*.,2002).

Identification of early and mild stages of subcortical ischaemic vascular dementia will also be an important area for research because this form of vascular dementia is one of the commonest causes of cognitive decline in elderly people. SVD is commonly not recognised and remains undiagnosed, but it accounts for a significant number of cases of dementia and results in many admissions to nursing homes. Better recognition of the disease is necessary for maximum benefit to be derived from treatments that are currently available to delay disease progression, as well as the introduction of primary and secondary prevention measures.

2.4.2- Vascular Mild Cognitive Impairment (not dementia) with subcortical features

The most frequent diseases that cause dementia both at the population and clinical levels are Alzheimer's and cerebrovascular disease. Criteria to detect pre-clinical cases of Alzheimer's disease and mild cognitive impairment (MCI) have been developed with great emphasis on memory disturbances (Petersen *et al*.,1999). MCI patients perform memory tasks 1.5 standard deviations below an age-matched control population. MCI patients perform like unimpaired controls on measures of general cognition such as IQ tests. 25% of dementias developing in people with MCI are classified as VaD (Meyer *et al*.,2002), and in one study a substantial proportion of people with subcortical small vessel dementia exhibited prodromal MCI (Meyer *et al*.,2002).

However less effort have been devoted to identify pre-clinical cases of vascular dementia. Although substantial data indicates that vascular risk factors and general vascular conditions are associated with poorer cognitive performance (Polidori *et al*.,2001) , the operational definition of cognitive impairment not fulfilling criteria for dementia due to vascular causes has so far escaped a satisfactory definition. The issue is complicated by the fact that the clinical criteria for vascular dementia developed to date include etiologically and clinically heterogeneous conditions (Chui *et al*.,1992; Roman *et al*.,1993; Rockwood *et al*.,1999b). In agreement with this it has been recently proposed that patients with the subcortical form of vascular dementia represent a highly prevalent and homogeneous group (Erkinjuntti *et al*.,2000b). The primary clinical manifestation is a subcortical syndrome comprising progressive cognitive impairment with frontal features and parkinsonism non-responsive to levodopa.

An important but unresolved question is whether subcortical small-vessel disease by itself can lead to cognitive impairment of sufficient severity to meet the criteria for dementia. Hence the concept of *Subcortical ischaemic vascular disease without dementia.* In this work, we have used a modified version of this criteria to detect pre-dementia cases and this criteria has been called *mild cognitive*

impairment of the vascular type (MCI-V) (see Table 1). This category frequently manifests as white-matter lesions on MRI brain scans in the context of well-recognised vascular risk factors (Frisoni et al.,2002).

It is well known that white-matter lesions (WML) have important cognitive consequences even in the absence of dementia (Ylikoski *et al*.,1993; Breteler *et al*.,1994b; De Groot *et al*.,2001). Furthermore, WML have important non-cognitive consequences including depression and minor motor deficits (ie, gait disorder, imbalance, urinary frequency) that can severely impair the quality of life of these patients (Barber *et al*.,1999; O'Brien *et al*.,2000). WMH and lacunar infarcts demonstrated by MRI are generally considered to be evidence of small-vessel or microvascular ischemic disease. Pathologically, MRI white matter signal abnormalities reflect focal and diffuse lesions of the subcortical and periventricular white matter, as well as lacunes and microinfarcts of the central grey matter (Udaka *et al*.,2002). The typical neuropsychological profile of these patients is the 'dysexecutive syndrome' as was described above in the section on 'Subcortical vascular dementia', accompanied with mild memory deficit affecting the recall but with relative intact recognition and deriving benefit from cues. This cognitive impairment is progressive from a previously higher level of functioning but is not *per se* interfering with complex occupational and social activities. In those patients the reminder of cognitive functions are intact.

The prognosis is poor for the high frequency of adverse outcomes (cognitive and functional deterioration, nursing home placement, and death). Recognizing these individuals is preliminary to understand the mechanisms leading to adverse outcomes and to devising interventions aimed to delay their onset.

Table 1. Criteria used to define mild cognitive impairment with subcortical vascular features (MCI-V). Modified from Erkinjuntti *et al*.,2000b.

I. *All of the following:*

A. COGNITIVE SYNDROME including all of the following:

A.1 DYSEXECUTIVE SYNDROME: Impairment in goal formulation, initiation, planning, organizing, sequencing, executing, set-shifting and maintenance, and abstracting.

A.2. MEMORY DEFICIT (may be mild): Impaired recall, relative intact recognition, less severe forgetting, benefit from cues.

A.3. PROGRESSION: deterioration of A1 and A2 from a previous higher level of functioning that are not per se interfering with complex (executive) occupational and social activities.

B. CEREBROVASCULAR DISEASE including both B1 and B2.

B.1. EVIDENCE OF RELEVANT CEREBROVASCULAR DISEASE BY BRAIN IMAGING defined as the presence of both:

- extensive periventricular and deep white matter lesions: patchy areas of low attenuation (intermediate density between that of normal white matter and that of intraventricular cerebro-spinal fluid) or diffuse symmetrical areas of low attenuation with ill defined margins extending to the centrum semiovale plus at least one lacunar infarct, and
- absence of cortical and/or cortico-subcortical non-lacunar territorial infarcts and watershed infarcts, haemorrhages indicating large vessel disease, signs of normal pressure hydrocephalus, and specific causes of white matter lesions (e.g. multiple sclerosis, sarcoidosis, brain irradation).

B.2. PRESENCE OR A HISTORY OF NEUROLOGICAL SIGNS as evidence for cerebrovascular disease such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorder, extrapyramidal signs consistent with subcortical brain lesion(s).

II. *Clinical features supporting the diagnosis include the following:*

a. Episodes of mild upper motor neuron involvement such as drift, reflex assymetry, incoordination.

b. Early presence of a gait disturbance (small-step gait or marche a petits-pas magnetic, apraxic-ataxic or Parkinsonian gait).

c. History of unsteadiness and frequent, unprovoked falls.

d. Early urinary frequency, and other urinary symptoms not explained by urologic disease.

e. Dysarthria, dysphagia, extrapyramidal signs (hypokinesia, rigidity).

f. Behavioral and psychological symptoms such as depression, personality change, emotional incontinence, psychomotor retardation.

III. *Features that make the diagnosis uncertain or unlikely include:*

a. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging.

b. Absence of relevant cerebrovascular lesions on brain CT or MRI.

2.5- Magnetic resonance imaging (MRI) in small vessel disease (white matter hyperintensities and lacunar infarcts)

Some early studies showed that a considerable number of cerebral infarcts were clinically silent (Boon *et al*.,1994; Jørgensen *et al*.,1994; Shinkawa *et al*.,1995), although they were associated with significant behavioral changes (Price *et al*.,1997; Longstreth *et al*.,1998) and low cognitive performance (Garner *et al*.,1998; Swan *et al*.,2000). In the population-based Cardiovascular Health Study, about a quarter of 3660 subjects aged 65 or older had one or more lacunes on MRI (Longstreth *et al*.,1998). Most lacunes (89%) were clinically silent or were manifested as gait problems and subtle cognitive impairments that were not recognised as stroke. In other population-based studies the prevalence of silent lacunes ranged from 11% to 24% (Kase *et al*.,1989; Giroud *et al*.,1991; Shinkawa *et al*.,1995; Vermeer *et al*.,2002).

Cerebral infarctions seen on MRI are also significantly associated with white matter hyperintensities (WMH) (DeCarli *et al*.,1999; Longstreth *et al*.,1996). According to several population-based studies, the prevalence of cerebral WMH on MRI in elderly people is in the range of 62-95% (Breteler *et al*.,1994b; Lindgren *et al*.,1994; Ylikoski *et al*.,1995; Liao *et al*.,1997). These lesions are associated with advancing age, lacunes, hypertension, heart disease, orthostatic hypotension, smoking, and lower income and education (Breteler *et al*.,1994b; Lindgren *et al*.,1994; Ylikoski *et al*.,1995; Longstreth *et al*.,1996; Roman,1996; Liao *et al*.,1997).

The fact that WMH significantly predict future stroke and mortality lends further support to the notion that WMH and other brain changes in the absence of clinically apparent stroke are part of a spectrum of vascular related brain injury (DeCarli *et al*.,1999). Extensive WMH, therefore, may serve as a marker for impaired subcortical perfusion resulting in brain atrophy including hippocampal atrophy. Some epidemiological studies consistently showed moderate associations between brain atrophy or WMH volumes and diminished cognitive impairment (Longstreth *et al*.,1996; De Groot *et al*.,1998; De Groot *et al*.,2000; Breteler, 2000).

For example, Burton *et al*.(2003) found that significant associations existed between cognitive impairments and both the severity of white matter lesions and atrophy in key frontostriatal areas. Processing speed, attentional measures and executive function were associated with hyperintensities in the internal capsule, caudate and thalamus.

Severity of cognitive impairment in SVD correlates more strongly with the degree of hippocampal, medial temporal lobe and cerebral atrophy than with severity of white-matter hyperintensities and consequently predict faster progression of cognitive impairment (Fein *et al*.,2000; Pohjasvaara *et al*.,2000; Mungas *et al*.,2001; Mungas *et al*.,2002). Nonetheless, cerebral atrophy and white matter lesions are related. Quantitative MRI reveals widespread atrophy in SVD that is not only due to focal infarction.

The etiology of hippocampal and neocortical atrophy associated with vascular cognitive impairment remains unknown. Several possibilities should be considered. Firstly, the presence of atrophy in vascular dementia (VaD) may reflect concomitant Alzheimer disease (AD) (Laakso *et al*.,1996) . Pathological study of three cases with VaD and hippocampal atrophy showed the presence of neurofibrillary tangles in those patients (Fein *et al*.,2000). The authors also noted significant correlations between the extent of WMH and grey matter volume across the range of VaD patients. Secondly, vascular brain injury may lead to secondary (deafferentation) neuronal degeneration following primary subcortical injury. This would represent the structural corollary to the traditional notion that cortical hypoperfusion in SVD results from functional deafferentation of cerebral cortex (Brown *et al*.,1993). Thirdly, hippocampal atrophy may result directly from the ischaemic process. White matter injury resulting in WMH may lead to brain atrophy, but this relation has not been studied in detail.

In summary, the data suggests that the pathogenesis of hippocampal atrophy in subcortical vascular impairment is variable and may reflect a combination of degenerative and ischaemic pathologies. Wu *et al*.(2001), noted that the presence of extensive WMH and hippocampal atrophy were each

independently associated with an increased risk for dementia, but this effect was additive in the presence of both brain changes.

Vascular risk factors may predispose not only to vascular dementia but also to the development of Alzheimer's disease (de la Torre, 2002). These factors include hypertension, carotid-artery wall thickness, hypercholesterolaemia, peripheral vascular disease, apolipoprotein E ε4 allele, and hyperhomocysteinaemia. Du *et al*.(2002) showed that patients with SVD had smaller volumes of the enthorinal cortex (ERC) and hippocampus than normal controls. However, despite similar degrees of severity of dementia severity, these MRI volumes were significantly smaller in AD than in SVD. The authors suggested that the deafferentation of afferent pathways to enthorinal cortex and hippocampus, rather than direct vascular lesions, are responsible for volume loss in those regions. The same authors were found that cortical grey matter volume was inversely related to WMH volume while ERC and hippocampal volumes were not (Du *et al*.,2005). They concluded that the ERC and hippocampus might be less vulnerable to vascular disease than the cortex because these structures have fewer direct connections to subcortical regions. In a separate study brain atrophy rates in patients with Lewy bodies, AD, and VaD, were compared, and the rate of brain atrophy, compared with control subjects, was found to be similar (O'Brien *et al*.,2001). Unfortunately, our understanding of the pathological processes leading to hippocampal atrophy remains unclear and more studies are needed.

2.6- Clinical, cognitive and functional outcome of lacunar strokes and patients with MCI-V.

Prognosis for survival and recurrence

Compared with other stroke subtypes, the prognosis after lacunar infarction (LI) is usually much better with almost no acute mortality, a generally excellent recovery, a low risk of recurrent stroke (which is normally of the same subtype as the first stroke), and little or no effect on long-term survival. Most studies of LI found a low risk of death immediately after stroke onset. This fact is not surprising because the primary lesion is small and the rate of recovery is

usually rapid (which decreases the risk of death due to secondary complications), and cardiac comorbidities are less common than in most other stroke types. The mean case fatality was 2.5% (rangre 0-10%) at 30 days, and 2.8% (range 2-15%) at 1 year. However, after 5 years of follow-up about a quarter of all patients had died (mean value 27.4%; range 17-38%). The average death rate per year was 2.8% (range 3-15%) in all studies, but notably higher (mean 5.1%; range 3-7%) in studies with follow-up times of 4 years or more (Norrving, 2003).

Predictive factors of death determined by multivariate analysis have been reported in some studies. The most important factors were: age (Clavier *et al*.,1994; Salgado *et al*.,1996; Staaf *et al*.,2001; De Jong *et al*.,2002), diabetes (Clavier *et al*.,1994; De Jong *et al*.,2002), smoking (Clavier *et al*.,1994), disability score (Salgado *et al*.,1996), sex and non-use of aspirin (Staaf *et al*.,2001). For example, De Jong and colleagues (De Jong *et al*.,2002) reported that patients who had both asymptomatic LI on computarized tomography (CT) and WMH (19%) versus patients without any of these findings (59%), presented with higher death rates.

In patients with lacunar stroke, the presence of extensive white matter lesions is a poor prognostic sign and increases the risk of recurrent stroke (odds ratio=6.4), dementia (odds ratio=11.1), and death (odds ratio=4.6) (Longstreth *et al*.,1998). The average rate of recurrent stroke at 1 year in most studies was about 7.7% (range 2-12%) whereas the rate at 4-5 years was about 22.4% (range 15-28%) (Sacco *et al*.,1991; Staaf *et al*.,2001; Eriksson *et al*.,2001; Yamamoto *et al*.,2002). In most studies the risk of recurrent stroke after the first year was about 4-6% per year. However, Staaf *et al*.(2001) demonstrated that the annual rate of stroke recurrence decreased from about 5% during the first 5 years, to less than 1% between 5 and 10 years after the first stroke.

Studies outcomes differ as to weather the risk of recurrent stroke is different after lacunar infarcts compared to other stroke subtypes. A low rate of recurrence in LI was reported in three studies (Bamford *et al*.,1987; Landi *et al*.,1992; Nadeau *et al*.,1993), but no difference was seen in three other studies (Hier *et al*.,1991; Brainin *et al*.,1992; Boiten *et al*.,1993). Thus, there is little

evidence for the suggestion that lacunar infarcts carry a more benign prognosis for recurrent stroke than other ischaemic stroke subtypes.

Indeed, other reports provide strong evidence that vascular risk factors and severity of cerebral small-vessel disease at baseline are important determinants of the risk of future stroke after LI, as suggested by one earlier study (Miyao *et al*.,1992). Further, a preliminary report from the Secondary Prevention of Small Subcortical Strokes (SPS3) pilot trial showed a very high recurrence rate (22% per year) among 59 Hispanic-American patients, of whom 84% had hypertension and 64% had diabetes (Benavente *et al*.,2002). The risk of recurrence is thus far from uniform among patients with LIs.

There is substantial variation between studies on the subtype of recurrent strokes, with proportions of new strokes due to LI ranging from 17% to 84%. However, the data were more uniform in some larger studies, in which 50-72% of new strokes were of the same type as the first stroke among patients with LIs (Kappelle *et al*.,1995; Samuelsson *et al*.,1996a; Yamamoto *et al*.,1998; De Jong *et al*.,2002). However, up to half of all recurrent strokes are of other subtypes illustrating that causes of recurrent stroke are also heterogeneous in this patient group (Arboix et al.,2007).

Besides survival and risk of recurrence, there is also a need to think of the prognosis in a broader context, including long-term disability, the risk of developing cognitive decline, dementia and other behavioral dysfunctions, as well as the progression of small-vessel disease.

Prognosis for cognitive outcome

After LI, cognitive function is normally unaffected in the acute phase (Fisher, 1982; Fisher, 1991; Bamford, 2001), but the development of cognitive impairment and dementia is a matter of concern in the long-term. As reported above, remarkable focal neuropsychological impairments involving verbal fluency, memory function, and abulia may occur after strategically localised single LI (Ferro *et al*.,1984; Tanridag *et al*.,1985; Kooistra *et al*.,1988; Tatemichi *et al*.,1992; Pullicino *et al*.,1994; Yamanaka *et al*.,1996; Schneider *et al*.,1996). Patients with

single symptomatic supratentorial lacunar infarcts had a normal ability on most neuropsychological tests, but impairments were seen in tasks that were particularly stenuous and required the effective use of several capacities (Van Zandvoort *et al*.,1998).

The risk of dementia has been assessed in only a few studies of patients with LI. Dementia was reported in 11% of patients 2-3 years after LI (Miyao *et al*.,1992; Samuelsson *et al*.,1996), whereas 15% of patients had dementia after 9 years (Yamamoto *et al*.,2002). Dementia commonly developed in conjunction with recurrent strokes. Prospective, community-based studies and short-term clinical trials indicate that control of risk factors for vascular disease, such as hypertension (Birkenhager *et al*.,2001) and hyperlipidaemia (Jick *et al*.,2000), reduces the risk of cognitive impairment. The cognitive dysfunction and development of dementia after symptomatic LI may be due, at least in part, to coexisting leukoaraiosis and multiple, clinically silent, small deep infarcts, and synergistic effects can also occur (Longstreth *et al*.,1998). In particular, a few LIs in the basal ganglia, thalamus, or deep white matter increased the risk of clinical dementia by 20 times.

Vascular cognitive impairment is considered to increase the risk of death and institutionalization and progresses to dementia in approximately half of the cases (Rockwood *et al*.,2000; Wentzel *et al*.,2001). Epidemiological studies have reported that one fourth of elderly patients meet the criteria for dementia three months after ischemic stroke (Desmond *et al*.,2002). Furthermore, about 10% of patients with mild cognitive impairment related to cerebrovascular disease develop vascular dementia (VaD) within 1 year (Wentzel *et al*.,2001; Tham *et al*.,2001; Ingles *et al*.,2002; Ballard *et al*.,2003). However, some authors have reported a general functional improvement during the first year in 2.7% to 31.0% of these patients (Kotila *et al*.,1984; Wentzel *et al*.,2001; Tham *et al*.,2001; Patel *et al*.,2003) or even the second year (Rasquin *et al*.,2005), while others found a progressive decline of the cognitive impairment in general (Desmond *et al*.,1996; Sachdev *et al*.,2004). Despite these findings, data about cognitive prognosis after stroke in general and in small vessel disease (SVD) in particular is scarce (Schmidkte *et al*.,2005).

Prognosis for functional outcome

The long-term prognosis for functional outcome after LI has received less attention than the prognosis for survival and recurrent stroke. Most studies have focused on the level of independence in activities of daily living (ADL). From them we know that a large component of impairment in ADL, in particular instrumental ADL, is dependent on executive function, the cognitive function mainly affected in those patients (Boyle *et al*.,2002). Mok *et al*.(2004) found that executive dysfunction predicted impairment in complex ADL among patients with SVD.

Compared with patients with other subtypes of stroke, patients with LI tend to have a more favourable functional outcome (Bamford *et al*.,1991; Petty *et al*.,2000). However, the proportion of patients with LI that are dependent is as high as 18-33% at 1 year (Bamford *et al*.,1991; Clavier *et al*.,1994; Samuelsson *et al*.,1996a; Petty *et al*.,2000), 36% at 2 years (Giroud *et al*.,1991) and 42% at 3 years (Samuelsson *et al*.,1996b). About 10% of the patients who were independent in activities of daily living had decreased function in other domains that restricted customary social relations or recreational activities (Samuelsson *et al*.,1996b). A small proportion of patients (5-12%) were already dependent due to other factors before the stroke (Bamford *et al*.,1991; Petty *et al*.,2000). In many cases, there is deterioration in functional ability in conjunction with a recurrent stroke (Samuelsson *et al*.,1996b; Yamamoto *et al*.,1998). There are no data available for disability beyond 3 years after the first stroke.

Predictive factors of disability have been analysed in only a few studies, which showed age, diabetes, initial severity of stroke, measured with the NIHSS scale (National Institute of Health Stroke Scale) (Mok *et al*.,2004) and type of lacunar syndrome (Clavier *et al*.,1994; Samuelsson *et al*.,1996b) to be associated with an unfavourable prognosis. In some studies carried out with patients with subcortical SVD, motor impairment significantly predicted physical dependence in those subjects (Clavier *et al*.,1994; Samuelsson *et al*.,1996b). Interestingly, the presence of asymptomatic LI and leukoaraiosis were also independent predictors (Samuelsson *et al*.,1996b; De Jong *et al*.,2002), suggesting that more advanced

cerebral small-artery disease may limit the possibility of functional recovery of the brain after a small focal lesion.

Quality of life after lacunar stroke has been determined by the Sickness Impact Profile in 82 patients (De Haan *et al*.,1995). Compared with other types of stroke and haemorrhage, patients with LI had significantly less dysfunction in almost all quality of life categories. However, about a quarter of patients with lacunar stroke reported severely impaired quality of life overall or in the psychosocial life domains (Van Zandvoort *et al*.,1998). For example, some behavioral symptoms, such as depression and emotional lability can affect those domains and consequently the quality of life of those patients (Burns *et al*.,1999).

3- AIMS OF THE STUDY

The subject of this research is the study of the neuropsychological profile and cognitive impairment in subcortical small vessel disease (lacunar infarcts and white matter hyperintensities), as well as the outcome of these patients over 18 months following the stroke. This subject merits study because subcortical small vessel disease is one of the most common causes of VaD and the knowledge of the prodromal state and their main risk factors would provide us a useful tool for develop preventive strategies. This topic merits study also because although there are many studies studies examining the outcome and the neuropychological sequelae in large vessel disease, studies about the effect of a first-ever LI and the long-term outcome of these patients are scarce. Finally, there are no studies investigating the neuropsychological profile of different lacunar syndromes (according Miller-Fisher) and their long-term outcome.

The objectives of the thesis are as follows:

1) - (a) To determine the frequency and features of neuropsychological abnormalities in patients with a first-ever lacunar infarct.

(b) To assess whether the topography of infarction, presence of isolated or multiple lacunar infarcts and white matter hyperintensities is related to cognitive impairment in those patients.

2) - To determine the neuroradiological features, white matter hyperintensities and grey matter volume characteristics in lacunar stroke patients that fulfil criteria for MCI-V as compared to those lacunar patients without cognitive impairment.

3) - To compare the long-term outcome (18 months) of cognitive function and structural brain measures (grey matter volumes and white matter hyperintensities) in LI patients fulfilling the MCI-V criteria versus lacunar patients without cognitive impairment.

4) - To determine the topographical distribution of white matter hyperintensities (WMH) in lacunar patients and the differences in the frequency, severity and topography of WMH comparing patients with first-ever LI and single lacunae versus patients with multiple silent LI.

4- METHODOLOGY

This thesis consists of four studies examining the neurological, neuropsychological and neuroanatomical characteristics of the brain of patients with lacunar stroke. Different neurological, neuropsychological and MRI approaches have been employed.

- All patients were **neurologically assessed** by a senior neurologist and classified into different lacunar syndromes (pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand, and atypical lacunar syndrome).
- For the **neuropsychological assessment** the following tests were used:
  - ❖ For verbal memory, a modified version of the Auditory Verbal Learning Test was used (Lezak et al.,2004).
  - ❖ Visual memory function was evaluated with the Visual Reproduction of the Wechsler Memory Scale-III (Lezak et al.,2004).
  - ❖ Language performance was assessed with a short versions of the Boston Naming Test and Token Test (Lezak et al.,2004).
  - ❖ The evaluation of verbal fluency was done with two tasks: a) phonetic fluency was assessed with a modified version of the Controlled Oral Word Association Test (Artiola I Fortuny et al.,1999). Subjects were instructed to generate words that began with the letters P, M and R in three separate trials; b) semantic fluency was assessed generating words when cued with a particular category (animals).
  - ❖ Visuo-spatial and visuo-constructive functions were evaluated using the Benton Judgement of Line Orientation Test (BJLOT) and Block Design Tests (WAIS-III), respectively (Wechsler D, 1997-98).
  - ❖ Executive functions were assessed by the Trail Making Test B (TMT-B), Stroop Test (Interference T-score) and the above mentioned verbal fluencies.
  - ❖ Luria's Premotor Sequences were used as a measure of prefrontal functions (Lezak et al.,2004).

- ❖ Trail Making Test A (TMT-A), Digit Symbol Substitution Test (WAIS-III) and Digit Span Forward (WAIS-III) were used to assess attention and short-term memory (Wechsler D, 1997-98).
- ❖ Working memory was tested using the Digit Span Backward Test (WAIS-III) (Wechsler D, 1997-98).

- **Structural MRI techniques** used in the present thesis:
  - ❖ The presence of acute or chronic, single and/or multiple silent lacunar infarcts and its location were determined by means of visual inspection using the T1-weighted, FLAIR, T2-weighted and diffusion sequences of MRI scans.
  - ❖ White matter hyperintensities were evaluated from T2-weighted images, and periventricular, white matter, subcortical and infratentorial hyperintensities were evaluated in axial slices according to the Schelten's scale (Schelten's et al.,1993). This scale is a visual semiquantitative method used to quantify the severity of white matter hyperintensities. Values for white matter, subcortical, and infratentorial hyperintensities range from 0 (absence) to 6 (confluent), and for periventricular hyperintensities from 0 (absence) to 2 (>5mm). According to the number of regions to be assessed, maximum scores are 24 for white matter (four lobes) and infratentorial (cerebellum, mesencephal, protuberance, bulb) hyperintensities; 30 for subcortical hyperintensities (putamen, globus pallidus, thalamus, internal capsule); and 6 for periventricular hyperintensities (occipital horn, frontal horn, lateral ventricle rim).
  - ❖ A voxel-based morphometry approach was performed using SMP2 (Statistical Parametric Mapping) software running in Matlab 6.5 (MathWorks, Natick, MA) following the main steps of the optimized method proposed by Good et al.,2001. This procedure allows the automatic detection of whole-brain morphological differences by assigning each brain voxel a probability of being grey matter, white matter and cerebrospinal fluid (CSF).
  - ❖ Region of interest (ROI) analysis was performed using the Wake Forest University of School of Medicine Pickatlas software (WFU Pickatlas v2) comprising the hippocampi and the parahippocampal gyri.

- **Statistical analysis** of the data was done using the Statistical Package for Social Sciences (SPSS v.11.5, 12.0 and 14.0). This was used to investigate the group differences in demographic, clinical and neuropsychological performance by means of ANOVA. The Student's *t* test was used for continuous data and the chi-square (χ^2) test or the Fisher's exact probability test was used for categorical variables (when appropiate).

  For the analyses of structural MRI data, the Statistical Parametric Mapping (SPM2) software, running in Matlab 6.5 (MathWorks, Natick, MA) was used. Comparisons of grey-matter volumes and correlations between white-matter hyperintensities and grey-matter atrophy derived from the statistical maps were analyzed with the 'two-sample t test' and 'simple regression (correlation)' in the baseline and with 'repeated measures ANOVA' (age and gender as covariates) and 'multiple regression' (age and gender as nuisance variables). All these models were provided by SPM2.

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5. RESULTS

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Neuropsychological abnormalities associated with lacunar infarction ☆

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Abstract

The objective of this study was to assess neuropsychological abnormalities in 40 patients with lacunar infarction. Topography of infarction, presence of isolated or multiple silent infarcts and white matter hyperintensities were correlated with results of neuropsychological tests and subtypes of lacunar infarction. Patients were studied within 1 month after stroke. A total of 21 patients were males and the mean age was 70.7 years; 30% had a single infarction (mean number of infarctions was 3.4). Twelve patients had pure motor hemiparesis, 9 pure sensory stroke, 8 dysarthria-clumsy hand/ataxic hemiparesis, 8 atypical lacunar syndrome, and 3 sensorimotor stroke. The mean score of the Mini-Mental State Examination was 28.4. Mild cognitive impairment of subcortical vascular features occurred in 23 patients and isolated executive disturbances in 4. Neuropsychological results showed that patients with atypical lacunar syndrome followed by pure motor hemiparesis showed significantly more cognitive executive disturbances. Patients with dysarthria-clumsy hand/ataxic hemiparesis accounted for the best scores in some tests of visuoconstructive function and visual memory. In summary, mild neuropsychological disturbances (57.5%) are not infrequent in acute lacunar infarcts especially in patients with atypical lacunar syndrome and pure motor hemiparesis. Neuropsychological impairment should be considered as common clinical feature in acute lacunar infarction.

Keywords: Lacunar stroke; Cognitive impairment; Neuropsychological tests; Atypical lacunar syndrome; Pure motor hemiparesis; Pure sensory stroke; Sensorimotor stroke; Dysarthria-clumsy hand; Ataxic hemiparesis

1. Introduction

Lacunar infarcts, small (<15 mm in diameter) subcortical infarcts that result from occlusion of a single perforating artery, account for about 20–25% of all ischemic strokes. Compared with other stroke subtypes, the prognosis after lacunar infarction is much better with almost no acute mortality, a generally excellent recovery, a low risk of recurrence and little or no effect on long-term survival [1]. Data regarding the prognosis of lacunar stroke in relation to the risk of developing cognitive decline, dementia and other behavioral dysfunction is based on a small series of patients or single case reports. Capsular genu infarcts have been associated with severe verbal memory loss and cognitive deficits consistent with dementia [2], contextual amnesia [3], and recurrent memory loss [4]. A persistent hemispatial neglect developed in a patient following a small infarction of the posterior limb of the right internal capsule [5]. Atypical aphasia syndromes were associated with circumscribed non-hemorrhagic infarctions of the anterior limb of the internal capsule and of the striatum, in the dominant hemisphere [6].

There is little information available on neuropsychological abnormalities in a large series of patients with lacunar infarction. To contribute to the knowledge of the cognitive impairment in lacunar stroke, we carried out a prospective study of 40 patients with lacunar infarction, with the following objectives: (a) to determine the frequency of neuropsychological abnormalities in lacunar stroke, and (b) to assess whether the topography of infarction, presence of isolated or multiple silent infarcts and white matter hyperintensities showed a relationship with cognitive impairment.

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2. Patients and methods

2.1. Study population

All patients with first-ever stroke presenting as a lacunar infarction admitted consecutively to the Department of Neurology of Hospital of Sagrat Cor (an acute-care 350-bed teaching hospital in the city of Barcelona, Spain) between January 2003 and February 2005 were included in the study provided that at least a single symptomatic acute lacunar infarction (>2 mm and <15 mm in maximal diameter) in the internal capsule, thalamus, basal ganglia, corona radiata, pons or centrum ovale was confirmed by brain MRI. Exclusion criteria were as follows: cortical and/or subcortical non-lacunar infarcts or intracerebral hemorrhage documented by MRI; severe cardiovascular, renal, hepatic, neoplastic, or chronic disease; psychiatric comorbidity (DSM-IV); major depression (Hamilton Rating Scale for Depression score ≥18); and dementia (Mini-Mental State Examination [MMSE] score<24). The definitions of cerebrovascular risk factors and lacunar syndromes (pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand, and atypical lacunar syndromes) were those used in previous studies [7–9]. During the study period, 60 patients with first-ever lacunar stroke were diagnosed. However, 20 patients were excluded from the study for the following reasons: cortical and/or subcortical non-lacunar infarcts documented by MRI (n=13); normal MRI findings (n=2); cavernous angioma (n=1); major depression (n=1); dementia (n=1); retained shrapnel particles in the head (n=1); and MRI contraindication (cardiac pacemaker) (n=1).

2.2. MRI examination

MRI acquisitions were obtained using a General Electric 1.5 Tesla Sigma System. To distinguish between acute and chronic silent lacunar infarcts and to rate the degree of white matter hyperintensities, MRI was performed in the following sequences: T1-weighted (SAG/SE/T1: TR=479 ms, TE=13 ms, FOV=270/1.1, slice thickness 5.0 mm, GAP 1.0; T2-weighted and TRA/SE/T1: TR=539 ms, TE=15 ms, FOV=240/1.1, slice thickness 5.0 mm, GAP 1.0); T2-weighted (COR/TSE/T2: TR=4885 ms, TE=120 ms, FOV=220/1.1, slide thickness 5.0 mm, GAP 2.0); fluid-attenuated inversion recovery (FLAIR) (TRA/FLAIR: TR=8000 ms, TE=120 ms, FOV=240/1.1, slide thickness 5.0 mm, GAP 1.2); protonic density (TRA/DUAL: TR=3400 ms, TE=17 ms, FOV=240/1.1, slide thickness 5.0, GAP 1.0); and diffusion sequences (DW/SSH/100: TR=3350 ms, TE=74 ms, FOV=250/1.1, slide thickness 5.0 mm, GAP 1.0).

The presence of acute or chronic, single and/or multiple silent lacunar infarcts and its location were determined by two senior neuroradiologists by means of visual inspection using the T1, FLAIR, and T2 sequences of MRI scans. White matter lesions were evaluated from T2-weighted images, and periventricular, white matter, subcortical, and infratentorial hyperintensities were evaluated in axial slices according to the Scheltens' scale [10]. Values for white matter, subcortical, and infratentorial hyperintensities range from 0 (absence) to 6 (confluent), and for periventricular hyperintensities from 0 (absence) to 2 (>5 mm). According to the number of regions to be assessed, maximum scores are 24 for white matter (four lobes) and infratentorial (cerebellum, mesencephalon, protuberance, bulb) hyperintensities; 30 for subcortical hyperintensities (putamen, globus pallidus, thalamus, internal capsule); and 6 for periventricular hyperintensities (occipital cap, frontal cap, lateral ventricle rim).

2.3. Neuropsychological assessment

All subjects were administered an extensive battery of neuropsychological tests 1 month after the index admission. The neuropsychological assessment was accomplished with the following tests: Rey Auditory Verbal Learning Test (RAVLT), Visual Reproduction (VR) subtest of the Wechsler Memory Scale (WMS-III), Trail Making Test A and B (TMT-A, TMT-B), Stroop Test, Phonetic Verbal Fluency Test, Verbal Category Fluency Test (animal naming), Luria's Premotor Sequences, Boston Naming Test; Shortened Token Test, Digit Symbol Test, (WAIS-III) Digit Span Forward and Backward Test, (WAIS-III) Block Design Test; and Benton Judgment of Line Orientation Test (BJLOT). The scores used were scaled scores for the WAIS-III and WMS-III subtests and direct values for the remaining tests.

Mild cognitive impairment of the vascular type (MCI-V) [11,12] was considered in non-demented patients exhibiting cognitive impairment mainly as a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease.

According to criteria of Frisoni et al. [11] MCI-V patients were those with scores equal to or less than −1.5 SD according to age- and gender-matched standardized norms on at least one of the following tests assessing frontal lobe function: verbal fluency, TMT-A and TMT-B, and Stroop Test. Patients within this cognitive group also scored equal to or less than −1 SD on one of the following declarative memory tests: immediate, delayed recall or recognition of RAVLT and Visual Reproduction of WMS-III.

2.4. Statistical analysis

Clinical variables, neuroimaging data, and results of neuropsychological tests in the different groups of lacunar syndromes were analyzed with the Student's t test for continuous data. For this purpose and to avoid multiple comparisons for each neuropsychological test, results on each test for the different patient groups were compared with the remaining patients. The chi-square (χ^2) test or the Fisher's exact probability test (when appropriate) was used

for categorical variables. Statistical significance was set at $P<0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 11.0).

3. Results

Twenty one out of 40 patients were men and 19 were women with a mean (standard deviation, SD) age of 70.7 (12.2) years. Clinically, there were 12 patients with pure motor hemiparesis; 9 patients with pure sensory stroke; 8 patients with dysarthria-clumsy hand/ataxic hemiparesis (dysarthria-clumsy hand 7, ataxic hemiparesis 1); 8 patients with atypical lacunar syndrome, and 3 patients with sensorimotor stroke. There were no significant differences among these groups with regard to demographic data and education level (years attending school) (Table 1).

3.1. Topography of infarcts and clinical lacunar syndromes

Topographically, the most frequent lesions were observed in the protuberance in 27.5% of patients followed by the thalamus and centrum ovale in 22.5%, the basal ganglia and the internal capsule in 20% of patients, and corona radiata in 10%. Twelve patients presented single lacunar infarcts and the remaining 28 had multiple infarcts. The mean (SD) number of infarctions was 3.4 (2.2). As shown in Table 1, lacunar infarcts in the basal ganglia were significantly more frequent within the group of atypical lacunar syndromes (50%) as compared to the number of infarcts within each other group ($\chi^2=5.625$, $P<0.037$). Lacunar infarctions in the internal capsule were significantly more frequent in the group of sensorimotor stroke (66.6%) compared with the remaining groups ($\chi^2=4.414$, $P<0.036$).

3.2. MRI hyperintensities and clinical lacunar syndromes

In the whole group of lacunar stroke patients, mean (SD) value of MRI hyperintensities according to the Scheltens' scale was 15.6 (10.1), without significant differences according to the different lacunar syndromes. On the other hand, white matter and periventricular hyperintensities were similarly distributed among the different lacunar syndromes but subcortical hyperintensities were significantly less frequent in patients with sensorimotor stroke ($t=2.235$, $P=0.031$) and infratentorial hyperintensities significantly less frequent in patients with pure sensory stroke ($t=2.259$, $P=0.030$) compared with the remaining patients (Table 1).

3.3. Cognitive function and clinical lacunar syndromes

The mean (SD) MMSE score was 28.4 (1.7). The group of patients with dysarthria-clumsy hand/ataxic hemiparesis scored higher 29.5 (1.2) than the remaining groups ($t=2.088$, $P=0.044$). A total of 23 patients (57.5%) fulfilled criteria of MCI-V (pure motor hemiparesis 7/12 (58.3%), pure sensory stroke 6/9 (66.6%), dysarthria-clumsy hand/ataxic hemiparesis 3/8 (37.5%) and atypical lacunar syndrome 7/8 (87.5%). Additionally, 4 patients (10%), one patient in each lacunar stroke group, showed isolated dysexecutive impairment. Other neuropsychological impairments included verbal memory impairment (immediate recall 20%, delayed recall 52.5%), visual memory impairment (immediate recall 22.5%, delayed recall 20%), anomia (7.5%) and 1 subject (2.5%) with a mild deficit in visuoconstructive praxis.

Mean (SD) scores of neuropsychological tests are shown in Table 2. Most cognitive disturbances occurred in patients with atypical lacunar syndrome, with statistically significant lower scores in those tests assessing executive functions,

Table 1
Demographic data and neuroimaging findings in 40 patients with lacunar infarction

Data	Total patients ($n=40$)	Lacunar syndromes					P value
		Pure motor hemiparesis ($n=12$)	Pure sensory stroke ($n=9$)	Sensorimotor stroke ($n=3$)	Dysarthria-clumsy hand ataxic hemiparesis ($n=8$)	Atypical lacunar syndrome ($n=8$)	
Sex, no. (%)							NS
Men	21 (52.5)	8 (66.6)	4 (44.4)	1 (33.3)	5 (62.5)	3 (37.5)	
Women	9 (47.5)	4 (33.3)	5 (55.5)	2 (66.6)	3 (37.5)	5 (62.5)	
Age, years, mean (SD)	70.7 (12.2)	73.6 (13.4)	69.2 (12.2)	72.0 (11.5)	68.1 (13.4)	70.5 (12.4)	NS
Education, years, mean (SD)	9.4 (3.9)	8.8 (5.0)	10.4 (2.2)	7.3 (0.6)	11.0 (5.4)	8.6 (2.5)	NS
Topography, no. (%)							
Basal ganglia	8 (20)	1 (8.3)	2 (22.2)	0	0	4 (50)	0.037
Internal capsule	8 (20)	3 (25)	1 (11.1)	2 (66.6)	1 (12.5)	1 (12.5)	0.036
Centrum ovale	9 (22.5)	3 (25)	3 (33.3)	0	1 (12.5)	2 (25)	NS
Corona radiata	4 (10)	1 (8.3)	1 (11.1)	0	3 (37.5)	1 (12.5)	NS
Protuberance	11 (27.5)	4 (33.3)	1 (11.1)	0	2 (25)	4 (50)	NS
Thalamus	9 (22.5)	3 (25)	4 (44.4)	0	0	2 (25)	NS
MRI hyperintensities, mean (SD)	15.6 (10.1)	19.3 (7.6)	13.0 (10.4)	5.6 (5.1)	14.6 (11.3)	17.9 (11.8)	NS
White matter	6.1 (6.2)	7.2 (6.3)	6.0 (5.8)	1.0 (1.0)	6.4 (6.5)	6.3 (7.6)	NS
Periventricular	3.3 (1.9)	4.1 (1.7)	2.8 (1.9)	2.7 (3.1)	3.1 (2.2)	3.1 (1.4)	ns
Subcortical	4.5 (2.9)	5.6 (2.1)	3.9 (3.3)	1.0 (1.7)	3.4 (2.9)	6.0 (2.9)	0.031
Infratentorial	1.7 (2.2)	2.4 (2.6)	0.3 (1.0)	1.0 (1.7)	1.7 (2.1)	2.5 (2.4)	0.030

Table 2
Results of neuropsychological assessment in 40 patients with lacunar infarction

Data	Total patients (n=40)	Lacunar syndromes					P value
		Pure motor hemiparesis (n=12)	Pure sensory stroke (n=9)	Sensorimotor stroke (n=3)	Dysarthria-clumsy hand ataxic hemiparesis (n=8)	Atypical lacunar syndrome (n=8)	
MMSE	28.4 (1.7)	28.2 (1.8)	28 (2.1)	29.3 (0.6)	**29.5 (1.2)**	27.7 (1.7)	**0.044**
Rey Auditory Verbal Learning Test							
Immediate recall	4.0 (1.6)	3.8 (1.4)	4.7 (2.2)	3.7 (1.5)	4.1 (1.8)	3.6 (1.1)	NS
Delayed recall	5.3 (3.2)	4.4 (3.4)	4.7 (4.4)	7.0 (2.0)	7.1 (3.1)	5.0 (1.6)	NS
Recognition	10.6 (3.2)	10.8 (3.3)	**8.4 (4.5)**	11.0 (1.0)	12.3 (1.7)	11.2 (2.4)	**0.020**
Visual Reproduction subscale WMS-III							
Immediate recall	11.1 (9.6)	8.9 (4.2)	16.0 (19.8)	9.3 (2.5)	13.1 (2.5)	7.1 (3.1)	NS
Delayed recall	10.2 (4.2)	9.1 (3.7)	9.1 (5.3)	12.3 (4.0)	**12.6 (2.5)**	8.6 (3.3)	**0.014**
Recognition	10.4 (2.9)	9.7 (3.5)	9.7 (3.0)	12.0 (3.0)	**12.3 (2.7)**	9.7 (1.7)	**0.050**
Trail Making Test A	79.8 (48.8)	102.3 (76.3)	72.9 (25.7)	51.0 (13.5)	54.3 (25.2)	89.1 (34.1)	NS
Trail Making Test B	212.3 (116.2)	242 (123.5)	179.7 (79.3)	143.6 (66.5)	198.9 (176.3)	230 (86.8)	NS
Stroop Test	51.6 (6.9)	48.8 (4.4)	47.9 (9.0)	52.0 (9.2)	55.7 (4.7)	55.7 (85.9)	NS
Phonetic Verbal Fluency Test	23.9 (14.1)	23 (15.2)	24.6 (10.9)	35.7 (12.0)	30.6 (17.1)	**14.0 (6.8)**	**0.018**
Verbal Category Fluency Test	13.4 (6.4)	13.3 (6.7)	13.5 (4.9)	16.3 (2.5)	17.1 (9.4)	**9.2 (4.3)**	**0.034**
Luria's Premotor Sequences							
Motor	1.4 (0.8)	**0.9 (0.8)**	1.7 (0.7)	1.6 (0.6)	1.6 (0.8)	1.4 (0.8)	**0.009**
Rhythm set-shifting	1.4 (0.7)	1.4 (0.6)	1.8 (0.4)	2.0 (0.0)	1.6 (0.8)	**0.7 (0.8)**	**0.001**
Rhythm reproduction	1.4 (1.7)	1.1 (1.1)	1.0 (1.1)	0 (0)	1.1 (1.5)	**3.4 (2.2)**	**<0.001**
Boston Naming Test	24.6 (3.6)	23.6 (4.9)	24.2 (2.9)	27.0 (0.0)	26.3 (3.3)	23.6 (2.8)	NS
Shortened Token Test	34.1 (1.4)	**33.3 (1.8)**	34.4 (0.9)	34.0 (0.0)	34.5 (1.7)	23.6 (2.8)	**0.008**
Digit Symbol Test	25.4 (12.8)	22.9 (13.6)	28.4 (12.5)	32.0 (16.1)	33.1 (12.5)	**16.4 (6.7)**	**0.029**
WAIS-III Digit Span Forward Backward Test	12.5 (2.6)	11.7 (2.2)	12.7 (3.4)	14.6 (2.3)	13.0 (1.6)	12.1 (3.3)	NS
WAIS-III Block Design	11.6 (2.7)	10.4 (2–7)	11.3 (2.5)	13.3 (1.5)	**13.3 (2.9)**	10.7 (2.4)	**0.036**
Benton Judgement of Line Orientation Test	16.1 (1.5)	15.6 (2.1)	16.4 (1.1)	16.0 (1.7)	16.6 (1.1)	16.0 (1.6)	NS

Data as mean (SD). Statistically significant differences in bold. Values in the Stroop Test reflect the Stroop effect score.

such as phonetic verbal fluency test, verbal category fluency test, and attention and premotor functions, such as digit symbol test and rhythm reproduction, respectively. The second group with worst cognitive performance was pure motor hemiparesis with low scores in language comprehension (Token Test) and in premotor function (Luria's Premotor Sequences). On the other hand, dysarthria-clumsy hand/ataxic hemiparesis was the group with the most favorable scores in tests assessing parietal lobe such as visuoconstructive function (WAIS-III block design) and right temporal lobe such as visual memory (delayed recall and recognition of the visual reproduction subscale of WMS-III) (Table 2).

4. Discussion

The present results indicate that mild neuropsychological disturbances (mainly executive disorders) are not infrequent in acute lacunar stroke victims. On the other hand, MRI studies have shown that chronic or silent subcortical cerebrovascular changes may account in part for the neuropsychological decline associated with aging [13–15]. Therefore, although these reports suggest a relationship between brain lesions caused by lacunar infarction and a specific neuropsychological impairment, little is known regarding the frequency and type of neuropsychological dysfunction in acute lacunar stroke patients. Moreover, no previous study has examined the occurrence of neuropsychological impartment in the different subtypes of lacunar infarction — a particular novel aspect of this study.

We found that the five lacunar clinical syndromes were similar in relation to the topography of the brain lesion, although basal ganglia topography was more common in atypical lacunar syndrome, internal capsule topography in sensorimotor stroke and thalamic involvement in pure sensory stroke. A relationship between lacunar infarcts in the basal ganglia and thalamus and cognitive function in lacunar infarct patients has been reported previously [2,16] despite these findings were challenged by a report by Appelros et al. [17] observing a lack of correlation between basal ganglia lacunes and cognitive decline. A number of studies have also shown a relationship between leukoaraiosis (white matter changes) and lacunar infarction [18]. The presence of leukoaraiosis has been associated with cognitive dysfunction [19], mainly of the frontal lobe such as speed procession measures, executive functions and verbal fluency [20].

With regard to subcortical features, the clinical subgroups did not differ significantly in the overall severity of white matter hyperintensities. When white matter hyperintensities

were analyzed for the different brain regions, higher severity in the periventricular area for the group of pure motor hemiparesis was observed, but the differences were not statistically significant.

The group of atypical lacunar syndrome and pure motor hemiparesis had a higher severity of white matter hyperintensities in the basal ganglia. On the other hand, pure sensory stroke showed a lower severity of infratentorial white matter hyperintensities, and sensorimotor stroke a lower severity in a basal ganglia hyperintensities, although this difference should be interpreted taking into account that only three patients had this lacunar clinical syndromes.

Cognitive function is not impaired in the acute phase of a lacunar stroke [21–23] but cognitive impairment or dementia may develop on the long-term. In clinical studies, the proportion of vascular dementia caused by small-vessel disease ranges from 36% to 67% [24].

A comparison of neuropsychological performance in the different lacunar clinical syndromes revealed that patients with dysarthria-clumsy hand/ataxic hemiparesis showed the highest score in the MMSE. Furthermore, this group did not show any poorer punctuation compared to the remaining patients and obtained the best scores in tests assessing parietal lobe such as visuoconstructive function and right temporal lobe function such as visual memory. Patients with atypical lacunar syndrome showed the lowest general cognitive function (MMSE score) and were those who exhibited more cognitive disturbances especially in tests assessing executive functions such as verbal fluency, attention and premotor sequences. The second group with the less favorable cognitive performance was pure motor hemiparesis who obtained low scores in language comprehension and in premotor function. These results may explain why patients with atypical lacunar syndrome showed a tendency to have multiple infarctions, a higher proportion of lesions in the basal ganglia and a higher severity of basal ganglia white matter hyperintensities. Moreover, this group shows the poorest performance in executive functions.

On the other hand, the pure motor hemiparesis group also presents a tendency to suffer high severity white matter hyperintensities in the basal ganglia and a higher severity in a periventricular white matter hyperintensities. The neuropsychological performance of this group is the second poorer, particularly in a language comprehension and in premotor sequences. It is known that a lacunar infarction in the basal ganglia, thalamus or deep white matter increases 20 times the risk for clinical dementia [25]. These impairments probably result from the interruption of prefrontal–subcortical loops by the lacunar infarction in the striatum, globus pallidus or thalamus, or by white matter lesions interrupting the prefrontal or anterior cingulate cortices from their basal ganglia or thalamocortical connections [26,27]. Interruption of the dorsolateral prefrontal–subcortical loop results in executive dysfunction [28]. It is well known that a large component of impairment in the activities of daily living especially instrumental activities is dependent on executive function [28]. For this reason, atypical lacunar syndrome and pure motor hemiparesis might have a long-term worse prognosis, in particular the group of atypical lacunar syndrome. Therefore, the identification of early and mild stages of subcortical ischemic vascular dementia is clinically relevant since dementia is a major public health problem with enormous costs to society.

In summary, first-ever acute lacunar infarction is usually a non-severe vascular lesion with favorable recovery of neurological dysfunction, mild neuropsychological disturbances mainly executive disorders are not infrequent, particularly in patients with atypical lacunar syndrome and pure motor hemiparesis. Accordingly, neuropsychological deficit may be considered as a common clinical feature in acute lacunar infarction.

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Higher severity of frontal periventricular white matter and basal ganglia hyperintensities in first-ever lacunar stroke with multiple silent lacunes

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Abstract

We investigated whether patients with a lacunar infarct (LI) syndrome exhibiting unique LI or multiple LI on MRI examinations differed in terms of topography and severity of white matter hyperintensities (WMH) ratings. Forty consecutive patients with a first-ever acute LI, who presented a lacunar syndrome according to Miller-Fisher's classification were recruited and were classified into a group presenting isolated LI on MRI (n=17) or multiple LI (n=23). Despite equivalent demographic, clinical and cognitive characteristics, patients with multiple LI were associated with increased ratings of WMH specifically in frontal periventricular white matter and in and in subcortical regions (thalamus). Present findings provide support to previous hypothesis considering single and multiple LI MRI presentations of lacunar infarct patients as distinct entities.

Introduction

The lacunes or lacunar infarcts (LI) are described as small ischemic infarcts (no more than 15 mm) in the territory of the perforant arterioles and suppose almost 25% of the ischemic infarcts, increasing their incidence with age. The main etiologic factor of LI is hypertension [1], which is also associated to white matter hyperintensities (WMH), a prevalent finding in the general population [2].

WMH seen in T2-weighted MRI acquisitions are associated with small vessel disease affecting the deep penetrating arteries [3]. LI appear to be more closely associated with WMH than cortical ischemic stroke. Previous studies [4,5] have suggested that single and multiple LI constitute distinct entities because patients with multiple LI more often have hypertension and diabetes. Further, the presence of lipohyalinosis is more frequent in patients with multiple LI, whereas in patients with a unique LI there is a higher prevalence of microatheromatosis [4]. If isolated and multiple lacunar infarct MRI presentations constitute two distinct etiological entities, some characteristics frequently coexistent with LI such as WMH could differ between both groups of patients. Indeed, a few studies have investigated whether the severity of WMH in patients presenting a lacunar syndrome is higher in patients with multiple LIs versus patients with unique LI, leading to positive [6,7] and negative findings [8]. Further, there is evidence that in healthy aged individuals the presence of WMH are especially prevalent in frontal and occipital regions [9]. However, no data is available investigating the specific topographic distribution of WMH associated with multiple or unique LI. Here, we investigate the severity of WMH in patients with a lacunar infarct syndrome comparing cases with isolated and multiple lacunar infarcts with the specific aim to study the possible distinct topographic distribution of these MRI findings.

Methods

Patients

We recruited forty consecutive patients admitted to the Department of Neurology of the Hospital del Sagrat Cor (Barcelona, Spain) with a first-ever acute LI, who presented a lacunar syndrome according to Miller-Fisher's

classification [10]. The cognitive performance was assessed with the Mini Mental State Examination (MMSE). Exclusion criteria were: cortical and/or subcortical non-lacunar infarcts or intracerebral hemorrhage documented by MRI as well as any severe systemic or psychiatric disease and dementia (MMSE score <24).

MRI Examination

Structural magnetic resonance images (MRI) were acquired using a General Electric 1.5 Tesla Sigma system. To distinguish between acute and chronic silent lacunar infarcts and to rate the degree of white matter hyperintensities, MRI was performed in the following sequences: T1-weighted (TR= 479 ms, TE= 13 ms, FOV = 270/1.1, slice thickness 5.0 mm, GAP 1.0); T2-weighted (TR= 4885 ms, TE= 120 ms, FOV = 220/1.1, slice thickness 5.0 mm, GAP 2.0); fluid-attenuated inversion recovery (FLAIR, TR = 8000 ms, TE = 120 ms, FOV = 240/1.1, slice thickness 5.0 mm, GAP 1.2); proton density (TR = 3400 ms, TE = 17 ms, FOV = 240/1.1, slice thickness 5.0, GAP 1.0); and diffusion sequences (TR = 3350 ms, TE = 74 ms, FOV = 250/1.1, slice thickness 5.0 mm, GAP 1.0).

LI and WMH quantification

The presence of acute or chronic, single and/or multiple silent lacunar infarcts and its location were determined by consensus of two senior neuroradiologists. Patients were classified into two groups according whether the LI was isolated (ILI) or it coexisted with multiple silent LI (MLIs). Periventricular, white matter, subcortical, and infratentorial hyperintensities were evaluated in axial T2-weighted MRI slices according to the Scheltens' scale [11].

Statistical Analysis

Demographic and clinical variables and WMH ratings between groups were analyzed with the Student's *t* test for continuous data. Correlations between the number of LI and WMH ratings were analyzed using the Pearson. The chi-square (χ^2) test or the Fisher's exact probability tests (when appropriate) were used for categorical variables. Statistical significance was set at $p < 0.05$.

Results

Seventeen patients from the original sample of 40 cases (42.5%) presented an ILI and 23 patients (57.5%) MLIs. There were no significant differences between groups in gender, age, education and MMSE scores. Similarly, clinical syndromes were equally distributed between groups (χ^2=0.31, p<0.73, not shown in the table). Multiple LI patients showed a significant trend towards higher prevalence of a diagnosis of hypertension. The total Scheltens' Scale score was significantly higher in patients with MLIs vs ILI. This effect was explained by higher ratings of WMH in the periventricular and basal ganglia regions. Further analysis confirmed increased WMH ratings in the frontal (t=3.41, p<0.002) and occipital (t=2.47, p<0.02) lobes for the periventricular measure as well as the caudate (t=2.25, p<0.03) and the thalamus (t=2.48, p<0.02) for basal ganglia scores (see table and figure).

Finally, and to determine which variable or combination of variables best classified our patients as regards their pertinence to one or another clinical group (unique vs multiple LIs), a logistic regression analysis was undertaken including the variables in table 2 as predictor independent variables and the clinical group as the dependent variable. In this analysis, performed using a forward stepwise procedure to include predictor variables in the model, the PVH, SBH and BGH were entered considering the sub items in the Schelten's scale (occiptal, frontal and periventricular hyperintensities for PVH; frontal, occipital, temporal and parietal for SBH; and caudate, thalamus and internal capsule for the BGH) to obtain more precise information regarding which particular WMH topography could best classify our patients. A new generated independent variable separating patients with both hypertension *and* diabetes was also included. The results of the logistic analysis revealed that a model containing frontal PVH (B=2.79, p<0.03) and thalamic BGH (B=1.71, p<0.02) as well as age of participants (B=-0.12, p<0.03) best classified our patients (goodness-of-fit of the model: χ^2=3.65; p<0.88; R^2=0.58). The overall percentage of patients classified correctly according to this model was 77.5% (64.7% for ILI and 87% for MLI).

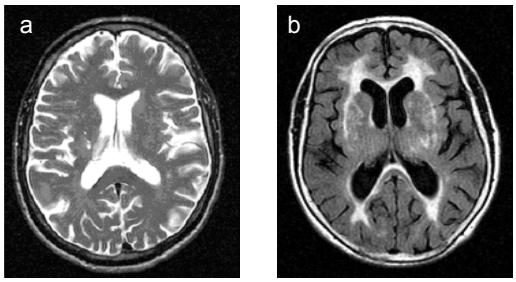

Figure. T2-Weighted (a) and FLAIR (b) MRI horizontal slices showing: (a) a representative case of a patient with an isolated lacunar infarct (ILI) in the centrum semiovale / posterior limb of the internal capsule and mild WMH and, (b) a patient with multiple LI (MLIs) and severe WMH in the region surrounding the basal ganglia.

Table. Demographic, clinical, cognitive and WMH features in single ILI vs MLIs patients.

	ILI=19	**MLIs=23**	**χ^2/ t**	**p**
Age	70.76 (13.19)	70.30 (11.62)	0.12	0.81
Female	9 (52.9%)	10 (52.6%)	0.55	0.39
Education	9.05 (3.97)	9.74 (3.80)	0.55	0.59
MMSE	28.18 (1.63)	28.65 (1.75)	0.88	0.39
HTA	10 (58.8%)	19 (82.6%)	2.78	0.09
DM	3 (17.6%)	8 (34.8%)	0.23	0.20
DL	4 (23.5%)	6 (26.1%)	0.85	0.58
Total WMH	9.76 (10.38)	19.35 (8.09)	3.28	0.002
PVH	2.29 (2.11)	4.0 (1.4)	3.18	0.003
Subc. WMH	3.88 (6.22)	7.5 (5.9)	1.86	0.07
BGH	2.65 (2.87)	5.8 (2.4)	3.75	0.001
Infrat H	0.94 (1.75)	2.0 (2.3)	1.67	0.10

LI= lacunar infarct, Education= years of formal education, MMSE= Mini Mental State Examination, HTA= number of cases (frequency) diagnosed with hypertension, DM= diabetes mellitus, DL= dyslipaemia, WMH= white matter hyperintensities, PVH= periventricular hyperintensities, Subc. WMH= subcortical WMH, BGH= basal ganglia hyperintensities, Infrat H= infratentorial hyperintensities.

Discussion

In this prospective study we found that more than 50% of patients presenting a first-ever LI with a clinical lacunar syndrome could be classified as presenting multiple infarcts on MRI examinations. This fact illustrates the higher sensitivity of MRI to detect these particular lesions as compared to classic CT findings which, by only detecting a minority of most affected cases with WML and/or silent lacunar lesions, may have facilitated dichotomized thinking in terms of two separated types of small vessel disease. We also observed that despite similar demographic, cognitive and clinical characteristics, first-ever lacunar stroke patients with MLIs visible on MRI are characterized by exhibiting higher severity of WMH as compared to patients with an ILI. These findings confirm previous MRI observations in these kind of patients [6,7]. Further, the novelty of this study is the observation that hyperintensities in particular brain areas such as the periventricular frontal region and the basal ganglia (thalamus) best differentiate ILIs and MLIs cases. Age also had some relevance (despite lower than the MRI measures) in accounting for this association. In this regard, it is of mention that our data indicates that that higher rates of frontal PVH and thalamic BGH are specially associated with the probability of being classified as MLI specifically for the less older patients. Finally, patients with multiple LI also showed a non-significant trend towards higher frequency of diagnoses of hypertension. Overall, present results provide further support for considering single LI and multiple LI MRI forms of lacunar patients as constituting separable entities [4].

Higher severity of periventricular WMH characterized our MLIs patients whereas there were no differences in subcortical WMH ratings. Despite the mechanisms underlying putative differences between peri-ventricular and sub-cortical white matter vascular anatomy or vascular pathology as regards to its differential vulnerability to ischemic damage are not well understood, there is evidence that elevated blood pressure [12], arterial fibrilation [13] and the severity of aortic atherosclerosis [14], are more strongly associated with periventricular as compared to subcortical white matter lesions. From these studies, it has been suggested that these conditions implying ischaemia or a decrease of cerebral

blood flow could make the periventricular white matter region particularly vulnerable, given the fact that it is an arterial border zone already marginally perfused under physiologic circumstances, whereas in contrast, subcortical white matter is not a watershed area. Our findings provide further evidence indicating a more vulnerable periventricular white matter region among patients with multiple lacunar infarcts. Finally, periventricular WMH particularly in the frontal lobes relates to poorer performance in speed processing and executive tasks [15]. We could not evidence such a cognitive effect probably because only the MMSE was used which has low sensitivity in the assessment of cognitive impairment due to subcortical lesions. More detailed neuropsychological evaluations are required to evaluate the putative differential influence of WMH on cognitive performance between ILI vs MLIs.

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Mild Cognitive Impairment after Lacunar Infarction: Voxel-Based Morphometry and Neuropsychological Assessment

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Key Words
Lacunar infarction · Mild cognitive impairment · Voxel-based morphometry · Neuropsychological tests

Abstract
Background: The aim of the present study was to investigate whether there were differences in neuroradiological features, including white-matter lesions and gray-matter volumes, between patients with lacunar infarction with and without mild cognitive impairment of the vascular type (MCI-V). ***Methods:*** A total of 40 patients with lacunar infarction were studied within 1 month after stroke. ***Results:*** MCI-V was found in 22 patients, who in comparison with patients without cognitive impairment were significantly older and had fewer years of formal education. MRI subcortical hyperintensities especially in the basal ganglia (putamen and thalamus) were significantly more frequent in the MCI-V group. In the voxel-based morphometric study, patients with MCI-V showed more atrophy bilaterally in the middle temporal gyrus, right and left frontal and posterior bilateral occipitoparietal regions including the posterior cingulate as well as in the cerebellum. A region of interest analysis restricted to the parahippocampi and hippocampi showed further reduced bilateral parahippocampal gyrus and right hippocampus volume reductions in this group of patients. Finally, the amount of white-matter lesions among MCI-V showed negative correlations with gray-matter volume in frontal and temporal areas as well as with the thalamus and mesencephalon. ***Conclusions:*** The present findings provide support for an anatomical substrate of the MCI entity in patients with lacunar infarction. Both gray- and white-matter changes seem to contribute to the cognitive impairment of such patients.

Mild cognitive impairment of the vascular type (MCI-V) identifies a population of nondemented patients exhibiting cognitive impairment mainly as a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease [1, 2]. Epidemiological studies have reported that one fourth of elderly patients meet criteria for dementia 3 months after ischemic stroke [3]. On the other hand, it has recently been reported that brain changes other than those directly related to subcortical cerebrovascular damage, such as global or regional gray-matter shrinkage (i.e. hippocampal atrophy) [4–6], may also account for cognitive deficits in cerebral vascular lesions.

Previous views assumed that lacunar strokes occurring in nondemented patients had no impact on cognitive

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functioning [7]. However, an increasing body of evidence indicates that lacunar infarction does influence cognitive performance [8–10]. In this regard, lacunar stroke may be included in the list of vascular diseases causing MCI-V. No previous study has applied the operative criteria for MCI-V [1] among lacunar stroke patients in order to investigate the influence of single or multiple lacunar infarctions or other cerebral changes, including white-matter abnormalities or gray-matter shrinkages on cognitive impairment of the vascular type. Therefore, the study was conducted to determine the neuroradiological features and gray-matter volume characteristics in lacunar stroke patients classified as MCI-V as compared to those without cognitive impairment.

Patients and Methods

Study Population

Patients with a first-ever stroke presenting as a lacunar infarction were admitted consecutively to the Department of Neurology of Hospital of Sagrat Cor (an acute-care 350-bed teaching hospital in the city of Barcelona, Spain) between January 2003 and February 2005 and were included in the study provided that at least a single symptomatic acute lacunar infarction (>2 and <15 mm in maximal diameter) in the internal capsule, thalamus, basal ganglia, corona radiata, pons or centrum ovale was confirmed by brain MRI. Exclusion criteria were as follows: cortical and/or subcortical nonlacunar infarcts or intracerebral hemorrhage documented by MRI; severe cardiovascular, renal, hepatic, neoplastic or chronic disease; psychiatric comorbidity (DSM-IV); major depression (Hamilton Rating Scale for Depression score ≥18), and dementia [Mini-Mental State Examination (MMSE) score <24]. The definitions of cerebrovascular risk factors and lacunar syndromes, including pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand and atypical lacunar syndrome (patients presenting isolated dysarthria, dysarthria facial paresis or isolated hemiataxia), were those used in previous studies [11–13].

Neuropsychological Assessment

All subjects were administered an extensive battery of neuropsychological tests after 1 month of the index admission. The neuropsychological assessment was accomplished with the following tests: Rey Auditory Verbal Learning Test (RAVLT), Visual Reproduction subtest of the Wechsler Memory Scale (WMS-III), Trail Making Test A and B (TMT-A, TMT-B), Stroop Test, Phonetic Verbal Fluency Test, Verbal Category Fluency Test (animal naming), Luria's Premotor Sequences, Boston Naming Test; Shortened Token Test, Digit Symbol Substitution Test (WAIS-III), Digit Span Forward and Backward Test (WAIS-III), Block Design Test (WAIS-III) and Benton Judgment of Line Orientation Test.

MCI-V [1] was considered in nondemented patients exhibiting cognitive impairment mainly as a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease.

According to the criteria of Frisoni et al. [1] for MCI-V which emphasize impairment in executive function whereas the memory dysfunction may be considered as mild, MCI-V patients were those showing dysfunction in at least one of the following tests assessing executive functions: Verbal Fluency, TMT-A and TMT-B, and Stroop Test and in one of the following declarative memory tests: immediate, delayed recall or recognition of RAVLT and Visual Reproduction of WMS-III. We defined cognitive dysfunction in our study using a cutoff of –1.5 SD for executive functions because this cutoff point is employed in 'nonvascular' MCI to define impairment in the declarative memory domain [14]. On the other hand, since the memory dysfunction might be mild in MCI-V [1], we used a less strict cutoff for memory impairment set to –1 SD so as to include individuals with mild impairment. Previously published normative data in healthy elderly people with similar demographic characteristics were used to determine the cutoff value for each neuropsychological test [15–17].

MRI Examination

MRI acquisitions were obtained using a General Electric 1.5-tesla Sigma system. To distinguish between acute and chronic silent lacunar infarcts and to rate the degree of white-matter hyperintensities, MRI was performed in the following sequences: 3D/FSPGR (TR = 13.1 ms, TE = 4.2 ms, FOV 24 × 18, slide thickness 3.0 mm, gap 0.0), TRA/SE/T1 (TR = 460 ms, TE = 14 ms, FOV 24 × 18, slide thickness 5.0 mm, gap 2.5), TRA/DUAL DP-T2 (TR = 3,980 ms, TE 20/100, FOV 24 × 18, slide thickness 5.0 mm, gap 2.5), fluid-attenuated inversion recovery (FLAIR; TR = 10,002 ms, TE = 148.5 ms, FOV 24 × 24, slide thickness 5.0 mm, gap 2.5) and diffusion sequences (TR = 10,000 ms, TE = 125.7 ms, FOV 34 × 25.5, slide thickness 5.0 mm, gap 0.0). The comparison between T_1-weighted and FLAIR sequences was used to reduce the possibility of confounding lacunar infarctions with Virchow-Robin spaces since these only appear in FLAIR as hypointensities but not in T_1-weighted images. The presence of acute or chronic, single and/or multiple silent lacunar infarcts and its location were determined by two senior neuroradiologists (J.C.S. and M.R.) by means of visual inspection using the T_1-weighted, FLAIR and T_2-weighted sequences of MRI scans. The neuroradiologists were unaware of the results of neuropsychological tests with regard to the patients' cognitive status. White-matter lesions were evaluated from T_2-weighted images, and periventricular, white-matter, subcortical and infratentorial hyperintensities were evaluated in axial slices according to the scale of Scheltens et al. [18]. Scores of ratings were established by consensus.

Voxel-Based Morphometry

Optimized voxel-based morphometry was performed using the SPM2 (Statistical Parametric Mapping) software and following the procedure described by Good et al. [19]. This procedure allows the automatic detection of whole-brain morphological differences by assigning each brain voxel a probability of being gray matter, white matter and cerebrospinal fluid (CSF). t-Statistic maps were obtained from the analyses of smoothed images with 1 × 1 × 1 mm voxel size and thresholded at $p < 0.001$ (uncorrected for multiple comparisons). Since previous studies have indicated that medial temporal lobe regions are compromised in cerebrovascular patients [4–6], a subsequent hypothesis-driven region of interest (ROI) analysis was performed using the Wake Forest University of School of Medicine Pickatlas software (WFU

Pickatlas v2) comprising the hippocampi and the parahippocampal gyri. Results derived from the ROI analyses were thresholded at $p < 0.05$ voxel level with a false discovery rate (FDR) correction for multiple comparisons. For all analyses, in addition to the threshold set at a voxel level, a given cluster was considered as significant by taking into account only clusters showing a corrected value of $p \leq 0.05$ and with an extent threshold of 20 voxels. To interpret the specific brain regions that emerged from the voxel-based morphometry analyses into the Talairach coordinates space, SPM coordinates, given in Montreal Neurological Institute, were corrected (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Total intracranial volume and gray-matter volumes were calculated using the 'segment' option provided in SPM2. We started the analyses beginning with the raw images correctly oriented (AC-PC origin) in the native space. The second step included the automated partition of the original image into separate images representing probability maps for gray matter, white matter and CSF using the combined pixel intensity and a priori knowledge approach integrated in SPM. The resultant images were inspected for adequate segmentation into the different tissue types, and no gross abnormalities could be appreciated despite the fact that lacunar infarcts were frequently misclassified as CSF. Following this process we used the routine 'seg-vol' implemented in MATLAB which calculates the volume of each tissue separately. The last step was adding the value of the 3 compartments to obtain total intracranial volume. For each segmented subject we checked gray-matter, white-matter and CSF compartments.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 11.0). Clinical variables and the ratings of lacunar infarcts and white-matter hyperintensities in the 2 groups of patients were analyzed with Student's t test or the analysis of variance (when covariates were considered) for continuous data and the χ^2 test or the Fisher's exact probability test (when appropriate) for categorical variables. Comparisons of gray-matter volumes and correlations between white-matter hyperintensities and gray-matter atrophy derived from the statistical maps were analyzed with the 'two-sample t test' and 'simple regression (correlation)' models provided by SPM2.

Results

During the study period, 60 patients with first-ever lacunar stroke were diagnosed. However, 20 patients were excluded from the study for the following reasons: cortical and/or subcortical nonlacunar infarcts documented by MRI (n = 13); normal MRI findings (n = 2); cavernous angioma (n = 1); major depression (n = 1); dementia (n = 1); retained shrapnel particles in the head (n = 1), and MRI contraindication (cardiac pacemaker; n = 1).

The lacunar study population finally included 40 patients, 19 men and 21 women, with a mean age of 70.8 years (standard deviation, SD, 12.2). The clinical syndromes included 12 patients with pure motor hemiparesis, 9 with pure sensory stroke, 8 with dysarthria-clumsy hand/ataxic hemiparesis, 8 with atypical lacunar syndrome and 3 with sensorimotor stroke. Twenty-two patients (55%) met criteria for diagnosis of MCI-V. Patients in the MCI-V group compared with patients without cognitive impairment were older (mean age 77.4 ± 11 vs. 65.9 ± 11.9 years, p = 0.02) and less educated (mean years attending school 8.1 ± 2.6 vs. 11 ± 4.6, p = 0.03). The mean MMSE score was 27.6 (SD 1.8) in the MCI-V group and 29.4 (0.8) in the non-MCI-V group ($p < 0.001$). The mean number of infarctions was 3.7 (1.9) in the MCI-V group and 2.9 (2.5) in the non-MCI-V group (p = 0.28). The percentage of cases showing 1 vs. multiple infarcts in both groups did not reach statistical significance (MCI-V group vs. non-MCI-V group, single lacunar infarction 18.2 vs. 44.4%; multiple lacunar infarctions 81.8 vs. 55.5%; $\chi^2 = 3.570$, p = 0.061).

As shown in table 1, overall subcortical and basal ganglion hyperintensities were significantly more frequent in the MCI-V group. The specific regions where MCI-V showed increased hyperintensities were the putamen and the thalamus. Differences between the study groups with regard to MRI hyperintensities remained after adjusting for age and years attending school.

Table 1. Significant differences on MRI hyperintensities between lacunar stroke patients with and without MCI-V (means with SD in parentheses)

MRI hyperintensities	MCI-V		t	p value
	present n = 22	absent n = 18		
Subcortical, overall	18.1 (10.4)	11.9 (8.9)	2.01	0.05
Periventricular, total	3.3 (1.5)	3.2 (2.3)	0.21	0.84
Occipital	1.0 (0.7)	0.9 (0.9)	0.23	0.82
Frontal	1.2 (0.6)	1.0 (0.8)	0.78	0.44
Periventricular	1.2 (0.6)	1.3 (0.8)	0.47	0.64
White matter, total	7.4 (6.9)	4.3 (4.5)	1.64	0.12
Frontal	2.4 (2.2)	1.8 (2.2)	0.89	0.38
Parietal	2.3 (2.5)	1.1 (1.6)	1.85	0.07
Occipital	1.9 (2.1)	1.0 (1.1)	1.58	0.12
Temporal	0.8 (1.7)	0.3 (0.6)	1.31	0.20
Basal ganglia, total	5.5 (2.9)	3.0 (2.6)	2.84	0.007
Caudate nucleus	0.7 (0.8)	0.7 (1.0)	0.10	0.92
Putamen	1.4 (1.1)	0.5 (0.6)	3.17	0.003
Globus pallidus	1.4 (1.1)	0.7 (1.2)	1.96	0.06
Thalamus	1.2 (1.3)	0.2 (0.4)	3.36	0.002
Internal capsule	1.2 (0.8)	1.1 (1.8)	0.12	0.88
Infratentorial, total	1.9 (2.3)	1.4 (2.0)	0.61	0.54

Table 2. Gray-matter regions where lacunar stroke patients with MCI-V showed reduced volumes compared with lacunar stroke patients without cognitive impairment

Cluster		Voxel		
No. of voxels	p corrected	t value	MNI corrected coordinates, (x, y, z)	cerebral region
6,368	<0.001	6.34	58, 3, –23	right middle temporal gyrus (BA 21)
2,280	0.003	5.90	–61, –13, 27	left precentral gyrus (BA 1–3)
1,648	0.015	5.84	–26, –73, 30	left middle temporal gyrus (BA 39)/gyrus occipitalis (BA 19)
10,447	<0.001	5.49	–40, –6, –12	left middle temporal gyrus (BA 21)
6,128	<0.001	5.32	21, –6, 59	right superior frontal gyrus (BA 6)
3,514	<0.001	4.33	–29, –53, –24	left cerebellum
3,270	<0.001	4.28	22, –73, 26	right cuneus/precuneus (BA 18/19)
3,270	0.026	4.14	7, –59, –27	right posterior cingulated gyrus (BA 31)[1]

MNI = Montreal Neurological Institute; BA = Brodmann's area. Voxel size: 1 × 1 × 1 mm. p corrected refers to the cluster level value; threshold for all voxels at $p < 0.001$. The anatomical regions correspond to the voxel with the highest statistical significance within the cluster.

[1] Significant region within the cluster with peak maxima at 22, –73, 26.

Total intracranial volume did not differ between the MCI-V and the non-MCI-V groups (mean 1,511.47 ± 160.50 vs. 1,594.88 ± 167.84 mm^3, $p = 0.12$), but patients with cognitive impairment showed reduced whole gray-matter volume (628.41 ± 74.63 mm^3) compared with patients without cognitive impairment (mean 728.79 ± 77.82 mm^3; $p < 0.001$). This difference remained when age was used as a covariate ($p < 0.001$) and when the index gray-matter/total intracranial volume was compared instead of only comparing gray-matter values ($p < 0.005$). The interpretation of the statistical parametric maps showed that, regionally, MCI-V patients were characterized by shrinkage of gray-matter volume bilaterally at the temporal and frontal lobes, a posterior region including the right parietal-occipital and posterior cingulate region and the left cerebellum (table 2, fig. 1). The ROI analyses focused on the hippocampi and parahippocampal gyri further revealed a more atrophic bilateral parahippocampal gyrus (x, y, z: 36, –26, –25; cluster size 9,485 voxels, $P_{FDR\text{-}corrected}$: 0.026; x, y, z: –32, –10, –11; cluster size 8,326 voxels, $P_{FDR\text{-}corrected}$: 0.026) and right hippocampus (x, y, z: 27, –20, –12; cluster size 1,003 voxels, $P_{FDR\text{-}corrected}$: 0.030, fig. 2) in the MCI-V group.

Significant inverse correlations between subcortical hyperintensities and regional gray-matter volumes were observed among the MCI-V group in frontal and temporal regions such as the medial frontal gyrus (BA 9, x, y, z: –15, 43, 20; cluster size 1,524 voxels, and BA 6, x, y, z: –33, 15, 55; cluster size 2,246), the left posterior thalamus (x, y, z: –22, –27, 9; cluster size 1,218 voxels) and in right areas including the precentral and paracentral gyri (BA 4/5, x, y, z: 7, –35, 68; cluster size 8,273 voxels, and BA 6, x, y, z: 44, 0, 46; cluster size 2,256 voxels) as well as the right mesencephalic region (x, y, z: 10, –27, –4; cluster size 1,526 voxels; fig. 3). In patients without cognitive impairment, no negative correlations between gray-matter volume and subcortical hyperintensities were observed.

Discussion

In the present clinical study of 40 patients with first-ever lacunar infarction, 22 of them (55%) fulfilled the criteria of MCI-V. Accordingly, patients suffering from a lacunar stroke may constitute a relevant subgroup of the general vascular patients identified as MCI-V. The higher percentage of patients with lacunar infarction showing cognitive impairment in our series compared with previous reports in similar patients may be explained not only by the definition of cognitive impairment, but also by differences in the battery of neuropsychological tests used for the assessment of cognitive domains. In our study, cognitive function was assessed with a comprehensive and accurate battery of neuropsychological tests to maximize the homogeneity of our sample. It should be noted that published neuropsychological controls were used to determine the cutoff value for each neuropsychological test. This may be considered a limitation because, ideally,

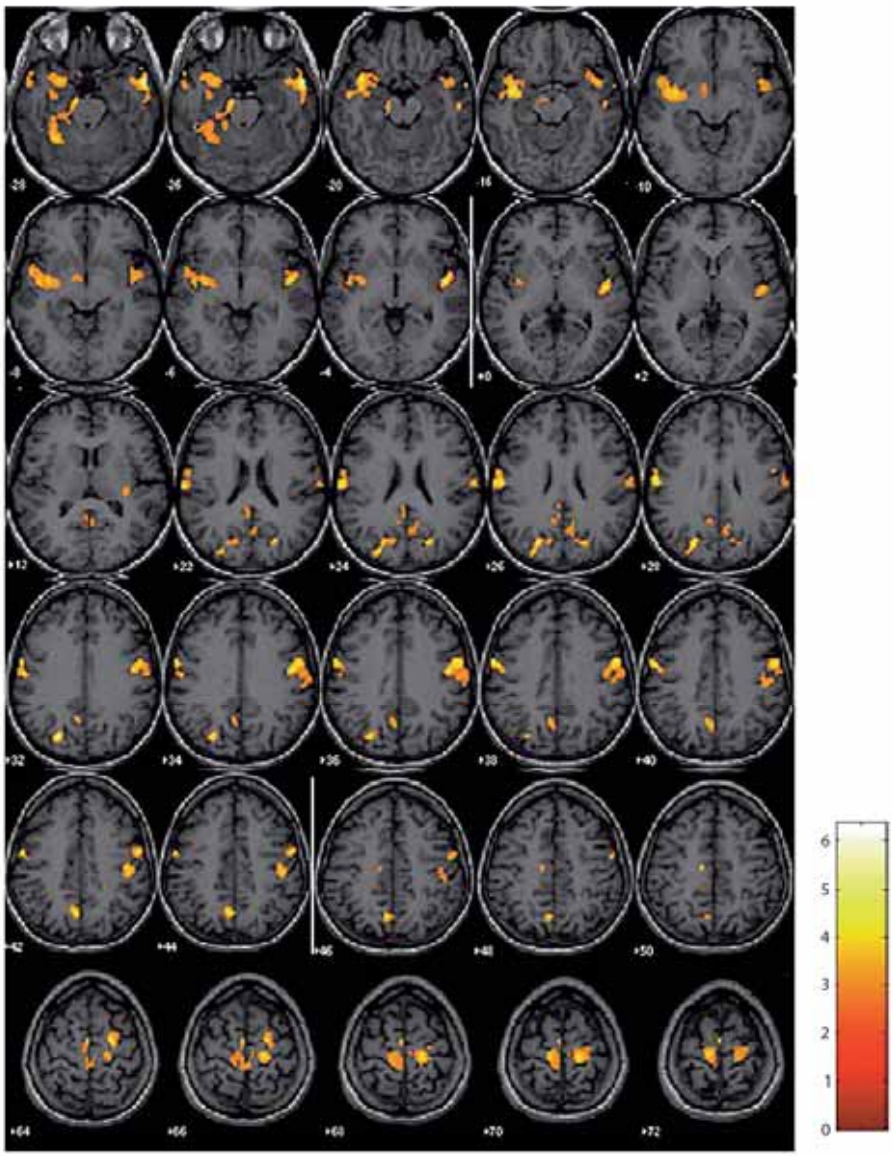

Fig. 1. Cerebral horizontal slices displaying decreased gray-matter volumes in MCI-V relative to non-MCI-V patients (for anatomical localization of significant regions, see table 2). Statistical parametric maps are represented according to neurological convention (left corresponding to the left hemisphere). The color bar represents t values derived from the voxel-based analysis. Clusters are scaled with the yellow-white regions being more significant than the red ones. Depicted results are representative of the group comparison but are displayed on a normalized brain image of a single subject.

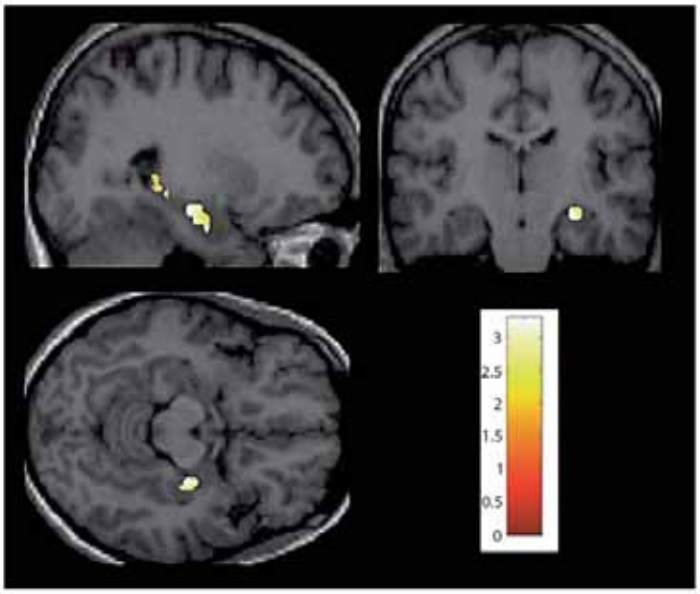

Fig. 2. ROI analysis result showing reduced right hippocampus volume in MCI-V as compared to the group without cognitive impairment. See main text for precise anatomical localization of the significant cluster. Statistical parametric maps are represented according to neurological convention (left corresponding to the left hemisphere). The color bar represents t values derived from the voxel-based analysis. Clusters are scaled with the yellow-white regions being more significant than the red ones. Depicted results are representative of the group comparison but are displayed on a normalized brain image of a single subject.

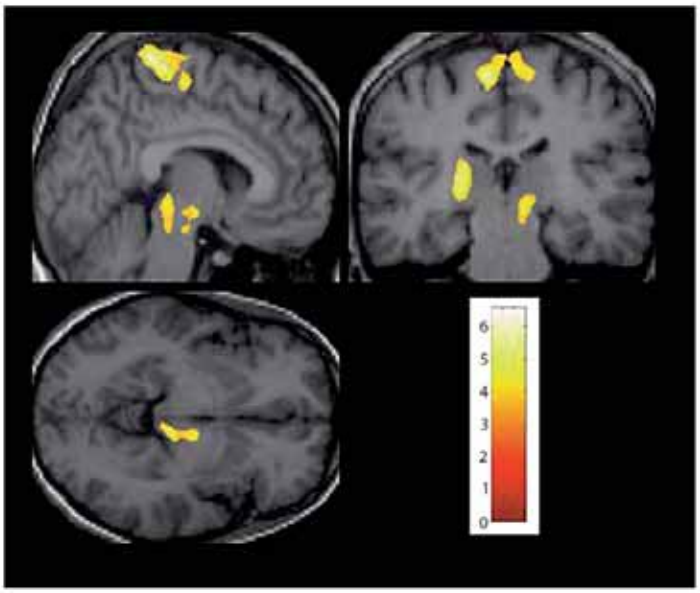

Fig. 3. Significant negative correlations between subcortical ratings (Scheltens' scale) and gray-matter volumes among MCI-V. See main text for precise anatomical localization of all significant clusters. Statistical parametric maps are represented according to neurological convention (left corresponding to the left hemisphere). The color bar represents t values derived from the voxel-based analysis. Clusters are scaled with the yellow-white regions being the ones showing the highest negative correlations. Depicted results are representative of the group comparison but are displayed on a normalized brain image of a single subject.

it would be better to use data from a control population matched to the study group in which the risk factor profile was known. In a lacunar infarction cohort of 200 patients, Yamamoto et al. [20] found cognitive impairment and dementia in 40 (20.5%) of cases. In that study however, the Clinical Dementia Rating Scale and Hasegawa's Dementia Rating Scale Revised were used as measures of cognitive function and no neuropsychological evaluations were included. In other studies [3, 21] cognitive impairment in small-vessel disease patients have only been assessed with a general screening as MMSE. Loeb et al. [21] found that 23.1% of the patients with lacunar infarcts developed dementia after 4 years of follow-up. Although classical descriptions of clinical lacunar syndromes are presumed to imply preserved cognitive functioning [7], our findings add further evidence to the accumulating knowledge using formal neuropsychological testing indicating that the clinical manifestations of a first-ever lacunar infarct are frequently associated with some degree of neuropsychological impairment [8, 10, 22–24].

Despite the poor correlation between radiological and pathological findings observed in previous investigations [25], it seems feasible that most of the rating scores attributed to the subcortical nuclei (thalamus, putamen, globus pallidus, internal capsule) correspond to lacunar infarcts. In this regard, our findings would be consistent with recently published neuropathological and imaging data showing that lacunes in the thalamus and the basal ganglia strongly correlated with cognitive status [25–27], suggesting that cognitive deterioration in patients with lacunar infarcts may result from the disruption of subcortical-frontal circuits.

Using voxel-based morphometry to assess gray-matter atrophy, we were able to show gray-matter shrinkages in our cognitively impaired patients mainly affecting bilaterally the temporal lobes, parietal and frontal regions and the left cerebellum as well as bilaterally the parahippocampal gyri and the right hippocampus, although these latter structures only emerged when a hypothesis-driven ROI analysis restricted to these specific regions was performed. These findings might be interpreted as corroborating and extending findings from the functional neuroimaging literature on the remote effects of subcortical damage beyond the immediate area of infarction [28, 29]. Hence, in addition to the aforementioned subcortical abnormalities in the basal ganglia, our results indicate that regional gray-matter damage contributes to the cognitive picture of MCI-V. However, it should be noted that some of our findings might be related to particular characteristics of the operational criteria used to define MCI-V. Besides a typical subcortical cognitive pattern of brain dysfunction (e.g. executive function), a mild impairment of declarative memory was also required [1]. Because secondary memory is related to the medial and lateral temporal lobe integrity [30–32], the present findings of reduced volumes in these areas may be reflecting the specificity of the classification criteria. In this regard, further studies assessing anatomical correlates of vascular cognitive impairment based just on subcortical functions may show different results.

Recently, patients with lacunar infarction have shown a decrease in the N-acetyl-aspartate/creatine ratio of the centrum semiovale at a distance from the infarct in both the ipsilateral and contralateral hemispheres and this decrease has been related to a reduced cognitive capacity [10]. Moreover, MRI studies using manual delimitations of regional volumes reported hippocampal, frontal and cortical gray-matter atrophy as predictors of cognitive impairment [5, 6, 33, 34]. In agreement with previous studies [5, 35–37], we found significant correlations between gray-matter volume reduction in the frontal, parietal and temporal lobes, as well as in the thalamus and overall subcortical hyperintensities, especially in the basal ganglion region. In addition, correlations between scores of subcortical hyperintensities and gray-matter volumes were limited to the group of lacunar stroke patients with MCI-V.

With regard to quantification of white-matter hyperintensities, two limitations should be acknowledged. Firstly, a visual semiquantitative method based on T_2-weighted and FLAIR sequences was only used. This method is probably less accurate than measuring white-matter high-signal volume. High correlations between both procedures have been reported [38, 39] but volume measurements have higher reliability [39] and sensitivity [38, 39]. In our study, volume measurements would have been inaccurate because T_2-weighted and FLAIR images had interslice gaps of 2.5 mm. Secondly, recent studies provided evidence that white-matter damage assessed by diffusion tensor imaging showed better correlations with cognitive function than T_2-weighted or FLAIR sequences [40, 41]. However, this technique was not used in the present study. Thus, the use of diffusion tensor images could have led to the detection of further differences in white-matter damage observed in two groups that differed as a function of their cognitive profile. A further related limitation in white-matter quantification is inherent to the automatic segmentation procedure used by SPM. Specifically, lacunar infarcts and white-matter hyperintensities were found to be misclassified mostly as CSF due to their

intensity characteristics. However, these limitations may have little relevance for the gray-matter analysis.

Whether gray-matter volume reductions correspond to neuron loss or a specific neuropathological process in our patients cannot be determined by the methodological approach used in the present study. It is of note however that most brain regions we found to be atrophied in our MCI-V patients have also recently been reported to be affected in 'nonvascular' MCI patients [42–44]. This pattern of gray-matter loss in mild cognitive impairment is highly consistent with the course of neurofibrillary tangles across aging and Alzheimer's disease [44] and has been evidenced in a voxel-based study mapping the rapid conversion of MCI to Alzheimer's disease [45]. In that study, regions, such as the hippocampus, the inferior and middle temporal gyrus as well as the posterior cingulate and precuneus, that were found to be reduced among MCI-V in our report were the ones showing greater gray-matter loss in MCI patients evidencing rapid conversion to Alzheimer's disease.

Additionally, in the recent literature, one report found that patients with vascular dementia exhibited neuron loss of the CA1 region comparable to that observed in Alzheimer's disease [46], whereas other results indicate that the number of neurons is significantly reduced in Alzheimer's disease as compared to ischemic vascular disease patients but that it correlates with MRI volumes of the structure [47]. Thus, despite the fact that evidence derived from close conditions suggests that it is possible that gray-matter atrophy in our study reflects neuronal loss or some type of neuropathological findings, future MRI studies combined with autopsy data are needed to clarify this issue.

In summary, our data provide evidence suggesting that a significant percentage of patients presenting clinically with a lacunar infarct may be identified as MCI-V patients. The MRI correlates that best explained cognitive performance among these patients were abnormalities found in the basal ganglion region as well as total gray-matter volume reductions but additional shrinkages in the hippocampus, lateral temporal and parietal cortices as well as in the cerebellum were also observed when compared to patients without cognitive dysfunction. The nature of the correlations found between cerebrovascular subcortical damage and gray-matter atrophy in these patients needs to be established in clinicopathological studies.

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Progressive gray matter atrophy in lacunar patients with Mild Cognitive Impairment Vascular (MCI-V)

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ABSTRACT

We investigated the progression of cognitive and cerebral changes in patients with mild cognitive impairment (MCI) related to small vessel disease. Thirty patients with a first-ever LI (15 MCI-V and 15 NCI-V) were followed-up during 18±6 months after the stroke. All cases underwent neurological, neuropsychological and MRI assessments (ratings of white matter hyperintensities, (WMH) and automated gray matter volume measures) at baseline and follow-up examinations. At follow-up, MCI-V patients were more impaired in a task reflecting attention and maintenance of short-term memory. Both groups showed similar significant increases in WMH severity over time but only MCI-V patients presented extensive shrinkages of gray-matter volumes involving the frontal and temporal lobes, the pons, the cerebellum and the caudate nucleus. Frontal lobe dysfunction and gray-matter atrophy best differentiate the clinical course of LI patients with and without cognitive impairment. Disproportionate progressive gray matter atrophy among MCI-V might reflect a concomitant neurodegenerative process.

KEYWORDS: Lacunar infarcts, Structural Magnetic Resonance, Cognitive Impairment, Neuropsychology, follow-up study

1. Introduction

Cerebral changes related to small vessel disease, such as lacunar infarcts (LI) and white matter hyperintensities (WMH) seen in MRI, have been associated with cognitive impairment in the elderly population (de Groot et al., 2001, Gunning-Dixon and Raz 2003, Junqué et al., 1990, Takashima et al., 2003, van Zandvoort et al., 2001, 2005, Vermeer et al., 2003). Mild cognitive impairment of vascular type (MCI-V) identifies non-demented patients exhibiting mainly a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease (Bowler and Hachinski 2002, Frisoni et al., 2002). In this regard, lacunar stroke may be included in the list of vascular diseases causing MCI-V, being possibly the most frequent subtype of 'vascular cognitive impairment' (VCI) (Schmidtke and Hüll 2005). Additionally, WMH in patients with LI are related to future functional impairment (Bennett et al., 2002) and with acceleration of cognitive decline in patients with MCI (Wolf et al., 2000, Wu et al., 2002). Recent studies have reported that besides the effect of subcortical cerebrovascular damage there are other factors, such as global or regional gray matter shrinkage (i.e. hippocampal atrophy), also related to cognitive deficits in cerebral vascular lesions (den Heijer et al., 2005, Fein et al., 2000, Gainotti et al., 2004, Korf et al., 2005, Laakso et al., 1996, Mungas et al., 2001). In this regard, in our previous study we found that both gray- and white-matter changes contributed to the cognitive impairment of patients with MCI-V (Grau-Olivares et al., 2007). However, there is divergent evidence as regards the progression of cognitive decline in cerebrovascular disease patients, with some studies evidencing a progressive decline and others relative stability within the first or even second year after the vascular event (Desmond et al., 1996, Kotila et al., 1984, Patel et al., 2003, Rasquin et al., 2005, Sachdev et al., 2004, Tham et al., 2002, Wentzel et al., 2001). Particularly, no data is

available regarding the progression of cognitive deficits and cerebral measures of patients with a first-ever lacunar infarct that fulfill criteria for MCI-V.

We aimed to compare the long-term outcome of cognitive function and structural brain measurements (gray matter volumes and WMH) in LI patients fulfilling the MCI-V vs lacunar patients without cognitive impairment. This knowledge should help in our understanding of the cerebral characteristics related to cognitive prognosis of patients with LI and could be used in further clinical studies aiming to implement preventive treatments and rehabilitation programmes in these patients.

2. Materials and Methods

2.1 Study population

Patients presenting a first-ever LI were admitted consecutively at the Department of Neurology of the Hospital del Sagrat Cor (Barcelona, Spain) between January 2003 and February 2005 and were included in the study provided that at least a single symptomatic acute lacunar infarction (> 2 mm and < 15 mm in maximal diameter) in the internal capsule, thalamus, basal ganglia, corona radiata, pons or centrum ovale was confirmed by brain MRI. Exclusion criteria were as follows: cortical and/or subcortical non-lacunar infarcts or intracerebral hemorrhage documented by MRI as well as any severe systemic, neurological or psychiatric disease including major depression (Hamilton Rating Scale for Depression score ≥18); and dementia (MMSE score <24). None of our patients fulfilled diagnostic criteria for substance abuse including alcoholism. The definitions of cerebrovascular risk factors and lacunar syndromes (pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand, and atypical lacunar syndromes) were those used in previous studies (Desmond et al., 1996, Rasquin et al., 2005, Sachdev et al., 2004). The initial study sample consisted of 40 patients which has been investigated cross-sectionally in a previous report (Grau-Olivares et al., 2007). All patients were

neurologically, neuropsychologically and MRI assessed in the baseline (1 month after the event). The sample was classified into two groups according to the presence of cognitive impairment of vascular type (MCI-V) or its absence (NCI-V). MCI-V was considered in non-demented patients exhibiting cognitive impairment mainly as a prominent dysexecutive syndrome and clinical and radiological manifestations of subcortical cerebrovascular disease. According to criteria of Frisoni et al. (2002) for MCI-V which emphasize impairment in executive function whereas the memory dysfunction may be considered as mild, MCI-V patients were those showing dysfunction on at least one of the following tests assessing executive functions: verbal fluency, TMT-A and TMT-B, and Stroop test and on one of the following declarative memory tests: immediate, delayed recall or recognition of RAVLT and Visual Reproduction of WMS-III. We defined cognitive dysfunction in our study using a cutoff of -1.5 SD for executive functions because this cut-off point is employed in 'non-vascular' MCI to define impairment in the declarative memory domain (Petersen et al., 1999). On the other hand, since the memory dysfunction might be mild in MCI-V (Frisoni et al., 2002), we used and a less strict cut-off for memory impairment set to –1 SD so as to include individuals with mild impairment.

For the present study, 32 patients from the original sample of 40 cases (16 originally classified as MCI-V and 16 NCI-V) underwent a second neurological, neuropsychological and MRI examination after a mean follow-up period of 18±6 months. The eight causes could not be included in the follow-up study for these reasons: five cases did not accept to continue with the follow-up, two patients (one MCI-V and the other NCI-V) died during the follow-up period, and three could not be contacted. The study was approved by the local ethics committee, and all the participants gave informed consent for their participation.

2.2 Neuropsychological assessment

For memory assessment, we used the Rey Auditory Verbal Learning Test (RAVLT) as a verbal memory task and visual memory was assessed with Visual Reproduction (VR) subtest of the Wechsler Memory Scale (WMS-III). Executive functions were evaluated with the Trail Making Test B (TMT-B), Stroop Test (Interference T-score), Phonetic Verbal Fluency Test and Verbal Category Fluency Test (animal naming). Luria's Premotor Sequences were used as a measure of premotor functions and Trail Making Test A (TMT-A), Digit Symbol Substitution Test (WAIS-III) and Digit Span Forward (WAIS-III) were used to assess attention and short-term memory. Working memory was tested using the Digit Span Backward Test (WAIS-III). The tests were administered to all patients both at baseline and at follow-up examinations and equivalent versions of these tests were used when possible.

2.3 MRI examination

MRI acquisitions were obtained at base-line and at follow-up using the same protocol in a General Electric 1.5 Tesla Sigma System. The following sequences were used: 3D/FSPGR (TR = 13.1 ms, TE = 4.2 ms, FOV 24x18, slice thickness 3.0 mm, GAP 0.0), TRA/SE/T1 (TR = 460 ms, TE = 14 ms, FOV 24x18, slice thickness 5.0 mm, GAP 2.5), TRA/DUAL DP-T2 (TR = 3980 ms, TE 20/100, FOV 24x18, slice thickness 5.0 mm, GAP 2.5), fluid-attenuated inversion recovery (FLAIR) (TR = 10002 ms, TE = 148.5 ms, FOV 24x24, slice thickness 5.0 mm, GAP 2.5), and diffusion sequences (TR = 10000 ms, TE = 125.7 ms, FOV 34x25.5, slice thickness 5.0 mm, GAP 0.0). The comparison between T1-weighted and FLAIR sequences was used to reduce the possibility of confounding lacunar infarctions with Virchow-Robin spaces as these only appear in FLAIR as hypointensities but not in T1. The presence of acute or chronic, and quantification of single and/or multiple silent lacunar infarcts and its location was determined by a senior neuroradiologist (MR) using the T1, FLAIR, and T2 sequences of MRI scans.

2.4 Image analysis

WMH were evaluated at base-line and at follow-up from T2-weighted images using the Schelten's scale (Scheltens et al., 1993). Accordingly, periventricular, white matter, subcortical, and infratentorial hyperintensities were rated in axial slices. Scores of ratings were established by consensus of two experienced raters.

Optimized voxel-based morphometry (VBM) was performed to analyze gray matter volume changes using SPM2 (Statistical Parametric Mapping) software running in Matlab 6.5 (MathWorks, Natick, MA) following the main steps reported in Good et al. (2001). Briefly, an anatomical template was first created from the 60 T1 anatomical images (30 acquisitions at baseline and 30 at follow-up), so that each MRI was transformed into a standardized coordinate system. All the 60 structural images (in a native space) were then transformed to the same stereotactic space using the template created. The spatially normalized images were automatically partitioned into separate images representing probability maps for gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the combined pixel intensity and a priori knowledge approach integrated in SPM2. The normalized, segmented images were smoothed using an 8 mm FWHM isotropic Gaussian kernel. A separate gray matter template was created by averaging all the 60 smoothed normalized GM images. All the original images (in a native space) were segmented into gray and white matter images. The GM images extracted were normalized to the GM template and then segmented. The resulting GM images were further modulated by the Jacobian determinants derived from the spatial normalization step. Since some studies, including our previous report have indicated that the medial temporal lobe (MTL) and its structures are affected in cerebrovascular patients (Fein et al., 2000, Grau-Olivares et al., 2007, Laakso et al., 1996, Mungas et al., 2001), a subsequent hypothesis-driven region of interest (ROI) analysis was performed using the Wake Forest University of School of Medicine Pickatlas software (WFU Pickatlas v2) comprising the hippocampi.

2.5 Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 14.0). All neuropsychological and WMH variables at baseline and follow-up examinations were tested for normality using the Kolmogorov-Smirnov test. Only 'intratentorial WMH' and premotor tasks (motor alternances, rhythm reproduction and reproducing a sequence of movements (fist/edge/palm)) variables did not follow a normal distribution and non-parametric and χ^2 tests were used to compare differences across groups and/or moment of evaluation, respectively (since for premotor tasks we rated 1=able to perform the task correctly, 0=unable to perform the task correctly). For the remaining analyses parametric tests were used. Demographic and clinical measures of NCI-V and MCI-V were compared using Student's t-tests. To investigate neuropsychological and WMH changes across both evaluations (baseline and follow-up) and across clinical groups (NCI-V and MCI-V) we used a two-factor ANOVA with a within factor being the moment of evaluation and a between factor being the clinical group. Repeated measures t-test for each group, were further employed to reveal the direction of changes in the variables where the interaction of moment x clinical group emerged as significant in the ANOVA.

To analyze changes in regional gray matter volumes from baseline to follow-up evaluations, we used the paired repeated measures ANOVA procedure (adjusting for whole GM volumes) implemented in SPM2. Whole-brain GM modulated images were compared using the following contrasts: a) MCI-V at baseline > MCI-V at follow-up, b) MCI-V at follow-up > MCI-V at baseline, and c) NCI-V at baseline > NCI-V at follow-up, d) NCI-V at follow-up > NCI-V at baseline. Correlations between WMH and GM volumes were performed using the '*multiple regression*' approach implemented in SPM2. All VBM results were considered as significant if they survived a threshold of $p<0.001$ at voxel-level (uncorrected for multiple comparisons) and a corrected value of

p<0.05 at cluster level (corrected). Only clusters comprising 10 or more voxels were considered. Results derived from the ROI analyses of the hippocampi were thresholded at p<0.05 voxel level with FWE rate correction for multiple comparisons. To interpret the specific brain regions that emerged from the voxel-based morphometry analyses into the Talairach coordinates space, SPM coordinates, given in the Montreal Neurological Institute (MNI), were corrected (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

3. Results

Demographic and clinical features of the sample are shown in Table 1. MCI-V patients were more impaired in global cognitive function (MMSE) . These patients were also older and more frequently females but differences did not reach statistical significance. At the end of the follow-up period 60 % of the 15 MCI-V patients (n=9) and 33.3 (n=5) % of the 15 NCI-V patients still presented neurological sequelae from the first-ever LI (χ^2=0.27, p<0.14). One patient in each group fulfilled criteria for dementia.

Insert table 1 approximately here

3.1 Neuropsychological performance

We found a significant interaction for moment of evaluation x clinical group factors for the following subtests: Digits forward (WAIS-III) (F=4.59;p=0.04), visual memory recognition (F=8.60;p=0.007), and digit symbol (F=4.39;p=0.046) suggesting that the change during the follow-up period was different between MCI-V and NCI-V. Further repeated measures t-test for these test evidenced that for MCI-V, attention was more impaired at follow-up, but memory performance showed a slight improvement. Finally, the frequency of patients unable to correctly perform premotor tasks at follow-

up as compared to baseline examinations was comparable in both groups. Table 2 shows cognitive differences for each clinical group separately. Results remained unchanged when age and education were introduced as covariates in the analysis.

Insert table 2 approximately here

3.2 MRI hyperintensities

No significant differences in any of the WMH measures were observed between MCI-V and NCI-V at baseline (not shown). Similarly, using ANOVA we observed non-significant interactions between clinical group and moment of evaluation for all measures: Schelten's scale total score ($F=0.67$; $p<0.42$); periventricular ($F=0$; $p=1$); subcortical ($F=1.26$; $p<0.27$), basal ganglia region ($F=0.07$; $p=0.79$). Table 3 shows the results of repeated t-test for each group separately. The WMH severity increases at follow-up period were significant for in all measures except for the basal ganglia hyperintensities in both groups and the infratentorial hyperintensities in the NCI-V group. Results remained unchanged when age and education were introduced as covariates in the analysis.

Insert table 3 approximately here

3.3 Voxel-Based morphometry

At baseline comparisons, no significant regions of gray matter volume reductions were observed when MCI-V patients were compared to NCI-V cases (data not shown). However, the interpretation of the statistical parametric maps showed that after 18±6 months of follow-up period, MCI-V patients were characterized by clear shrinkages of gray-matter volumes including the frontal and temporal lobes, the right posterior cingulate gyrus, the left pons, cerebellum and parahippocampal gyrus, and the right caudate nucleus (table 4 and figure). Those regions were included in a large

cluster (79624 voxels, p corrected cluster= p<0.0001). In patients without cognitive impairment no decrease in gray-matter volumes was observed. The ROI analyses focused on the hippocampi revealed a more atrophic left hippocampus only in the MCI-V group (x, y, z: -28 -36 -3; cluster size 94 voxels, FWE-corrected: p=0.035). When these analyses were repeated including age and gender as covariates, the main findings remained unchanged.

Insert table 4 and figure approximately here

3.4 Relationship between WMH and gray matter changes

Significant inverse correlations between subcortical and basal ganglia hyperintensities and regional GM volume were observed in the MCI-V group in the middle occipital gyrus (x, y, z: -32 -68 3; t=7.85; p<0.001; cluster size 4940 voxels,) at baseline. No significant correlations were found at follow-up evaluation. In patients without cognitive impairment, no negative correlations between gray-matter volume and WMH were observed at any time period.

4. Discussion

The main finding of the present study is that significant gray matter volume shrinkages in cortical and subcortical regions after a follow-up period of 18±6 months occurred only in MCI-V patients despite similar changes in WMH ratings between groups. As it will be discussed below, these observations may suggest that besides cerebrovascular damage of small-vessel disease origin, an additional neurodegenerative process might be a relevant mechanism explaining cognitive dysfunction among these patients. To our knowledge, this is the first investigation including complete neuropsychological and MRI examinations both at baseline and follow-up in these kinds of patients.

We observed a low rate of progression to dementia among our MCI-V patients. These findings are in agreement with other studies (Ballard et al., 2001, Patel et al., 2003, Rasquin et al., 2004), reporting low rates of conversion and higher rates of clinical stability in patients with similar characteristics. In the light of these results, some authors (Ballard et al., 2003, Frisoni et al., 2002) concluded that none of the criteria for early cognitive impairment of vascular type identified people at increased risk for vascular dementia. However, Meyer et al. (2002) found that among MCI patients, 55.6% developed vascular dementia over a 3±2 year follow-up period. Thus it is possible that longer follow-up periods are necessary to reveal conversion among patients fulfilling MCI-V.

Poorer performance in a task reflecting attentional capacity and maintenance of information in short-term memory, as reflected by reduced Digit Span scores only in the MCI-V at follow-up, was the most significant neuropsychological change overtime in these patients. Previous fMRI data indicate that prefrontal regions (along with inferior parietal areas) are recruited during digit span performance (Owen, 2000; Jantzen et al., 2004). A direct role of the dorsolateral prefrontal cortex in this task has been recently demonstrated by reversible disruption of this area using repetitive transcranial magnetic stimulation (Aleman and Van't Wout, 2008). Frontal lobe dysfunction is the core cognitive feature defining MCI-V patients (Frisoni et al., 2002). In this regard, it was previously reported that dementia could be predicted by low baseline scores on tests of memory and category fluency (a frontal lobe/executive test) after 5 years in patients with vascular cognitive impairment (Ingles et al., 2002). A recent study reported that greater executive dysfunction at initial assessment is associated with more rapid decline in instrumental activities of daily living (Cahn-Weiner et al., 2007) which may indicate an increased risk for dementia. In any case, although most of our patients did not develop dementia at follow-up, our results reveal that when exhaustive

neuropsychological evaluations are employed, progressive frontal lobe dysfunction can be detected during the clinical course of patients with lacunar infarct. Conversely, we observed mild but significant improvements in visual recognition memory only in the MCI-V group at follow-up. These findings are in accordance with previous studies demonstrating that the frequency of post-stroke MCI is high but that improvement or stabilization of cognitive function at follow-up is possible (Rasquin et al., 2005a; Rasquin et al., 2005b; Del Ser et al., 2005). In accordance with the criteria for MCI-V (Frisoni et al., 2002), our observations reinforce the finding that that frontal lobe functions but not memory performance is the most vulnerable cognitive feature in these patients.

In the present study we observed accumulative white matter changes in both groups of patients during the 18-month follow-up interval. Since WMH increase with age in the general population (Vernooij et al., 2007) and since a group of healthy elders was not included for comparison, we can not determine if significant white matter changes during our follow-up period are particular to LI patients or would have also been observed in healthy subjects. However, in agreement with our previous study (Grau-Olivares et al., 2007), and others (Du et al., 2005) we found significant negative correlations between gray-matter volume reductions in middle occipital gyrus and overall subcortical hyperintensities, especially in the basal ganglia region. These correlations were restricted to the MCI-V group and were only observed at baseline examinations. This fact indicates that after the follow-up period the widespread gray matter damage was unrelated to the number of white matter lesions suggesting the possibility that a parallel neurodegenerative process relatively independent of the primary small-vessel disease injury is at work in these patients.

As regards gray matter atrophy changes overtime, we found significant shrinkages among LI patients classified as MCI-V in frontal and temporal cortices, the

cingulate and parahippocampal gyri, the caudate nucleus and the left hippocampus. However when we compared baseline gray matter volumes we did not observe significant differences between MCI-V and NCI-V groups. An explanation accounting for these findings would be that vascular brain injury leads to secondary (deafferentation) neuronal degeneration following primary subcortical injury. However, this is not supported by the observation that patients with NCI-V (which presented similar rates of WMH) did not exhibit gray matter volume reductions. Further, some critical regions with an established prognostic value for Alzheimer's disease (AD) such as the hippocampus, the medial temporal lobe and the posterior cingulate cortex (Chételat et al., 2005, Geroldi et al., 2006, Jack et al., 1999) were specifically affected in MCI-V patients, underscoring the interpretation of a possible existence of a concomitant primary neurodegenerative process. Other authors (Gainotti et al., 2004) reported that hippocampal atrophy (a central characteristic of AD dementia) is a better predictor of dementia and cognitive impairment than the number of vascular lesions in patients with subcortical infarcts.

Our study has several characteristics that should be taken into account when interpreting the results. First, a positive point of this investigation is the use of automated procedures to measure whole-brain regional gray matter changes overtime in our patients. Most studies published to date in patients with cerebrovascular diseases used manual and visual semiquantitative methods to asses the gray matter atrophy and focused on particular brain regions such as the MTL (den Heijer et al., 2005, Fein et al., 2000, Gainotti et al., 2004, Korf et al., 2005, Laakso et al., 1996, Mungas et al., 2001). On the contrary, a limitation of the present investigation relates to the quantification of white matter hyperintensities since a visual semiquantitative method based on T2 weighted and FLAIR sequences only was used. This method might be less accurate than measuring white-matter high-signal volumes (Chen et al., 2007, Urresta et al., 2003). Furthermore, we performed neuropsychological

assessments of the patients between 1 and 1,5 months after the lacunar event whereas most other reports have tested the sample 3 months after the stroke (Madureira et al., 2001, Pohjasvaara et al., 1997, Tatemichi et al., 1994). In any case, our empirical observations indicate that using neuropsychological tests as performed here we have been able to classify MCI-V and NCI-V cases in the context of comparable gray matter volumes and WMH ratings at baseline. Considering the clear divergent progression in terms of regional gray matter volume loss observed between groups during the follow-up period, our results suggest that neuropsychological testing within a short time period after the LI is a useful approach to identify patients that are at high risk of suffering progressive cerebral atrophy in critical regions in the near future.

Finally, we did not consider the effects of post-stroke treatments as anti-platelet and anticoagulant drugs or blood pressure regulation in cognitive performance of our patients at the follow-up period. This limitation, as well as the relatively reduced samples sizes studied should be taken into consideration for further studies.

In summary, our data provides evidence suggesting that increased gray matter volume reductions in several cortical and subcortical areas and frontal lobe dysfunction are particular brain characteristics that define the clinical course of patients with MCI-V. In this regard, continued automated volumetric gray matter assessments combined with neuropsychological examinations tapping on this cognitive area could be a sensitive approach for detecting subclinical dementia in these cases, despite only longer follow-up evaluations will be able to determine this issue.

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Table 1. Demographic and clinical features (baseline) of the sample

	MCI-V n= 15	**NCI-V n=15**	**p/χ^2 value**
Age	71.7 (12.0)	65.1 (11.3)	0.13
Gender (male/female)	7/8	11/4	0.08
Years of formal education	8.7 (2.6)	11.3 (4.9)	0.08
MMSE	27.6 (1.9)	29.5 (0.8)	0.002

All values except Gender are given in mean (SD). MMSE: Mini Mental state Examination; MCI-V: Mild Cognitive Impairment of vascular type; NCI-V: Non cognitive impairment of vascular type.

Table 2. Within group comparisons of neuropsychological measures where change across time was significantly different according to the clinical subgroup (see main text).

	MCI-V baseline	MCI-V Follow-up	t / χ^2	*p*	NCI-V baseline	NCI-V Follow-up	t / χ^2	*p*
Digit Span WAIS-III	12.7 (2.6)	11.7 (2.8)	3.4	0.005	15.7 (2.9)	15.2 (3.8)	0.8	0.45
Digit Symbol WAIS-III	19.4 (8.6)	17.2 (10)	1.3	0.24	33.4 (11.8)	31.6 (10.5)	1.9	
Visual Memory recognition WMS-III	9.38 (2.3)	10.5 (1.6)	2.3	0.04	12 (1.9)	13 (1.9)	1.9	0.08
Motor alternances*	8	6	0.5	0.46	12	12	-	-
Rhythm* reproduction	7	4	1.3	0.26	12	13	0.2	0.62
Fist/edge/ Palm*	10	9	0.14	0.71	15	15	-	-

Values are given in means (scaled scores) and (SD). WAIS: Wechsler Adult Intelligence Scale. WMS: Wechsler Memory Scale. *Number of cases able to perform the task correctly. Statistical value for these variable corresponds to a χ^2 / Fischer's exact probability test.

Table 3. Within group comparisons WMH of changes across time evaluations.

	MCI-V baseline	MCI-V follow-up	t / Z	*p*	NCI-V baseline	NCI-V follow-up	t / Z	*p*
WMH total	13.6 (9.8)	19.1 (11.4)	4.8	<0.001	8.5 (7.8)	15.6 (12)	4.1	<0.01
PVH	3.1 (1.9)	4.2 (2.2)	3.5	0.004	2.4 (2.3)	3.5 (2.1)	2.9	0.01
WMH	6.7 (6.9)	9.8 (6.8)	3.7	0.003	2.9 (4.1)	7.6 (7.5)	3.7	<0.01
BGH	3.4 (2.3)	4.1 (3.2)	1.6	0.14	2.4 (2.1)	3.2 (2.2)	2.7	0.01
Infratent*	0.6 (1.02)	1 (1.24)	2.1	0.034	0.64 (1)	0.64 (1)	-	-

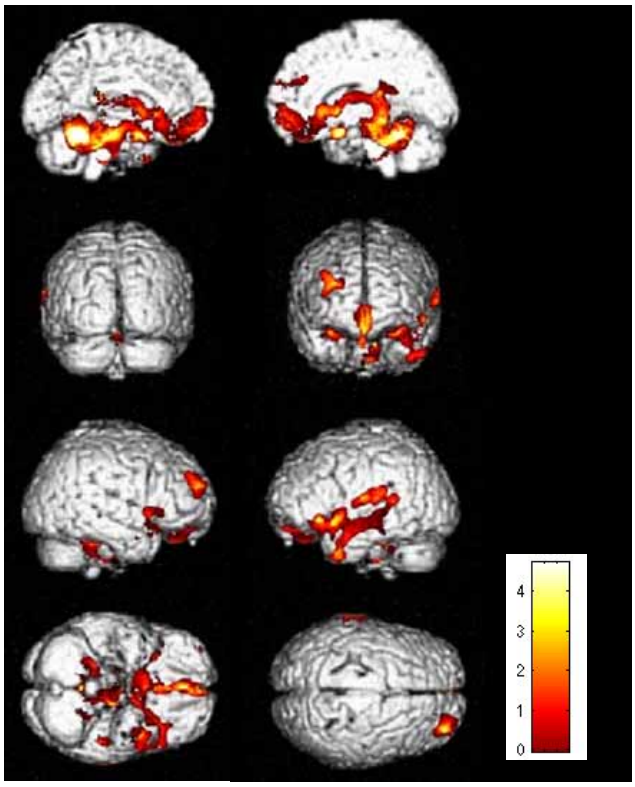
WMH= White matter hyperintensities; PVH= Periventricular hyperintensities; BGH= Basal ganglia hyperintensities; ITH= Infratentorial hyperintensities. *Z= statistical value for the non-parametric Wilcoxon rangs test.

Table 4. Gray matter regions where lacunar stroke patients with MCI-V showed reduced volumes after 18±6 months follow-up.

t value	Talairach's coordinates (x,y,z)	Cerebral region
4.87	-42 -45 7	Left medial temporal gyrus (BA 21)
4.36	24 5 -20	Right inferior frontal gyrus (BA 47)
4.45	-42 -27 -10	Left medial temporal gyrus (BA 20)
5.19	-6 -17 -19	Pons
4.51	-1 53 -2	Left central gyrus (BA 32)
4.73	13 -42 13	Right posterior cingulate gyrus (BA 29)
4.68	2 33 -27	Right orbital frontal gyrus (BA 11)
4.34	-3 -49 -18	Cerebellum
4.48	-10 -1 -19	Left parahippocampal gyrus (BA 34)
4.31	2 3 4	Right caudate nucleus

BA: Brodmann's area. Voxel size: 1x1x1 mm. The anatomical regions correspond to the voxel with the highest statistical significance within the cluster. All statistical values correspond to voxels $p<0.001$ uncorrected.

Figure. Three-dimensional views in a representative brain of cortical and subcortical regions showing significant gray matter volume loss during the follow-up period in the MCI-V group (see table 4 for precise anatomical localization).



6- GENERAL DISCUSSION

In this work we have described accurately the cognitive profile and neuroanatomical features of patients with small vessel disease (first-ever LI and white-matter hyperintensities), for different lacunar syndromes and the prevalence of subjects that fulfil vascular mild cognitive impairment (MCI-V) criteria. The hypothesis of distinct lacunar infarct etiology is supported for one isolated LI and multiple LIs. Furthermore support is provided for the anatomical substrate of the MCI-V entity, identifying the main aspects that justify the cognitive impairment of those patients and which is their long-term prognosis and outcome. The aim of this work is the early identification of high risk patients able to develop vascular dementia or any neurodegenerative disease.

This work is the first to show the anatomical profile of patients with MCI-V using different techniques such as voxel-based morphometry (VBM), regions of interest (ROIs) and quantification of white-matter hyperintensities (Schelten's scale).

Hereafter a general discussion of the results of each study is presented.

In the first study we reported that mild neuropsychological disturbances (mainly executive disorders) are not infrequent in acute lacunar patients. Although there are some reports that suggest a relationship between brain lesions caused by lacunar infarction and a specific neuropsychological impairment (Van Swieten et al.,1996; De Groot et al.,2002; Wen et al.,2004), until now little was known regarding the frequency and type of neuropsychological dysfunction in acute lacunar stroke patients. Those results suggested that even an isolated LI may have a negative effect on cognitive performance.

This work has shown that the five lacunar clinical syndromes were similar in relation to the topography of the brain lesion, although basal ganglia topography was more common in atypical lacunar syndrome, internal capsule topography in sensoriomotor stroke and thalamic involvement in pure sensory stroke. A relationship between LI in the basal ganglia and thalamus and cognitive function in those patients had been reported previously (Tatemichi et al.,1992; Gold et al.,2005).

The association between leukoaraiosis or white matter hyperintensities (WMH) and lacunar infarction has also been reported (Pantoni and Garcia.,1997). The presence of WMH is associated with cognitive dysfunction, mainly of the frontal lobe affecting speed procession measures, executive functions and verbal fluency (Bartrés-Faz et al..2001).

Patients with atypical lacunar syndrome and pure motor hemiparesis had a higher severity of WMH in the basal ganglia. At the same time, a comparison of the neuropsychological performance in the different lacunar clinical syndromes, demonstrated that these two syndromes showed the lowest general cognitive function (Mini-Mental State Examination score), as well as more cognitive disturbances, especially in tests assessing executive functions (verbal fluency, attention and premotor sequences), in patients with atypical lacunar syndrome and language comprehension and premotor sequences in patients with pure motor hemiparesis. The group with atypical lacunar syndrome also showed a tendency to have multiple infarctions. On the other hand, the group with pure motor hemiparesis also presented a tendency to suffer high severity WMH in periventricular area.

Conversely, patients with dysarthria-clumsy hand/ataxic hemiparesis showed the highest score in MMSE. Furthermore this group did not show any poorer punctuation in neuropsychological tests and obtained the best scores in tests assessing parietal lobe (visuoconstructive function) and right temporal lobe function (visual memory).

It is well known that a LI in the basal ganglia, thalamus or deep white matter increases the risk for clinical dementia by approximately 20 times (Norving 2003). These impairments probably result from the interruption of prefrontal/subcortical loops by the LI in the striatum, globus pallidus or thalamus, or by white matter lesions interrupting the prefrontal or anterior cingulated cortices from their basal ganglia or thalamocortical connections (Cummings 1993; Mega and Cummings.,1994). Interruption of the dorsolateral prefrontal-subcortical loop results in executive dysfunction, which is responsible for a large component of impairment in the activities of daily living, especially instrumental activities (Boyle et al.,2002). For this reason, atypical lacunar syndrome and pure motor hemiparesis might have a worse long-term prognosis. Thus the identification of early and mild stages of subcortical

ischemic vascular dementia is clinically relevant since dementia is a major public health problem with enormous cost to society.

In the second study, it was noticed that despite similar demographic, cognitive and clinical characteristics, first-ever lacunar stroke patients with multiple lacunar infarcts (MLIs) were characterized by exhibiting a higher severity of cortical (frontal and occipital) WMH and basal ganglia hyperintensities as compared to patients with an isolated lacunar infarct. The results also indicated that a dichotomic rather than a quantitative analysis accurately differentiated these patients in terms of the severity of white matter lesions, since no correlations were observed between LI number and WMH ratings in the MLIs group. Finally, patients with multiple LI also showed a non-significant trend towards higher frequency of diagnoses of hypertension. These results provide further support for the consideration that single LI and multiple LI MRI forms of lacunar patients constitute separable entities (Boiten *et al*.,1993).

Further, the novelty of this study is the observation that hyperintensities in particular brain areas such as the periventricular frontal region and the basal ganglia (thalamus) best differentiate ILIs and MLIs cases. Age also had some relevance (despite lower than the MRI measures) in accounting for this association. In this regard, it is of mention that our data indicates that that higher rates of frontal PVH and thalamic BGH are specially associated with the probability of being classified as MLI specifically for the less older patients.

Higher severity of periventricular WMH characterized our MLIs patients whereas there were no differences in subcortical WMH ratings. Our findings provide further evidence indicating a more vulnerable periventricular white matter region among patients with multiple lacunar infarcts. Finally, periventricular WMH particularly in the frontal lobes relates to poorer performance in speed processing and executive tasks (Söderlund *et al*.,2006). In this work, this cognitive effect was not observed, probably because only the MMSE was used which has low sensitivity in the assessment of cognitive impairment due to subcortical lesions. More detailed neuropsychological evaluations are required to evaluate the putative differential influence of WMH on cognitive performance between one LI vs MLIs.

In the third study of this thesis, we found that 55% of patients with first-ever LI fulfilled criteria for MCI-V according Frisoni's criteria (Frisoni et al.,2002).

Although classical descriptions of lacunar syndromes are presumed to imply preserved cognitive functioning (Fisher 1982), in the present work further evidence to the accumulating knowledge is provided using formal neuropsychological tests, indicating that the clinical manifestations of a first-ever LI are frequently associated with some degree of cognitive impairment (Corbett et al.,1994; Van Zandvoort et al.,2001; Pantoni et al.,2001; Van Zandvoort et al.,2005; Jokkinen et al.,2006).

In this regard, the findings are consistent with recently published neuropathological and imaging data showing that lacunes in the thalamus and the basal ganglia are strongly related to cognitive impairment (Gold et al.,2005).

Using voxel-based morphometry to assess grey-matter atrophy, we found grey-matter shrinkages in patients MCI-V mainly affecting the following cerebral regions: billaterally the temporal lobes, parietal and frontal regions and the left cerebellum as well as billaterally the parahippocampal gyri and the right hippocampus (the latter two regions emerged when following ROI analysis restricted to these specific regions). These findings might be interpreted as corroborating those of the functional neuroimaging literature which describe the remote effects of subcortical damage beyond the immediate area of infarction (Kwan et al.,1999; Reed et al.,2004).

Results described here indicate that in addition to the subcortical abnormalities in the basal ganglia, the regional grey-matter damage contributes to the cognitive picture of MCI-V.

In agreement with previous studies (Fein et al.,2000; Zekry et al.,2002; Du et al.,2005; Van der Flier et al.,2005), significant correlations were found between grey-matter volume reduction in the frontal, parietal and temporal lobes, and in the thalamus and overall subcortical hyperintensities, especially in the basal ganglia region, but only in MCI-V group.

Most of brain regions we found to be atrophied in MCI-V patients have also been reported to be affected in ‘nonvascular’ patients (Chetelat et al.,2002; Karas et al.,2004; Pennanen et al.,2005). This pattern of grey-matter loss in mild cognitive impairment is highly consistent with the course of neurofibrillary tangles which occur during ageing and Alzheimer’s disease (Chetelat et al.,2002) and has been demonstrated during, for example, in the rapid

conversion of MCI to Alzheimer's disease in a voxel-based study mapping (Chetelat et al.,2005).

Thus, it is possible that grey-matter atrophy measured in this study reflects neuronal loss or some other type of neuropathological findings. However future MRI studies combined with autopsy data are needed to clarify this issue.

In the fourth study of this thesis the purpose was to compare the long-term outcome (18±6 months) of cognitive function and structural brain measurements in LI patients fulfilling the MCI-V criteria with lacunar patients not demonstrating cognitive impairment.

The main finding was that detectable gray matter shrinkages in cortical (frontal and temporal cortices) and subcortical regions (cingulated and parahippocampal gyri, the caudate nucleus and the left hippocampus) occurred in MCI-V patients over time within the context of relative stability of hyperintensities (WMH). These results suggest that a continued neurodegenerative process might be a relevant mechanism explaining cognitive dysfunction among patients with vascular cognitive impairment of small-vessel disease origin. In this way, the lacunar event may have induced or accelerated a progressive neurodegenerative process. An alternative explanation could be that vascular brain injury leads to secondary (deafferentation) neuronal degeneration following primary subcortical injury. However, lacunar patients without cognitive impairment (which presented similar rates of WMH) did not exhibit gray matter shrinkages over time. Also, some critical regions with an established prognostic value for Alzheimer's disease (AD) such as the hippocampus, the medial temporal lobe and the posterior cingulated cortex (Jack et al.,1999; Chételat et al.,2005; Geroldi et al.,2006) were specifically involved in MCI-V patients. These findings underscore the interpretation of a possible existence of a concomitant primary neurodegenerative process.

Other authors reported that hippocampal atrophy (a hallmark for AD patients) was a better predictor of dementia and cognitive impairment than the number of vascular lesions in patients with subcortical infarcts (Gainotti et al.,2004). Thus, although it is accepted that vascular and degenerative pathologies interact in terms of clinical expression of cognitive impairment

(Snowdon et al.,1997; Esiri et al.,1999), in agreement with our previous observations (Grau-Olivares et al.,2007), the present longitudinal findings indicate that gray matter atrophy changes most clearly reflect the clinical course among MCI-V patients.

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7- CONCLUSIONS

Below are presented the general conclusions of each one of the fourth studies presented in this thesis.

1)- First-ever acute lacunar infarct is usually a non-severe vascular lesion with good recovery of neurological dysfunction although mild neuropsychological disturbances mainly in executive functions are not infrequent, particularly in patients with atypical lacunar syndrome or pure motor hemiparesis. Thus, neuropsychological deficit may be considered as a common clinical feature in acute lacunar infarction.

2)- First-ever lacunar stroke patients with multiple lacunar infarcts visible on MRI are characterized by exhibiting higher severity of cortical (frontal and occipital) WMH and basal ganglia hyperintensities as compared to patients with an isolated lacunar infarction. Present results provide further support for considering single LI and multiple LI MRI forms of lacunar patients as constituting separable entities.

3)- A significant percentage of patients presenting clinically with a first-ever lacunar infarct may be identified as mild cognitive impairment of vascular type (MCI-V). The MRI correlates that best explained cognitive performance among these patients are the abnormalities found in the basal ganglia region as well as total gray-matter volume reductions but additional shrinkages in the hippocampus, lateral temporal and parietal cortices as well as in the cerebellum were also observed when compared to lacunar patients without cognitive dysfunction. No previous study has applied the operative criteria for MCI-V among lacunar stroke patients in order to investigate the influence of single and multiple lacunar infarction or other cerebral changes, including white matter abnormalities or gray-matter shrinkages on cognitive impairment of vascular type.

4)- Increased gray matter volume reductions in several cortical (frontal and temporal lobe, cingulate and parahippocampal gyrus, cerebellum) and subcortical (pons and caudate nucleus) areas and executive dysfunction are particular define the clinical course of patients with MCI-V. In this regard, continued automated volumetric gray matter assessments combined with neuropsychological examinations tapping on these functions could be a sensitive approach for detecting subclinical dementia in these cases.

8- SUMMARY OF THE THESIS (Resum de la tesi)

Títol

Introducció

L'infart cerebral és la segona causa de mort, així com d'incapacitació a nivell mundial (Di Carlo *et al.,*2000), essent responsable de múltiples seqüeles físiques i cognitives, incloent la demència. L'infart cerebral es caracteritza per una simptomatologia neurològica focal i sobtada en consonància amb la localització topogràfica de la lesió cerebral, un cop s'han exclòs altres possibles causes.

La demència vascular (DV) històricament s'ha basat en el model de demència multi-infart (Erkinjuntti *et al*.,2002), tot i que cada vegada hi ha una major evidència de que diferents patologies vasculars (malaltia vascular subcortical de petit vas o infarts llacunars), així com infarts corticals, poden contribuir a desenvolupar-la (Hachinski *et al*.,1974; Esiri *et al*.,1997; Rockwood *et al*.,1999; Erkinjuntti *et al*.,1999; Pohjasvaara *et al*.,2000; Ballard *et al*.,2000).

El terme 'Deteriorament cognitiu de tipus vascular' (DCL-V) va ser proposat per Sachdev (Sachdev,1999) per a definir els dèficits cognitius d'origen vascular que tenien una entitat suficient com per ésser diagnosticats com a trastorn, però no complien criteri de demència. Aquest terme feia referència a un ampli espectre de dèficits, des d'un deteriorament lleu a la demència de tipus vascular (Roman *et al.,*2004). El DCL-V s'aplica a subjectes que pateixen una afectació cognitiva relacionada amb un event vascular cerebral: múltiples infarts cerebrals, múltiples infarts subcorticals, enfermetat de petit vas amb hiperintensitats de la substància blanca i infarts llacunars. En la present tesi i en els estudis que la formen ens hem centrat en el DCL-V causat per aquestes dues últimes entitats (els infarts llacunars i les hiperintensitats de la substància blanca), que rep el nom de 'deteriorament cognitiu lleu vascular de tipus subcortical', els criteris del qual han estat definits per Frisoni i col.laboradors (Frisoni *et al*.,2002).

Els infarts llacunars (ILL) o llacunes són petites lesions isquèmiques (no més de 15 mm) en el territori de les arterioles perforants (Fisher, 1982). Aquest

tipus d'infart afecta sobretot els ganglis basals, especialment el putamen, el tàlem, la càpsula interna, la protuberància, el centre semioval i la corona radiata (Arboix et al.,1990).

Els ILL suposen del 20-25% de tots els infarts isquèmics (Fisher, 1982 ; Wardlaw, 2005), i afecten principalment a subjectes entre els 55 i els 75 anys, incrementant-se la seva incidència amb l'edat. El principal factor de risc per a patir-los és la hipertensió (Fisher, 1982; Wolf, 1985; Baumgartner *et al*.,2003; Arboix et al.,2004), seguit de la diabetis mellitus, l'hipercolesterolèmia i els antecedents de cardiopatia isquèmica.

Tot i que segons diversos estudis patològics i radiològics demostren que gairebé el 80% dels ILL són clínicament 'silents', són ben conegudes les característiques clíniques que presenten les síndromes llacunars simptomàtiques. Les síndromes llacunars clàssiques van ser descrites per Fisher i col.laboradors als anys 60. Aquestes síndromes són: l'hemiparèsia motora pura (Fisher and Curry, 1965), la síndrome sensitiva pura (Fisher, 1965), la síndrome sensitiu-motriu (Fisher, 1965), la síndrome de disàrtria-mà feixuga (Fisher, 1967) i l'hemiparèsia-atàxia (Fisher and Cole,1965). Posteriorment es va descriure la síndrome llacunar atípica, que inclou la disàrtria amb parèsia facial, la disàrtria aïllada, l'hemiatàxia aïllada i l'hemiparèsia motora pura amb afàsia subcortical transitòria, entre d'altres (Arboix et al.,2006).

Comparat amb altres tipus d'infart cerebral, el pronòstic dels ILLs sol ser favorable, amb un alt índex de recuperació de l'afectació neurològica i un baix índex de mortalitat i de recurrència (Clavier *et al*.,1994). Malgrat aquest bon pronòstic, aquests pacients solen presentar certs dèficits cognitius, especialment de tipus executiu, i segons les dades aportades per alguns estudis clínics, poden acabar fent demència de tipus vascular del 36 al 67% dels casos, depenent dels estudis (Chui, 2001). Aquests dèficits probablement son conseqüència de la interrupció dels circuits prefrontals-subcorticals deguts a infarts llacunars als ganglis basals, tàlem o substància blanca subcortical (Cummings,1993; Mega and Cummings, 1994).

Els ILL s'han relacionat amb la presència de canvis en la substància blanca cerebral, també coneguts com a hiperintensitats de la substància blanca (HSB), ja que es detecten com a tal en les tècniques de neuroimage com la

tomografia computarizada (TC) o la ressonància magnètica (RM). Es creu que les HSB són causades per infarts incomplets que afecten a les artèries penetrants profundes del cervell (Roman *et al*.,2002), i s'han associat a dèficits cognitius específics, com l'afectació de les funcions executives, depenents dels lòbuls frontals (Pantoni *et al*.,1999; Bartrés-Faz *et al*.,2001). Per altra banda, recentment s'han observat en aquests pacients amb afectació de petit vas (ILLs i HSB), la presència de canvis neurodegeneratius cerebrals, com atròfia global o regional de la substàcia grisa cerebral (Laakso *et al*.,1996; Fein *et al*.,2000; Mungas *et al*.,2001), que també contribueixen en l'afectació cognitiva que presenten aquests subjectes.

És per tot això que creiem que la identificació precoç de pacients amb deteriorament cognitiu causat per malaltia de petit vas podria ser un àrea de recerca interessant, ja que la demència vascular és una de les causes més comunes de deteriorament cognitiu en la gent gran. La patologia cerebral de petit vas molts cops no es reconeix i roman infradiagnosticada, tot i que justificaria molts casos de demència i d'institucionalització de persones de la tercera edat. Un millor reconeixement d'aquesta patologia podria derivar en un tractament precoç per tal d'enlentir la seva progressió a demència, així com a la introducció de mesures de prevenció primàries i secundàries.

2- Objectius de la tesi

L'objectiu d'aquesta recerca és l'estudi del perfil neuropsicològic i dels dèficits cognitius associats a la malaltia vascular cerebral de petit vas (infarts llacunars i lesions de la substància blanca), així com l'evolució d'aquests pacients després de 2 anys d'haver patit l'event vascular. Aquest tema mereix especial interès perque la malaltia vascular subcortical de petit vas és una de les causes més comunes de demència vascular (DV), i el fet de poder conèixer el seu estat prodròmic i poder previndre els principals factors de risc, ens podrien fer possible el desenvolupament d'estratègies preventives.

Aquesta àrea d'estudi també mereix atenció perque s'han fet molts estudis sobre l'evolució i les seqüeles cognitives en els infarts isquèmics de gran vas, però no hi ha gaire evidència sobre l'efecte d'un primer ILL i l'evolució

a llarg terme d'aquests pacients. Finalment, no hi ha estudis a la literatura sobre el perfil neuropsicològic de les diferents síndromes llacunars (segons Miller-Fisher) i la seva evolució a llarg terme.

Els objectius de la present tesi són els següents :

1)- (a) Determinar la freqüència i les característiques dels dèficits neuropsicològics en pacients amb un primer ILL.

(b) Avaluar si la topografia de l'infart, la presència d'un o múltiples ILLs i de canvis o hiperintensitats de la substància blanca (HSB) presenten alguna relació amb el deteriorament cognitiu d'aquests pacients.

2)- Determinar les característiques neuroradiològiques, les HSB i el volum de substància grisa en pacients amb ILL que compleixen criteris de deteriorament cognitiu lleu de tipus vascular (DCL-V), en comparació amb aquells pacients llacunars sense afectació cognitiva.

3)- Comparar l'evolució a llarg termini (2 anys) de la funció cognitiva i de les mesures estructurals cerebrals (volums de substància grisa cerebral i HSB) en pacients amb ILL que compleixen criteris de DCL-V, respecte els pacients amb ILL sense DCL-V.

4)- Determinar la distribució topogràfica de les HSB en els pacients llacunars, així com les diferències en la freqüència, la severitat i la topografia de les HSB en pacients amb un únic ILL i pacients amb múltiples ILLs.

3- Metodologia

La present tesi consisteix en quatre estudis que avaluen les bases neurològiques, neuropsicològiques i neuroanatòmiques dels cervells de pacients amb ILL. Per a desenvolupar-la s'han emprat diferents tècniques que abarquen des de l'exploració neurològica dels pacients, a l'avaluació neuropsicològica i l'anàlisi de neuroimatge estructural.

- Tots els pacients vàren ser **explorats neurològicament** per un neuròleg i vàren ser classificats segons les diferents síndromes llacunars (hemiparèsia motora pura, síndrome sensitiu pur, síndrome sensitiu-motriu, hemiparèsia-atàxia, disàrtria-mà feixuga i síndrome llacunar atípica).
- Per a **l'avaluació neuropsicològica** es vàren emprar els següents tests.

- ❖ Per a la memòria verbal, la versió modificada del Test d'Aprenentatge Auditiu- Verbal de Rey (Lezak *et al*.,2004), i per a la memòria visual, el Test de Reproducció Visual de la Wechsler Memory Scale-III (Lezak *et al*.,2004).
- ❖ El llenguatge es va avaluar amb les versions curtes del Test de Denominació de Boston i del Token Test (Lezak *et al*.,2004).
- ❖ L'avaluació de la fluència verbal es va realitzar mitjançant dues tasques: a) la fluència fonètica va ser avaluada amb una versió modificada del Controlled Oral Word Association Test (COWAT) (Artiola i Fortuny *et al*.,1999), on els subjectes havien de generar paraules que comencessin per P, M i R en tres assajos diferents; b) la fluència semàntica es va avaluar fent que els subjectes generessin paraules d'una determinada categoria durant un minut (animals).
- ❖ Les funcions visuo-espaial i visuo-constructiva: Test d'Orientació de Línies de Benton i el subtest de Cubs (WAIS-III), respectivament (Wechsler D, 1997-98).
- ❖ Les funcions executives es van avaluar amb el Test del Traçat part B (TMT-B), el Test d'Stroop (Puntuació d'Interferència) i les ja anomenades fluències verbals.
- ❖ Les funcions prefrontals es van avaluar amb les Seqüències Premotores de Luria (Lezak *et al*.,2004).
- ❖ El Test del Traçat A (TMT-A), el Digit Symbol Substitution Test (WAIS-III) I el subtest de Dígits (WAIS-III) es van emprar per avaluar l'atenció i la memòria immediata (Wechsler D, 1997-98).
- ❖ La memòria de treball es va valorar amb el subtest de Dígits (WAIS-III), part inversa (Wechsler D, 1997-98).

- Respecte a les tècniques de **ressonància magnètica estructural (RM)** emprades en aquesta tesi:
  - ❖ La presència d'ILL aguts o crònics, únics o multiples, i la seva localització es van determinar mitjançant measures d'inspecció visual a partir de les següents seqüències de RM estructural: T1, FLAIR,T2 i Difussió.
  - ❖ Les hiperintensitats de la substància blanca (HSB) es van quantificar a partir de les seqüències potenciades en T2 de RM en els talls axials, i mitjançant l'Escala de Scheltens (Schelten's *et al*.,1993). Aquesta escala és un mètode

visual semiquantitatiu per a avaluar i quantificar la severitat de les HSB. Els valors per a les hiperintensitats a la substància blanca subcortical i infratentorial van des d'una puntuació de 0 (absents) fins a una puntuació de 6 (confluents), i per a les hiperintensitats periventriculars (HPV) de 0 (absents) a 2 (<5 mm). Segons el nombre de regions avaluades, la puntuació màxima és 24 per a les HSB dels quatre lòbuls i les HSB infratentorial (cerebel, mesencèfal, protuberància i bulb); 30 per a les hiperintensitats subcorticals (putamen, globus pàl.lid, tàlem, càpsula interna); i de 6 per a les HPV (banyes occipitals, frontals i laterals dels ventricles).

- La tècnica de la Voxel-Based Morphometry (VBM) es va realitzar amb el programa SPM2 (Statistical Parametric Mapping) i Matlab 6.5 (MathWorks, Natick, MA) seguint les passes del mètode proposat per Good *et al*.,2001. Aquest procediment permet fer una detecció automàtica de les diferències cerebrals de tot el cervell, assignant a cada voxel del cervell la probabilitat de que sigui substància gris (SG), substància blanca (SB) o líquid cefaloraquidi (LCR).
- L'anàlisi de les Regions d' interès (ROI) que comprenen l'hipocamp i el girus hipocampal es van realitzar mitjançant el programa Wake Forest University of School of Medicine Pickatlas (WFU Pickatlas v2).

- **L'anàlisi estadística** de les dades es va realitzar mitjançant el programa Statistical Package for Social Sciences (SPSS v.11.5, 12.0 and 14.0). Aquést es va emprar per a estudiar les diferències grupals en les dades demogràfiques i clíniques, així com en l'execució neuropsicològica mitjançant l'anàlisi de la variança (ANOVA), amb la prova t d'Student per a les variables continues i amb la de Xi- quadrat (χ^2) o de probabilitat exacta de Fisher (quan va ser convenient) per a les variables categòriques.

Per a l'anàlisi de les dades de RM estructural vam emprar el programa Statistical Parametric Mapping (SPM2) en Matlab 6.5 (MathWorks, Natick, MA). Les comparacions de volums de SG i les correlacions entre les HSB i l'atròfia de la SG derivades dels mapes estadístics es van analitzar amb la prova

‘two-sample t test’ i amb una ‘correlació’ a la línea base i amb una ‘ANOVA de measures repetides’ (utilitzant l’edat i el gènere com a covariables) i una ‘regresió múltiple’ (utilitzant l’edat i el gènere com a variable ‘nuisance’).

4- Resultats

En el primer treball vàrem trobar que, respecte al rendiment cognitiu, el 57.5% (n= 23) dels pacients complia criteris de DCL-V. En les diferents síndromes llacunars vàrem observar que el grup de pacients amb disàrtria-mà feixuga/hemiparèsia-atàxia presentaven un millor rendiment cognitiu general (puntuació del MMSE: 29.5±1.2) respecte dels altres grups clínics (t=2.088; p=0.044), així com puntuacions significativament més altes en les funcions visuoconstructives (Blocs del WAIS-III:13.3±2.9; p= 0.036) i de memòria visual (subtest de memòria diferida del test de Reproducció visual de la WMS-III: 12.6±2.5; p= 0.014, subtest de reconeixement: 12.3±2.7; p= 0.050). Contràriament, els pacients amb síndrome llacunar atípica van presentar el rendiment cognitiu més baix, amb dèficits sobretot de tipus executiu com són la fluència fonètica (14.0±6.8; p=0.018), fluència categorial (9.2±4.3; p=0.034), atenció (Digit Symbol test: 16.4±6.7; p=0.029) i funcions premotores (reproducció de ritmes: 3.4±2.2; P<0.001, alternances motores: 0.7±0.8; p=0.001). El segon grup amb pitjor rendiment cognitiu va ser l'hemiparèsia motora pura, amb una major afectació en la comprensió del llenguatge (Token Test: 33.3±1.8; p= 0.008) i de les funcions premotores (alternances motores: 0.9±0.8; p= 0.009).

En quant a les HSB en general i les de la zona periventricular es distribuien de forma similar entre les diferents síndromes llacunars (hemiparèsia motora pura, sd. sensitiu pur, síndrome sensitiu-motriu, hemiparèsia-atàxia, disàrtria-mà feixuga i síndrome llacunar atípica). En canvi, les HSB subcorticals eren menys freqüents entre els pacients que presentaven una síndrome sensitiu-motriu (t=2.235; p=0.031), i les HSB infratentorials entre els pacients amb una síndrome sensitiva pura (t=2.259; p=0.030), en comparació amb la resta de síndromes clíniques llacunars.

En el segon estudi vam comparar pacients amb un únic ILL vs pacients amb múltiples ILLs que eren clínicament silents. Vàrem observar que de la mostra original de 40 casos el 42.5% (n=17) presentàven un únic ILL, i el 57.5% (n=23) tenien múltiples ILLs. En aquest últim grup vàrem observar una major severitat de les HSB global en l'Escala de Scheltens, respecte els

subjectes amb un únic ILL. Els subjectes amb múltiples ILLs també presentàven més HSB a les següents regions subcorticals: frontal ($t=3.41$, $p<0.002$) i occipital ($t=2.47$, $p<0.02$) de la regió periventricular, així com en el nucli caudat ($t=2.25$, $p<0.03$) i el tàlem ($t=2.48$, $p<0.02$). Finalment, i per determinar quina variable o conjunt de variables millor classificava els nostres pacients en quant a la pertenença d'un grup clínic o altre (únic vs múltiples ILLs), vàrem realitzar una regressió logística. Els resultats vàren revelar que un model incloent les hiperintensitats periventriculars frontals ($B=2.79$, $p<0.03$), i les hiperintensitats al tàlem ($B=1.71$, $p<0.02$), així com l'edat dels participants ($B=-0.12$, $p<0.03$), era el que millor classificava els nostres pacients ($\chi^2 = 3.65$; $p<0.88$; $R^2=0.58$). El percentatge total de pacients classificats correctament segons aquest model va ser del 77.5% (el 64.7% per els ILL únics i del 87% pels múltiples ILLs).

En el tercer estudi vàrem confirmar de nou que el 55% (n=22) dels pacients de la mostra complia criteris de DCL-V. En aquest treball vàrem comparar les característiques clíniques i neuroradiològiques de pacients llacunars amb DCL-V i sense. Mitjançant l'Escala de Scheltens vam observar que els subjectes amb DCL-V presentàven una major severitat d' HSB en general ($t= 2.01$; $p= 0.05$), i més concretament en els ganglis basals, com el putamen ($t= 3.17$;$p= 0.003$), i en el tàlem ($t= 3.36$; $p= 0.002$).

La tècnica de la voxel-based morphometry ens va permetre observar una reducció en el volum global de substància grisa en el grup amb DCL-V respecte els subjectes que no complien aquests criteris (volum mig: 628.41±74.63 mm^3 vs 728.79±77.82 mm^3; $p<0.001$). En el grup amb DCL-V també vam observar una pèrdua significativa de substància grisa en les següents regions cerebrals: en el lòbul temporal bilateral ($t= 6.34$; $p<0.001$), en el girus frontal superior ($t= 5.32$; $p<0.001$), cerebel ($t= 4.33$; $p<0.001$), cuneus/precuneus ($t= 4.28$; $p<0.001$) i girus cingulat posterior ($t= 4.14$; $p= 0.026$). L'hipocamp ($p= 0.030$) i el girus parahipocampal ($p= 0.026$) també van presentar un major nivell d'atròfia en aquests pacients (DCL-V) quan vam realitzar un anàlisi de ROI (regió d'interès). Finalment, vam trobar una correlació negativa entre les HSB subcorticals i el volum de substància grisa al girus frontal medial, el tàlem posterior esquerre, el girus precentral i paracentral i el mesencèfal.

En el quart treball que forma part de la present tesi vam fer el seguiment dels subjectes (18±6 mesos) amb DCL-V i sense, per tal de veure la seva evolució clínica, cognitiva i neuroradiològica. Al final del període de seguiment el 60% (n=9) de subjectes amb DCL-V i el 33.3% (n= 5) sense DCL-V, encara presentàven seqüeles neurològiques del primer ILL (χ^2=0.27, p<0.14). Respecte a l'execució neuropsicològica vam observar que els dos grups de pacients van evolucionar de forma diferent al llarg del temps, presentant el grup amb DCL-V un empitjorament en les funcions pròpies del lòbul frontal, com són l'atenció (Dígits del WAIS-III:F=4.59;p=0.04, digit symbol test: F=4.39;p=0.046), i les funcions premotores (reproducció de ritmes: F=4.35;p=0.047), tot i que també va presentar certa milloria en tasques de memòria (reconeixement en memòria visual: F=4.39; p=0.007).

A l'avaluar les HSB amb l'Escala de Scheltens vàrem observar que després del període de seguiment en tots dos grups, amb DCL-V i sense, hi havia un augment en la severitat de les HSB globals (F=36.1; p<0.001), així com en les següents regions: periventricular (F=19.97; p<0.001) i subcortical (F=33.99; p<0.001). Aquestes diferències continuaven sent significtives després de corregir per múltiples comparacions (valor significatiu de p<0.01).

Mitjançant la tècnica de la voxel-based morphometry vàrem observar que després de 18±6 mesos de seguiment, el grup de pacients amb DCL-V es caracteritzava per presentar una reducció del volum de la substància grisa al girus frontal inferior (t= 4.36; p<0.001) i orbital (t= 4.68; p<0.001), al girus temporal mig (t= 4.87; p<0.001), al girus central (t= 4.51; p<0.001), a la protuberancia (t= 5.19; p<0.001), al girus cingulat posterior (t= 4.73; p<0.001), al cerebel (t= 4.34; p<0.001), al girus parahipocampal (t= 4.48; p<0.001) i al nucli caudat (t= 4.31; p<0.001). La tècnica del ROI va mostrar també en el grup de pacients amb DCL-V una major atròfia de l'hipocamp (p=0.035).

5- Discussió general

A la present tesi describim de forma acurada el perfil neuropsicològic i les característiques neuroanatòmiques dels subjectes amb malaltia vascular cerebral de petit vas (primer ILL i HSB), així com les diferents síndromes llacunars i la prevalència de subjectes que compleixen criteris de deteriorament cognitiu lleu de tipus vascular (DCL-V). En aquest treball també donem suport a la hipòtesi de la diferent etiologia d'un únic ILL respecte als múltiples ILLs i dels substrat anatòmic de la categoria DCL-V, tot identificant els aspectes més importants d'aquest tipus d'afectació cognitiva i la seva evolució a llarg termini.
L'objectiu d'aquest treball és la prevenció i la identificació precoç de persones amb un alt risc de desenvolupar demència vascular o de tipus neurodegeneratiu. Per tant, aquest treball podria ser una primera aproximació al perfil neuroanatòmic de pacients amb DCL-V, tot emprant diferents tècniques com són la voxel-based morphometry (VBM), l'anàlisi de regions cerebrals d'interès (ROI) i la quantificació de les HSB amb l'Escala de Scheltens.
Tot seguit es presenta una discussió general dels resultats de cada estudi.

En el primer estudi vam veure que els dèficits neuropsicològics lleus, principalment de tipus executiu, no són infrequents en els pacients llacunars aguts. Tot i que hi ha alguns estudis (Van Swieten *et al*.,1996; De Groot *et al*.,2002; Wen *et al*.,2004) que suggereixen una relació entre les lesions cerebrals causades per un ILL i una afectació neuropsicològica específica, fins ara hi ha poc coneixement sobre la freqüència i el tipus de disfunció neuropsicològica en subjectes amb un ILL agut. Aquests resultats suggereixen que un únic ILL pot tenir un efecte negatiu en l'execució neuropsicològica.
També vam comprobar que les cinc síndromes llacunars eren similars en quant a la topografia de la lesió cerebral, tot i que les lesions als ganglis basals eren més freqüents en la síndrome llacunar atípica, les lesions a la càpsula interna en la síndrome sensitiu-motriu i l'afectació talàmica en el síndrome sensitiu pur.
Aquesta relació entre els ILLs als ganglis basals i al tàlem i l'afectació cognitiva ja havia estat descrita en treballs anteriors (Tatemichi *et al*.,1992; Gold *et al*.,2005). També és ben coneguda en la literatura la relació entre la leucoaraiosi o HSB i els ILLs (Pantoni and Garcia.,1997). La presència d'HSB

s'ha relacionat amb l'afectació cognitiva, especialment amb funcions frontals com la velocitat de processament cognitiu, les funcions executives i la fluència verbal (Bartrés-Faz *et al.,*2001).

En el nostre estudi vàrem trobar que els pacients amb una síndrome llacunar atípica o hemiparèsia motora pura presentaven un major grau d'HSB en els ganglis basals. De la mateixa manera, quan vam comparar l'execució neuropsicològica en les diferents síndromes llacunars, vàrem comprobar que aquestes dues síndromes presentaven el rendiment cognitiu general més baix (puntuació del MMSE), així com més afectació cognitiva, sobretot en els tests que avaluen funcions executives (fluència verbal, atenció i seqüències premotores) els pacients amb Sd.llacunar atípica, i amb afectació en la comprensió del llenguatge i seqüències premotores els pacients amb hemiparèsia motora pura.

Els subjectes amb Sd.llacunar atípica també van mostrar una major tendència a presentar infarts llacunars múltiples, i els subjectes amb hemiparèsia motora pura presentaven una major severitat de les HSB en la regió periventricular.

Contràriament, els pacients amb disàrtria- mà feixuga/ hemiparèsia- atàxia van mostrar els millors resultats en la puntuació del MMSE. A més a més, aquest grup no va presentar puntuacions baixes en cap de les mesures neuropsicològiques i va obtenir la puntuació més alta en els tests que avaluen funcions visuoconstructives i de memòria visual.

Se sap que els ILLs als ganglis basals, tàlem o a la substància blanca profunda augmenta per 20 el risc a patir demència (Norving 2003). L'afectació cognitiva produïda per els ILLs en aquestes regions es podria explicar per la interrupció dels circuits prefrontal/subcorticals, del cingulat anterior amb els ganglis basals o bé de les conexions tàlamocorticals (Cummings 1993; Mega and Cummings.,1994). La interrupció d'aquests circuits pot produir disfunció executiva (Boyle *et al*.,2002), i a conseqüència d'aquésta es poden afectar les activitats instrumentals de la vida diària. És per aquest motiu que la Sd.llacunar atípica i l'hemiparèsia motora pura podrien tenir un pitjor pronòstic a llarg terme. Per tant, l'identificació precoç dels primers estadis de demència de tipus vascular és clínicament rellevant, ja que la demència és un dels majors problemes de salut públicai que més cost econòmic causa a la població.

En el segon estudi vàrem trobar que malgrat presentar característiques demogràfiques, cognitives i clíniques similars, els pacients amb múltiples infarts llacunars es caracteritzen per presentar una major severitat de les HSB cortical (còrtex frontal i occipital) i en els ganglis basals, en comparació amb els pacients amb un únic ILL. Els pacients amb múltiples infarts llacunars també van mostrar una tendència a presentar major freqüència d'hipertensió arterial, tot i que no va ser estadísticament significativa. Aquests resultats dónen suport a la hipòtesi que considera que els ILL únics i múltiples constitueixen dues entitats diferents i per tant tenen diferent etiologia (Boiten *et al*.,1993).

Les HSB periventricular en els lòbuls frontals s'han relacionat amb un enlentiment de la velocitat de processament en la realització de tasques executives (Söderlund *et al*.,2006). Nosaltres no vam poder evidenciar l'efecte cognitiu que tenien la presència d'aquestes HSB, ja que només vàrem emprar el MMSE per a avaluar les funcions cognitives, i aquesta prova no és sensible per a detectar l'afectació cognitiva de tipus subcortical. Serien necessàries avaluacions neuropsicològiques més detallades per tal de detectar la influència de les HSB en l'execució cognitiva entre pacients amb un únic i múltiples infarts llacunars.

En el tercer estudi que forma part d'aquesta tesi, vàrem trobar que el 55% de pacients amb un primer ILL complien criteris de DCL-V segons els criteris de Frisoni (Frisoni *et al*.,2002). Tot i que la descripció clàssica de les síndromes llacunars implica la no afectació de les funcions cognitives (Fisher 1982), en el nostre treball afegim dades a l'evidència acumulada de que un primer ILL está freqüentment associat a cert grau d'afectació cognitiva (Corbett *et al*.,1994; Van Zandvoort *et al*.,2001; Pantoni *et al*.,2001; Van Zandvoort *et al*.,2005; Jokkinen *et al*..2006).

Seguint aquesta línia, les nostres troballes són consistents amb publicacions recents que aporten dades neuropatològiques i de neuroimatge de que les llacunes talàmiques i en els ganglis basals estàn fortament relacionades amb el deteriorament cognitiu (Gold *et al.,*2005).

Amb la tècnica de la VBM per avaluar l'atròfia de la substància grisa, vàrem trobar que el pacients amb DCL-V presentàven una major atròfia en les següents regions cerebrals: els dos lòbuls temporals, regions frontals i parietals, regions del cerebel esquerre, el girus parahipocampal bilateral i

l'hipocamp dret (aquestes dues regions van aparèixer quan vàrem realitzar un ROI d'aquestes regions específiques). Aquestes troballes corroborarien les dades aportades per la neuroimatge funcional a la literatura sobre els efectes remots produïts per lesions subcorticals (Kwan *et al.,*1999; Reed *et al*.,2004).
Les nostres dades indiquen que a més a més de l'afectació subcortical dels ganglis basals, l'afectació regional de la substància grisa contribueix a les característiques neuropsicològiques dels pacients amb DCL-V.

En la mateixa línia d'altres estudis (Fein *et al*., 2000; Zekry *et al*., 2002; Du *et al*., 2005 ; Van der Flier *et al*., 2005), vàrem trobar correlacions significatives entre una reducció del volum de la substància grisa en els lòbuls frontal, parietal i temporal i en el tàlem, i la severitat de les HSB subcortical en els ganglis basals, però només en els pacients llacunars que complien criteris de DCL-V. Moltes d'aquestes regions que vàrem veure en aquests pacients que presentàven atròfia, s'ha trobat en altres estudis que també estàven afectades en subjectes amb lesions no-vasculars, sinó de tipus neurodegeneratiu (Chételat *et al*.,2002; Karas *et al*.,2004; Pennanen *et al*.,2005). Per tant, és possible que l'atròfia de la substància grisa que veiem en el nostre estudi reflecteixi algún tipus de pèrdua neuronal o de troballa neuropatològica. Tot i així, calen futurs estudis de neuroimatge combinats amb autòpsies per tal d'aclarir aquesta qüestió.

En el quart i últim estudi, l'objectiu princial va ser comparar l'evolució a llarg terme (18±6 mesos) en el rendiment cognitiu i les característiques cerebrals estructurals de pacients llacunars que compleixen criteris de DCL-V en relació als pacients llacunars que no compleixen aquests criteris.

La nostra principal troballa va ser que en els pacients amb DCL-V es va detectar una afectació de la substància grisa cortical (còrtex frontal i temporal), així com a diferents regions subcorticals (girus cingulat i parahipocampal, nucli caudat i hipocamp esquerre) mentre que es produia una relativa estabilitat en la severitat de les HSB. Aquests resultats suggereixen que un procés neurodegeneratiu continu podria estar explicant el deteriorament cognitiu en aquests pacients, tot i que presenten un deteriorament associat a malaltia vascular de petit vas. En aquesta línia, doncs, l'event llacunar podria estar potenciant o accelerant el procés neurodegeneratiu. Una explicació alternativa

podria ser que el dany vascular cerebral portaria a una degeneració neuronal secundària (deaferentització) que seguiria a l'afectació subcortical primària. El fet de que els pacients llacunars sense afectació cognitiva (que presenten gairebé les mateixes HSB) no presentéssin afectació de la substància grisa durant el període de seguiment, així com el fet de que certes regions cerebrals crítiques per al diagnòstic de la Malaltia d'Alzheimer (MA), com l'hipocamp, el lòbul temporal medial i el còrtex cingulat posterior (Jack *et al*.,1999; Chételat *et al*.,2005; Geroldi *et al*.,2006) estiguéssin específicament involucrades en el pacients amb DCL-V, dóna suport a l'interpretació de la possible existència d'un procés neurodegeneratiu primari concomitant.

Segons alguns autors (Gainotti *et al*.,2004) l'atròfia de l'hipocamp (marca distintiva de la MA) és millor predictor de demència i de deteriorament cognitiu lleu que el nombre de lesions vasculars en els pacients amb infarts subcorticals. Per tant, tot i que s'accepta que les patologies vascular i neurodegenerativa interactuen en quan a l'expressió clínica del deteriorament cognitiu (Snowdon *et al*.,1997; Esiri *et al*.,1999), i que en efecte, els nostres resultats previs estaven en la mateixa línia (Grau-Olivares *et al*.,2007), aquests resultats longitudinals indiquen que l'atròfia de la substància grisa reflexa el curs clínic que segueixen els subjectes amb DCL-V.

7- Conclusions

Tot seguit es presenten les conclusions generals de cadascún dels quatre estudis que formen part de la present tesi.

1)- Un primer infart llacunar acostuma a ser una lesió vascular no-severa amb una bona recuperació de la disfunció neurològica, tot i que la presència d'alteracions neuropsicològiques lleus, especialment de les funcions executives, no és infreqüent, sobretot en pacients amb una síndrome llacunar atípica o hemiparèsia motora pura. Per tant, els dèficits neuropsicològics podrien ser considerats com una característica comuna en els infarts llacunars aguts.

2)- Els pacients amb múltiples infarts llacunars (detectats mitjançant ressonància magnètica) es caracteritzen per presentar una major severitat d'HSB cortical (frontal i occipital) i als ganglis basals, en comparació amb els pacients amb un únic ILL. Aquests resultats dónen suport a la hipòtesi de que els ILLs únics i els múltiples consitueixen dues entitats separades i tenen diferent etiologia.

3)- Un 57% de pacients amb un primer infart de tipus llacunar es podrien diagnosticar de deteriorament cognitiu lleu de tipus vascular (DCL-V) en el nostre estudi. Els correlats neuroradiològics que millor explicarien el deteriorament cognitiu que presenten aquests pacients comparat amb pacients llacunars sense afectació cognitiva, serien l'afectació de la regió dels ganglis basals, així com la reducció del volum global de substància grisa cortical i atròfia en certes estructures cerebrals com l'hipocamp, el lòbul temporal lateral, el còrtex parietal i el cerebel.

4)- El curs clínic de pacients amb DCL-V vindria definit per un major grau d'atròfia de la substància grisa cerebral en diferents regions corticals (còrtex frontal i temporal, girus cingulat i parahipocampal, i cerebel) i subcorticals (nucli caudat i protuberància) i per la major presència de disfunció executiva que presenten aquests pacients. En aquest aspecte, l'avaluació continuada de la

volumetria cerebral i de les funcions neuropsicològiques podria ser útil per a detectar la demència subclínica en aquests pacients.

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