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Raffaella Valenti

Cerebral Small Vessel Disease and Cerebral Amyloid Angiopathy

Neuroimaging markers, cognitive features and rehabilitative issues

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Introduction

Sporadic cerebral small vessel disease (SVD) is considered to be among the most common known neuropathological processes in the brain and has a crucial role in stroke, cognitive impairment, and functional loss in elderly persons [Pantoni L, Lancet Neurol 2010]. Recently SVD has received more attention even if clinicians have less to offer for the prevention and treatment of the disease [Charidimou A, et al. Int J Stroke 2016].

The most common forms of SVD are *sporadic non-amyloid microangiopathy* (*age- and hypertension-related SVD arteriolosclerosis*) and *cerebral amyloid angiopathy* (CAA) [Pantoni L, Lancet Neurol 2010; Charidimou A, et al. Int J Stroke 2016]. CAA is common in older individuals and it is a major cause of lobar symptomatic intracerebral hemorrhage and a key contributor to vascular cognitive impairment [Greenberg SM et al, Lancet Neurol 2014]. CADASIL is a genetic form of microangiopathy, considered as a model of SVD.

Even small vessel are difficult to be directly visualized with current techniques used, modern neuroimaging has revolutionized understanding of the consequences of SVD on the brain parenchyma [Charidimou A, et al. Int J Stroke 2016]. Neuroimaging expressions of SVD include hemorrhagic and non-hemorrhagic markers. Pathogenic mechanisms of SVD are probably not uniform, and marker on MRI may be found in different types of SVD [Pantoni L, Lancet Neurol 2010; Charidimou A, et al. Int J Stroke 2016].

There is an incorrect tendency to less contemplate hemorrhagic component of the SVD process [Pantoni L, Lancet Neurol 2010; Wardlaw JM et al, Lancet Neurol 2013]. A broader view of SVD should be maintained, particularly when considering preventive and therapeutic aspects, because patients with SVD also have an increased risk of hemorrhage [Pantoni L, Lancet Neurol 2010; Valenti R et al, Secondary Prevention In Patients With Ischemic Lacunar Stroke 2016]. Moreover, different forms of SVD can coexiste.

SVD is reputed to be a common cause of vascular cognitive impairment. Vascular cognitive impairment associated with SVD has recently received particular attention. Because it is thought to be relatively homogeneous in clinical and neuroimaging features [Erkinjuntti T et al, J Neural Transm Suppl 2000; Román GC et al, Lancet Neurol 2002], it is a possible target for implementing studies and therapeutic trials [Pantoni L, Lancet Neurol 2010]. At present, suited universal definition criteria for vascular cognitive impairment are not available.

In particular, vascular mild cognitive impairment (MCI) due to SVD is considered a progressive condition from normal cognitive status to dementia with progressive

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course, in which lacunar infarcts and white matter changes accumulation determines a gradual progression of cognitive impairment, from mild to more severe stages [Pantoni L et al, Neuroepidemiology 2005]. Concerning distribution of cognitive performances pattern, executive/attentional processing dysfunction is one of the prominent features of vascular cognitive impairment. Alterations in executive/attentional processing are critical to the daily functioning. At present, no treatment is available to prevent vascular dementia or to improve cognitive performances in patients with vascular MCI.

During my PhD, I focused research work on the subclinical hemorrhagic manifestation of SVD, global SVD-related brain injury on MRI, and their consequences on cognitive features in view of a possible treatment strategy.

Authors declaration

Part of research described in this thesis was completed during my time as a a Stroke Research Fellow at the Massachusetts General Hospital – J. Philip Kistler Stroke Research Center – Harvard Medical School – Boston Massachusetts during the second year of my PhD program (Supervisor: Professor Steven Greenber; Principal Investigator: Professor Anand Viswanathan).

Part 1

The cerebral small vessel disease and current concepts

Chapter 1
The cerebral small vessel disease

1. The cerebral small vessel disease

Cerebral small vessel disease (SVD) is a common age-related pathology and because life expectancy has increased, the burden of SVD is likely to grow, becoming an increasing global healthcare challenge. The cerebral SVD is considered to be among the most frequent known neuropathological processes in the brain and has a crucial role in stroke, cognitive impairment, and functional loss in elderly persons [Pantoni L, Lancet Neurol 2010; Charidimou A et al, Int J Stroke 2016; Inzitari D et al, BMJ 2009].

From nosologic point of view, SVD is a term used with various meanings and in different contexts to describe a range of pathological, clinical and neuroimaging aspects [Pantoni L, Lancet Neurol 2010]. The current definition of SVD encompasses a group of pathological processes with various etiologies that affect all vascular structures (ranging from around 5 mm to 2 mm in diameter) in the brain parenchyma or the subarachnoid space, including small arteries, arterioles, venules, and capillaries of the brain [Pantoni L, Lancet Neurol 2010].

Unlike large vessels, small vessels cannot be directly visualised in vivo and technically hardly accessible to image. Then, the parenchyma lesions that are thought to be caused by these vessel changes have been adopted as the marker of SVD and the term SVD is more frequently used to describe these brain parenchyma lesions rather than the underlying small vessel alterations [Pantoni L, Lancet Neurol 2010]. The consequences of SVD on the brain parenchyma are heterogeneous, encompassing ischaemic and hemorrhagic manifestations [Pantoni L, Lancet Neurol 2010]. These are lesions mainly located in the subcortical structures such as lacunar infarcts, white matter lesions, large hemorrhages, and microbleeds.

The underlying mechanisms and pathophysiological aspects in SVD processes remain relatively poorly understood [Pantoni L, Lancet Neurol 2010; Charidimou A et al, Int J Stroke 2016]. In the last years, recent advances were made and even though small vessel remain difficult to be directly visualized with current techniques used in clinical practice, modern neuroimaging has revolutionized our understanding of the consequences of vascular injury caused by SVD on the brain [Charidimou A et al, Int J Stroke 2016; Norrving B, J Stroke 2015].

There is an incorrect tendency to use the term SVD to describe only the ischemic component of the SVD process (i.e., lacunar infarcts and white matter lesions) [Pantoni L, Lancet Neurol 2010; Wardlaw JM et al, Lancet Neurol 2013; Valenti R et al,

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Secondary Prevention In Patients With Ischemic Lacunar Stroke 2016]. Instead, a broader view of SVD should be maintained, particularly when considering preventive and therapeutic aspects, because patients with SVD also have an increased risk of hemorrhage [Pantoni L, Lancet Neurol 2010; Valenti R et al, Secondary Prevention In Patients With Ischemic Lacunar Stroke 2016].

1.1 Epidemiology of cerebral Small Vessel Disease

Considering wide range of complex pathological processes and different neuroimaging technique used, the exact prevalence and incidence of SVD are difficult to estimate. It is known that imaging markers of SVD are frequently detected both in asymptomatic adults and in stroke patients. For example, the Rotterdam study reported that 27% of elderly participants had moderate to severe white matter changes [Breteler MM et al, Neurology 1994]. Silent brain infarcts as markers of SVD have been reported with an incidence of 3% per year among elderly people, and prevalence ranged around from 6% (in patients with 60 years) to 28% (in patients with 80 years) [Vermeer SE et al, Lancet Neurol 2007].

SVD prevalence increases with age and individuals between 65 and 69 years had a prevalence of 90% of any WMCs, with the occurrence of WMCs in subjects over 80 years of 98% [Longstreth WT Jr et al, Stroke 1996]. In addition, SVD is associated with three-time increased risk of mortality [Debette S et al, BMJ 2010; Altmann-Schneider I et al, Stroke 2011].

1.2 Pathogenesis of cerebral Small Vessel Disease

The underlying pathophysiological mechanisms of SVD and mechanisms linking SVD with parenchyma damage, either ischemic or hemorrhagic, are heterogeneous and relatively poorly understood, and therefore knowledge on prevention and treatment measures is still limited [Pantoni L, Lancet Neurol 2010; Valenti R et al, Secondary Prevention In Patients With Ischemic Lacunar Stroke 2016].

In ischaemic lesions caused by SVD, the vessel lumen restriction is thought to lead to a state of chronic hypoperfusion of the white matter, eventually resulting in degeneration of myelinated fibres because of repeated selective oligodendrocyte death [Pantoni L, Lancet Neurol 2010]. Alternatively, acute occlusion of a small vessel is hypothesized to occur, leading to focal and acute ischemia and complete tissue necrosis. Other mechanisms involved contributing to the final pathological picture of SVD are: blood–brain barrier damage [Wardlaw JM et al, Stroke 2003], local subclinical inflammation [Tomimoto H et al, Acta Neuropathol 2000; Rosenberg GA, Stroke 2009; Simpson JE et al, Neuropathol Appl Neurobiol 2007], and oligodendrocytes apoptosis [Brown WR et al, AJNR Am J Neuroradiol 2000].

The pathogenic mechanisms of neuroimaging markers of SVD are probably not uniform, and any marker may be found in different types of SVD [Gouw AA et al, J

Neurol Neurosurg Psychiatry 2011]. For example, in view of different topographical distribution of *sporadic non-amyloid microangiopathy* and *CAA*, it is hypothesized that cerebral microbleeds or parenchymal brain hemorrhage have a preferential location depending on the underlying small vessel pathology: sporadic non-amyloid microangiopathy is commonly associated with micro- or macrohemorrhage in deep brain regions, whereas CAA is characterized by cerebral microbleeds (CMBsI in a lobar distribution (cortical–subcortical) [Charidimou A et al, Future Neurol 2011]. A similar example even if with less strong evidences it applies to enlarged perivascular spaces: in CAA they are found predominantly in centrum semiovale while in deep hypertensive non-amyloid microangiopathy at level of basal ganglia and peribasal ganglia white matter [Charidimou A et al, J Neurol Neurosurg Psychiatry 2013; Martinez-Ramirez S et al, Neurology 2013].

1.3 Classification of cerebral Small Vessel Disease

An aetiopathogenic classification for different types of SVD was proposed (Figure 1) [Pantoni L, Lancet Neurol 2010].

The most prevalent forms are: 1. arteriolosclerosis (age- and hypertension-related SVD or hypertensive arteriopathy) ore more recently defined as sporadic non-amyloid microangiopathy and 2. sporadic and hereditary Cerebral Amyloid Angiopathy (CAA) [Pantoni L, Lancet Neurol 2010; Charidimou A, et al. Int J Stroke 2016]. A group of inherited or genetic cerebral SVD, as well as CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Ischaemic Strokes and Leukoencephalopathy) was included [Pantoni L, Lancet Neurol 2010] (Figure 1).

Type 1 SVD: The first form (*arteriolosclerosis/hypertensive arteriopathy*) was more recently defined as *sporadic non-amyloid microangiopathy*, with an alternative umbrella-term including more accurately a variety of sporadic SVD pathologies not accounted by sporadic CAA but not necessarily (or even often) related specifically to hypertension [Charidimou A, et al. Int J Stroke 2016; Lammie GA et al, Stroke 1997].

This is the more common form of sporadic SVD, that include the pathologic processes that primarily involve the small vessels that supply the deep white matter and grey nuclei causing parenchymal damage, mainly lacunes, white matter hyperintensities (WMH), intracerebral hemorrhage (ICH) and CMBs in deep areas of the brain (Figure 2). This form of the disease is strongly associated with vascular risk factors, in particular ageing, hypertension, diabetes and smoking [Furuta A et al, Stroke 1991].

Regarding pathological aspect, type 1 SVD are mainly characterized by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall. Pathological descriptors/subtypes include arteriolosclerosis, fibrinoid necrosis, and lipohyalinosis. Other possible pathological features of this form of microangiopathy are distal manifestations of atherosclerosis (microatheroma) and the presence of elongated and dilated vessels (microaneurysms) [Pantoni L, Lancet Neurol 2010]. These alterations in the vessel wall are often associated with enlargement of the surrounding perivascular spaces and sometimes with microinfarction, lacunes, thrombosis or microhemorrhage.

Some evidences allow hypothesizing that these pathological changes associated with *sporadic non-amyloid microangiopathy* presumably impair functional autoregulation and perfusion, drainage and transport of interstitial fluid along the vessel and vessels compliance. Other mechanisms that enhance small vessel permeability can be involved in SVD, in particular endothelial dysfunctions and genetic determinants [Poggesi A et al, J Cereb Blood Flow Metab 2015; CHARGE, SiGN, ISGC, 2016].

The type 2 of SVD is the *Sporadic* and *Hereditary Cerebral amyloid angiopathy* (CAA).

CAA is a chronic degenerative microangiopathy characterized pathologically by progressive deposition of amyloid-β (Aβ) in the media and adventitia of cortical and leptomeningeal small arteries, arterioles, and less often capillaries and veins [Charidimou A, et al. Int J Stroke 2016; Viswanathan A et al, Ann Neurol 2011; Reijmer YD et al, J Cerebr Blood Flow Metab 2015; Charidimou A et al, J Neurol Neurosurg Psychiatry 2012]. Similar to cerebral SVD, the term CAA encompasses not only a specific cerebrovascular pathological disorders, but also brain parenchymal lesions on neuroimaging [Charidimou A, et al. Int J Stroke 2016].

Pathological examination of blood vessels affected by Aβ in both sporadic and familial CAA show loss of smooth muscle cells, fibrinoid necrosis, vessel wall thickening, luminal narrowing, concentric splitting of the vessel wall, microaneurysm formation, and perivascular microhemorrhage [Attems J et al, Neuropathol Appl Neurobiol 2011].

The genetic abnormalities underlying sporadic CAA have not been fully elucidated, although several inherited familial forms of CAA have been described. Hereditary CAA goes beyond the scope of this thesis.

Because CAA represents a major cause of lobar hemorrhage as well as a contributor to cognitive impairment in the elderly, and sharing pathological features with Alzheimer's disease, CAA has drawn rapidly increasing interest over the past decades, almost a century after being first recognized [Boulouis G et al, Semin Neurol 2016; Charidimou A et al, Int. Stroke Soc 2015].

A separate paragraph of this thesis is dedicated to CAA (see below in the text).

Table 1 shows main vessel characteristic of the two main type of SVD (Table 1).

1.4 Neuroimaging markers of cerebral Small Vessel Diseases

Recently in an international working group position paper from the Centres of Excellence in Neurodegeneration under the acronym STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1) the definition of SVD was extensively revised [Wardlaw JM et al2, Lancet Neurol 2013]. According to this new classification, mainly based on neuroimaging, there are at least six types of lesions to consider in SVD [Wardlaw JM et al2, Lancet Neurol 2013; Valenti R et al, Secondary Prevention In Patients With Ischemic Lacunar Stroke 2016]: 1. recent small subcortical infarcts, 2. lacunes, 3. WMH, 4. enlarged perivascular spaces, 5. CMBs, and 6. brain atrophy [Wardlaw JM et al2, Lancet Neurol 2013] (Figure 3). The neuroimaging markers of SVD are specifically discussed in the Neuroimaging section of this thesis.

1.5 Clinical correlates and Small Vessel Disease-related disability

SVD has an important role in cerebrovascular disease in both acute and chronic phases (Table 2).

Approximately one third of symptomatic strokes are caused by cerebral perforating SVD [Charidimou A, et al. Int J Stroke 2016]. The consequences include lacunar stroke syndromes (about one fifth of all strokes) [Sudlow CLM et al, Stroke 1997; Fisher CM, Neurology 1982] and ICH, the most severe and lethal type of stroke [Greenberg SM. N Engl J Med 2006].

SVD causes widespread microvascular damage, which is not symptomatic itself but has important cumulative effects over time. In fact, SVD is a major contributor of cognitive decline [van der Flier WM et al, Stroke 2005], psychiatric disorders [Herrmann LL et al, J Neurol Neurosurg Psychiatry 2008] and functional loss in older people [Inzitari D et al, BMJ 2009; Gorelick PB et al, Stroke 2011]. In fact, SVD is the most common cause of vascular dementia [Gorelick PB et al, Stroke 2011] and a major contributor to mixed dementia [Snowdon DA et al, JAMA 1997; Neuropathology Group, Lancet 2001]. SVD is associated with specific cognitive deficits such as psychomotor retardation, deficits of attention, planning, and set-shifting, and dysexecutive syndrome [Ferro JM et al, J Neurol Sci 2002].

Patients with SVD have also other relevant functional deficits. For example, gait is frequently affected in patients with SVD that have an increased risk of falls [de Laat KF et al, Brain 2011; Blahak C et al, J Neurol Neurosurg Psychiatry 2009; Baezner H et al, Neurology 2008; Kreisel SH et al, Cerebrovasc Dis 2013]. Mood disturbances, particularly depressive symptoms and apathy [O'Brien JT et al, Am J Geriatr Psychiatry 2006; Verdelho A et al, J Neurol Neurosurg Psychiatry 2013; Reyes S et al, Neurology 2009], are also frequent, and urinary disturbances may be present [Poggesi A et al, J Am Geriatr Soc 2008].

Because white matter lesions are also associated with these other disturbances, it has been hypothesized that they are a neuroimaging correlate of age-associated disability. The multicenter study Leukoaraiosis and Disability (LADIS) was specifically focused on the investigation of this proposal [Pantoni L et al, Neuroepidemiology 2005]. More than 600 patients (aged 65–84 years), independent in daily living at baseline and with different degrees of white matter lesion on MRI, were enrolled and followed-up for up to 3 years with repeated and composite clinical assessments and MRI [Pantoni L et al, Neuroepidemiology 2005]. After 1 year, the rate of transition to disability was different across the three groups of patients with different levels of severity of white matter lesions (in particular, 9% in the mild group, 15% in the moderate group, and 26% in the severe group) [Pantoni L et al, Lancet Neurol 2010]. Patients with severe white matter lesions had more than double the risk of transition to disability than patients with mild lesions, independent of many other predictors of disability [Inzitari D et al, BMJ 2009; Inzitari D et al, Arch Intern Med 2007]. The yearly rate of transition or death was 10.5%, 15.1%, and 29.5% for patients with mild, moderate, or severe age-related white matter lesions, respectively (Kaplan-Meier log-rank

test p<0·001) [Inzitari D et al, BMJ 2009]. A comparison of the groups with severe versus mild age-related white matter lesions, with adjustment for clinical factors of functional decline, revealed a two-times higher risk of transition to disability or death in the severe group (hazard ratio 2.36; 95% CI 1.65–3.81). The effect of severe white matter lesions remained significant after correction for baseline degree of brain atrophy and infarct lesions [Inzitari D et al, BMJ 2009].

1.6 CADASIL: genetic form of cerebral Small Vessel Disease

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is the most common monogenetic cause of adult onset progressive cerebrovascular disease. It is rare genetic microangiopathy caused by missense point mutations of the *NOTCH3* gene (chromosome 19p13.1) [Joutel A et al, Nature 1996; Joutel A et al, Lancet 1997] and it is considered as a unique model to investigate the pathophysiology of subcortical ischemic vascular dementia related to SVD and to understand the pathogenesis of sporadic SVD [Pantoni L, Lancet Neurol 2010].

The exact prevalence of CADASIL is not known, and the disease is probably still underdiagnosed. Multiple small and national registries have estimated the minimum prevalence between 2-4 per 100,000 [Kalimo H et al, Brain Pathol 2002; Razvi SS et al, J Neurol Neurosurg Psychiatry 2005; Narayan SK et al, Neurology 2012; Bianchi S et al, J Neurol 2015].

The *NOTCH3* gene encodes for a transmembrane receptor protein involved in cellular differentiation and regulation, mainly expressed in vascular smooth muscle cells and capillary pericytes, but its specific role remains to be elucidated [Campos AH et al, Circ Res 2002; Bianchi S et al, Hum Genet 2005]. The pathologic hallmark of CADASIL is deposits of granular osmiophilic material within the media and adventitia of arterioles, progressive degeneration and loss of vascular smooth muscle cells and increased *NOTCH3* staining of the arterial wall, which can be evaluated in a skin biopsy [Ruchoux M et al, Neuropathol Appl Neurobiol 1998].

From the pathological point of view, CADASIL is a systemic non-amyloid, non-arteriolosclerotic disease affecting the wall of small arteries. As tipically in SVD, alterations of small cerebral arteries encompass thickening of the wall, mainly of the tunica media, degeneration of smooth muscle cells, and endothelial dysfunction [Ruchoux MM et al, Acta Neuropathol 1995; Kalaria RN, Trends Neurosci 2001].

The specific mechanisms leading from *NOTCH3* gene mutations to the clinical expression of the disease are unknown although the alterations of the small arteries are hypothesized to play a key role in the pathogenesis of the disease [Caronti B et al, Acta Neurol Scand 1998].

CADASIL is clinically characterized by recurrent transient ischemic attacks or stroke, early cognitive decline progressing to dementia (and leading to disability in some patients), a history of migraine (with and without aura), mood disturbances and apathy, and seizures, affecting middle-aged adults [Chabriat H et al, Lancet Neurol 2009]. The full clinical spectrum of CADASIL is usually observed during the fourth

and fifth decades of life, but migraine onset is usually in the second or third decade [Singhal S et al, Brain 2004]. Approximately 75% of affected individuals develop dementia, often accompanied by apathy [Dichgans M et al, Ann Neurol 1998; Opherk C et al, Brain 2004; Dichgans M, Stroke 2009; Reyes S et al, Neurology 2009]. The cognitive is progressive, with a concurrent stepwise deterioration due to recurrent strokes. The pattern of cognitive dysfunction is initially characterized by deficits in executive function, verbal fluency, and memory with benefit from clues [Peters N et al, Am J Psychiatry 2005].

The clinical–radiological phenotype of the disease is highly variable and this is only partially explained by the possible effect of other genetic or acquired factors [Singhal S et al, Brain 2004; Viswanathan A et al, Brain 2006; Ciolli L et al, Eur J Neurol 2014].

Typical neuroimaging features of the disease are diffuse leukoencephalopathy, frequently involving the temporal pole and the external capsule, multiple lacunar infarcts, and CMBs [Chabriat H et al, Lancet Neurol 2009]. In symptomatic individuals, WMH in T2-weighted and FLAIR sequences are confluent in the periventricular and deep white matter and particularly involve the anterior part of the temporal lobe and the external capsule (Figure 4) [Chabriat H et al, Neurology 1998]. Within the white matter, the frontal lobe is the site with the highest lesion load, followed by the temporal and parietal lobes [Chabriat H et al, Stroke 1999; Auer DP et al, Radiology 2001; O'Sullivan M et al, Neuroloy 2001]. CMBs were present in approximately one quarter to one half of symptomatic patients with CADASIL, most commonly affecting the thalami, basal ganglia, and brain stem [Viswanathan A et al, Brain 2006]. Dilated perivascular spaces are found in approximately 70%-80% of affected individuals [van Den Boom R et al, Radiology 2002; Cumurciuc R et al, Eur J Neurol 2006; Yao M et al, Cerebrovasc Dis 2014]. These MRI abnormalities have also been referred to as subcortical lacunar lesions [van Den Boom R et al, Radiology 2002].

CADASIL is typically considered a subcortical disease, but recent data suggest an involvement of the cortex early in the disease (Jouvent E et al, Brain 2008). The cortical changes, such as increase in the depth of cortical sulci, decrease in the cortical thickness and progression of global cerebral atrophy, seem to have a clinical influence (Jouvent E et al, Brain 2008; Jouvent E et al, Neurology 2011). Particularly, the alterations of global cognitive performance were demonstrated to be related to global brain atrophy, and the worsening of disability to cortical thinning and the reduction of performances in executive function, motor speed, or visuo-spatial skills were found to be significantly associated with the decrease in the sulcal depth.

The typical course of CADASIL is marked by clinical deterioration and radiologic progression with confluent white matter FLAIR changes within several years, particularly in the anterior temporal poles and external capsules. The diagnosis of CADASIL is established in a proband either by identification of a heterozygous *NOTCH3* pathogenic variant or, if molecular genetic testing is not definitive, by detection of characteristic findings by electron microscopy and immunohistochemistry of a skin biopsy. A CADASIL diagnostic screening tool has been proposed by Pescini et al [Pescini F et al, Stroke 2012]. A family history consistent with autosomal dominant inheritance supports the diagnosis but is not required [Dichgans M et al, Ann Neurol 1998], as affected family members may have been misdiagnosed [Razvi SS et

al, Acta Neurol Scand 2005]. Of note, the clinical presentation of CADASIL varies among and within families.

1.7 Therapeutic aspects in cerebral Small Vessel Diseases

In the absence of curative approaches, SVD treatment is today mainly based on general cerebrovascular disease management. Intervention for SVD is based on prevention of vascular risk factors in the adults but remains inadequately defined.

Because SVD and its various manifestations are associated with a three-time increased risk of stroke and death, early implementation of preventive measures and administration of treatments appropriate to the underlying cause are relevant. Furthermore, specific preventive and therapeutic measures to reduce the burden of functional loss caused by SVD are needed to implement the evidences in clinical practice.

Panel: Aetiopathogenic classification of cerebral small vessel diseases

Type 1: arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)
Fibrinoid necrosis
Lipohyalinosis
Microatheroma
Microaneurysms (saccular, lipohyalinotic, asymmetric fusiform, bleeding globe)
Segmental arterial disorganisation

Type 2: sporadic and hereditary cerebral amyloid angiopathy

Type 3: inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy
For example, CADASIL, CARASIL, hereditary multi-infarct dementia of the Swedish type, MELAS, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by *COL4A1* mutations

Type 4: inflammatory and immunologically mediated small vessel diseases
For example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis

Type 5: venous collagenosis

Type 6: other small vessel diseases
For example, post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer's disease

CADASIL=cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy. CARASIL=cerebral autosomal recessive arteriopathy with subcortical ischaemic strokes and leukoencephalopathy. MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

Figure 1. Aetiopathogenic classification of small vessel disease (adapted *from Pantoni et al, 2010*)

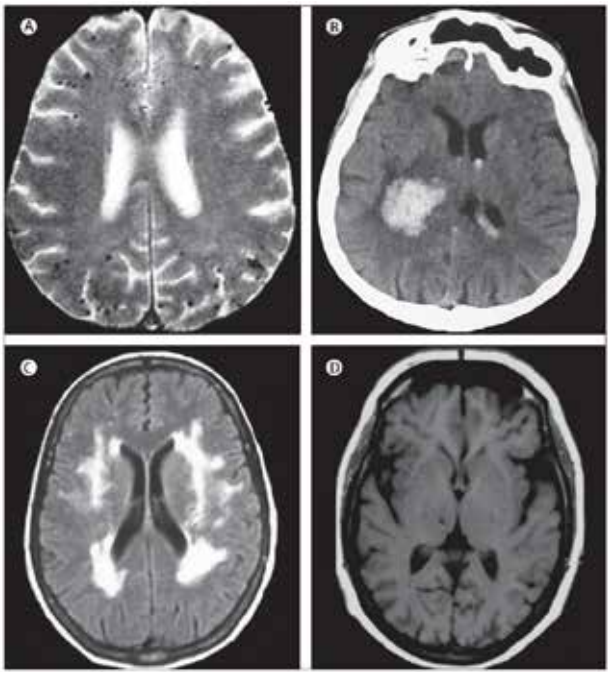

Figure 2. Neuroimaging features of small vessel disease (adapted from Pantoni et al, 2010)

(A) Multiple microbleeds (small foci of hypointensity) in the cortex of a patient with possible cerebral amyloid angiopathy as shown on a gradient-echo MRI sequence. (B) Acute haematoma on a CT scan. (C) White matter lesions or hyperintensities on MRI (FLAIR image). (D) A lacunar infarct in the right thalamus on a T1-weighted MRI. FLAIR=fl uid-attenuated inversion recovery

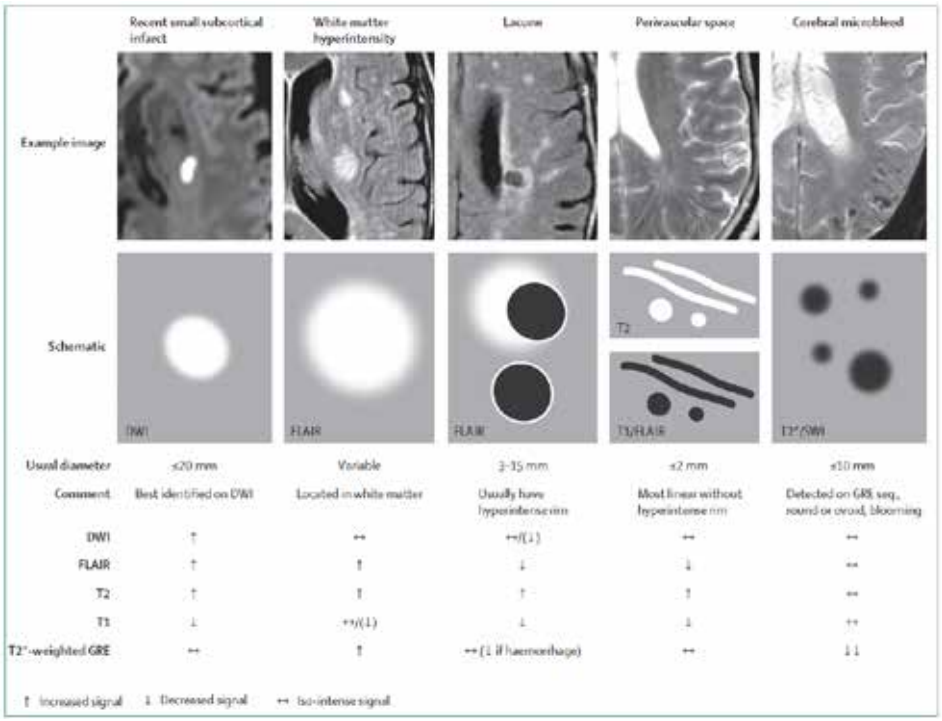

Figure 3. MRI findings for lesions related to small vessel disease

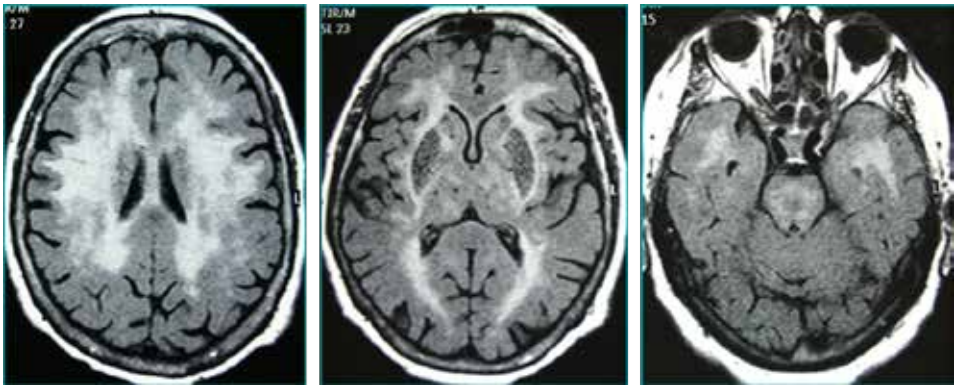

Figure 4. Periventricular and deep white matter changes, with bilateral involvement of temporal lobe and the external capsule

Characteristics	**Cerebral amyloid angiopathy**	**Sporadic non-amyloid microangiopathy (‘‘hypertensive arteriopathy’’)**
Small vessel pathology	Amyloid-β deposition and associated vasculopathy in cortical and leptomeningeal vessels	A range of different features, e.g. arteriolosclerosis, fibrinoid necrosis, mural damage, etc.
Intracerebral hemorrhage	Lobar (cortical–subcortical), cerebellar (?)	Typically deep: basal ganglia, thalamus, pons, cerebellum; sometimes lobar
Ischemic stroke	Not typically associated with lacunes Uncertain role other than affecting treatment decisions, e.g. antithrombotic drugs, thrombolysis, etc.	Lacunar syndromes
Other clinical syndromes	Transient focal neurological episodes (‘‘amyloid spells’’), cognitive impairment and dementia, inflammatory CAA	Vascular cognitive impairment and dementia
Cerebral microbleeds	Lobar	Deep
Cortical superficial siderosis	Very common: 40% in symptomatic CAA	Rare: <5%
MRI-visible perivascular spaces	Centrum semiovale (i.e. cerebral white matter)	Basal ganglia
White matter hyperintensities	Posterior predominance	No predilection for brain region

Table 1. Predominant neuropathological, clinical, and neuroimaging characteristics of the two major sporadic cerebral SVD subtypes: sporadic non-amyloid microangiopathy and cerebral amyloid angiopathy (from Charidimou A et al, 2016)

	Initial stage	Intermediate stage	Terminal stage
Cognitive performance	Mild defi cits (eg, in executive functions, attention, set-shifting abilities) appreciable only with appropriate cognitive tests	Clinically obvious cognitive deterioration not reaching the severity of dementia (corresponds to vascular subcortical mild cognitive impairment)	Dementia with associated memory defi cits (ie, subcortical vascular dementia)
Mood	Depressive symptoms	Depression	Not assessable
Sphincteric functions	From normal to urgency	Urinary incontinence episodes	Complete urinary incontinence, sometimes also faecal incontinence
Gait	From normal to mild slowing, subjective postural instability	Apraxic gait	Bedridden
Pseudo-bulbar signs	Absent (primitive reflexes on neurological examination can be present)	Dysphagia, dysarthria, pathological laughing, and crying	Severe dysphagia (PEG might be required), unintelligible speech
Daily living functions	Independence, small diffi culties in some IADL might be present	Functional impairment; notable alterations in IADL and some alterations in BADL	Complete loss of autonomy

Table 2. Types and severity of symptoms associated with cerebral small vessel disease

PEG=percutaneous endoscopic gastrostomy. IADL=instrumental activities of daily living. BADL=basic activity of daily living.

Chapter 2

Cerebral amyloid angiopathy

2. Cerebral amyloid angiopathy

Cerebral Amyloid Angiopathy (CAA) is a microangiopathy defined pathologically by progressive amyloid deposition in the walls of cortical and leptomeningeal small arteries, arterioles, and less often capillaries and veins of the brain [Viswanathan A et al, Ann Neurol 2011; Yamada M, J Stroke 2015; Yamada M et al, Prog Mol Biol Transl Sci 2012; Biffi A et al, J Clin Neurol Seoul Korea 2011], resulting in vessel dysfunction and brain parenchymal injury.

As mentioned above in the text, CAA is common in older individuals and it is a major cause of lobar symptomatic intracerebral and a key contributor to vascular cognitive impairment [Greenberg SM et al, Lancet Neurol 2014]. CAA is associated with a high prevalence of markers of SVD, including WMH and CMBs [Boulouis G et al, Semin Neurol 2016].

Similar to cerebral SVD, the term CAA encompasses not only a specific cerebrovascular pathological disorders, but also brain parenchymal lesions on neuroimaging [Charidimou A, et al. Int J Stroke 2016].

While definite diagnosis relies on pathology, a set of diagnostic clinical-radiological criteria known as the Boston criteria can reliably identify CAA in older patients with lobar ICH (Table 1) [Knudsen KA et al, Neurology 2001; Linn J et al, Neurology 2010].

Sharing pathological features with Alzheimer's Disease (AD), CAA has drawn rapidly increasing interest over the past decades [Charidimou A et al, Int J Stroke Off J Int Stroke Soc 2015], almost a century after being first recognized [Oppenheim G. Neurol Zentralbl 1909].

2.1 Epidemiology of Cerebral Amyloid Angiopathy

The prevalence of CAA is hard to evaluate in the general elderly population since a definite diagnosis still relies on pathological examination of the brain at autopsy. It is a frequent neuropathologic finding in older adults, being found at any level of severity in population-based autopsy studies in almost 70% of cases over 85 year [Tanskanen M et al, Neuropathol Appl Neurobiol 2012]. Recent results of the combined autopsy based Rush Memory and Aging Project and Religious Orders Study have

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shown a 78.9% proportion of older patients (median age 88.5 years at death) with pathological evidence of CAA [Boyle PA et al, Neurology 2015]. In the past years several findings have demonstrated a close relationship between AD and CAA, in fact CAA is more prevalent in patients who meet neuropathological criteria for AD (40-90%) [Brenowitz WD et al, Neurobiol Aging 2015]. Almost in all brains with AD is possible to find pathological sample of CAA and advanced CAA [Viswanathan A et al, Ann Neurol 2011]. This may suggest a common β amyloid–based pathogenesis for these diseases. However, despite the close molecular relationship between the 2 diseases, CAA remains a clinically distinct entity from AD.

The prevalence of CAA is of course much harder to estimate in living subjects [Boulouis G et al, Semin Neurol 2016]. In the population-based Rotterdam study, 633/4759 (13.3%) of patients over age 60 met the clinical-radiological criteria for possible or probable CAA (based on the presence of strictly lobar CMBs, according to Boston criteria) [Akoudad S et al, Circulation 2015].

2.2 Pathophysiology of Cerebral Amyloid Angiopathy

CAA is a microangiopathy, resulting from disruption of a complex balance between production, circulation and clearance of Aβ peptide in the brain [Boulouis G et al, Semin Neurol 2016]. In contrast to Aβ deposition in Alzheimer disease, a substantial proportion of Aβ in vascular deposits is the shorter Aβ40 species [Herzig MC et al, Nat. Neurosci 2004].

Although the exact source of vascular amyloid has not been elucidated, it has been suggested to be predominantly generated by neurons and subsequently deposited in the vessel wall. Impairment of one or more of the mechanism affects the balance between Aβ production, accumulation, circulation and clearance, potentially leading to Aβ deposition in the basement membranes of small vessels [Weller RO et al, Brain Pathol Zurich Switz 2008] and development of the disease. An alternative or complementary mechanism is the possible role of peripheral Aβ in the development of CAA and Aβ related brain pathology, as recently highlighted in a transgenic mouse model [Eisele YS et al, Science 2010].

Pathological examination of blood vessels in both sporadic and familial CAA show that Aβ vascular deposits are locally clustered resulting in loss of smooth muscle cells, vessel wall thickening, lumenal narrowing, concentric splitting of the vessel wall, microaneurysm formation, and perivascular microhemorrhage (Figure 5) [Vonsattel JP et al, Ann Neurol 1991].

These structural modifications may trigger secondary events, such as the release of pro-inflammatory components, oxidative stress, alteration of the blood–brain barrier permeability and cell toxicity [Hartz AMS et al, Stroke J Cereb Circ 2012].

2.3 Genetics risk factors for Cerebral Amyloid Angiopathy

The genetic abnormalities underlying sporadic CAA have not been fully elucidated, although several inherited familial forms of CAA have been described. The only specific genetic risk factor consistently identified for the sporadic disease has been the apolipoprotein E genotype as a risk for CAA-related ICH. The presence and combination of different Apolipoprotein E (ApoE) alleles (ε4, ε2 or ε3) are the best established genetic risk factor for CAA development [Verghese PB et al, Lancet Neurol 2011]. Furthermore, the presence of the ε2 or ε4 alleles of the apolipoprotein E gene is associated with an increased risk of CAA-related lobar ICH [Verghese PB et al, Lancet Neurol 2011; Biffi A et al, Lancet Neurol 2011].

It has been postulated that ApoE ε4 increases CAA severity by promoting amyloid-β deposition within small vessels, whilst ε2 by inducing structural (vasculopathic) changes in amyloid-laden vessels, ultimately leading to rupture [Boulouis G et al, Semin Neurol 2016; Biffi A et al, Lancet Neurol 2011; Montaner J. Lancet Neurol 2011]. A recent study showed that CSS and APOE ε2 are related to the hemorrhagic expression of the disease while APOE ε4 is enriched in nonhemorrhagic CAA [Charidimou A et al, Neurology 2015]. The authors emphasizes the concept of different CAA phenotypes, suggesting divergent pathophysiologic mechanisms.

2.4 Clinical manifestations in Cerebral Amyloid Angiopathy

***Transient Focal Neurological Episodes ("Amyloid Spells")*:** Transient Focal Neurological Episodes are found in around 14% of CAA patients. They are typically recurrent symptoms: stereotyped, transient episodes of 'positive' spreading sensory symptoms (paresthesia), weakness (seizure-like episodes) or visual disturbances (migrainous auras), typically brief (always <30 min), with onset spreading over seconds to minute (usually less than a few minutes) and are related to haemorrhagic components of CAA (cSS, CMBs and cSAH) in the cortical region corresponding to the spell [Charidimou A et al, Stroke J Cereb Circ 2012].

***Cognitive impairment*:** Cognitive decline is the most clinically salient manifestation of CAA. The pathophysiological mechanisms by which CAA could cause cognitive impairment have not been well established, also because the overlap with other age-related brain pathologies, that makes it hard to evaluate the specific contribution of CAA on cognitive dysfunction in the elderly [Cordonnier C et al, Brain J Neurol 2010]. CAA prevalence is consistently higher in demented versus cognitively intact patients in various population based studies, independently of the occurrence of hemorrhagic or ischemic strokes, independently of the combination of the different CAA brain insults at the microstructural level and, at a larger scale, their cumulative effect on brain connectivity [Keage HA et al, BMC Neurol 2009; Benedictus MR et al, Stroke 2015].

CAA is associated with lower performance in specific cognitive domains, in more than 1100 community-dwelling patients, such as perceptual speed or episodic

memory, independently of the effect of AD pathology [Arvanitakis Z et al, Ann Neurol 2011; Boyle PA et al, Neurology 2015]. Although not fully understood, the mechanism by which CAA affects cognitive performances is likely due to the combination of the different brain insults resulting from the above mentioned CAA pathology at the microstructural level (microinfarcts, white matter lesions, CMBs and their cumulative effect on brain connectivity [Benedictus MR et al, Stroke 2015].

2.5 Neuroimaging manifestations and Boston criteria for the diagnosis of Cerebral Amyloid Angiopathy

CAA is associated with high prevalence of characteristic neuroimaging markers of SVD, including hemorrhagic markers [CMBs, cortical superficial siderosis (cSS)] and nonhemorrhagic markers [WMH, enlarged perivascular spaces, cortical microinfarcts [Greenberg SM et al, Lancet Neurol 2014; Boulouis G et al, Semin Neurol 2016].

The Boston criteria for CAA-related ICH can be used to attribute an ICH with increasing certainty to CAA by using clinical data, imaging signs, and, if available, histopathologic findings [Knudsen KA et al, Neurology 2001]. However, these criteria are useful also for the diagnosis of CAA when other MRI hemorragic manifestations are present but not lobar ICH (Table 3). This holds true particularly for the modified version of the Boston criteria where cSS has been incorporated [Linn J et al, Neurology 2010].

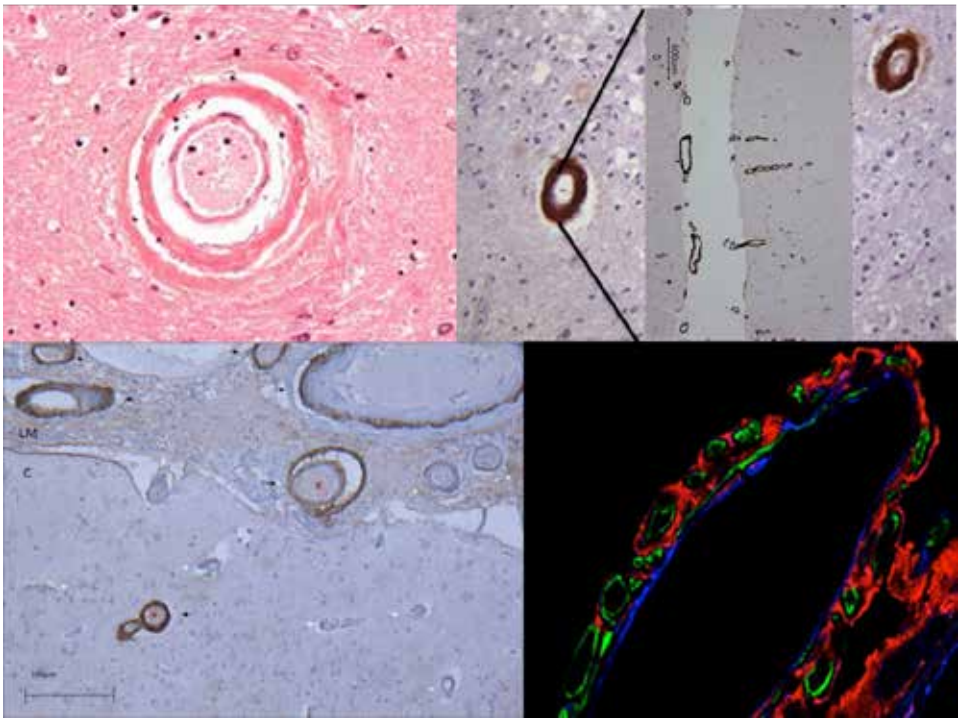

Figure 5. Key histopathological features of sporadic cerebral amyloid angiopathy.

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Brain histopathology section, eosinophilic (top left), immunostained for amyloid-β (dark brown) (top right and bottom left), electronic microscopy (bottom right). Multiple leptomeningeal small vessels of different diameters, viably affected by CAA and two cortical arterioles with amyloid deposition are seen (black arrows).

	Classic Boston Criteria	Modified Boston Criteria
Definite CAA	Full postmortem examination demonstrating: • Lobar, cortical, or corticosubcortical hemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesion	No modification
Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: • Lobar, cortical, or corticosubcortical hemorrhage • Some degree of CAA in specimen • Absence of other diagnostic lesion	No modification
Probable CAA	Clinical data and MRI or CT demonstrating: • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) • Age ≥55 years • Absence of other cause of hemorrhage	Clinical data and MRI or CT demonstrating: • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or Single lobar, cortical, or corticosubcortical hemorrhage and focal[a] or disseminated[b] superficial siderosis • Age ≥55 years • Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or corticosubcortical hemorrhage • Age ≥55 years • Absence of other cause of hemorrhage	Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or corticosubcortical hemorrhage or focal[a] or disseminated[b] superficial siderosis • Age ≥55 years • Absence of other cause of hemorrhage or superficial siderosis

Table 3. Classic and Modified Boston criteria for Diagnosis of CAA-Related Hemorrhage

CAA=Cerebral Amyloid Angiopathy

Siderosis restricted to 3 or fewer sulci

Siderosis affected at least 4 sulci

Chapter 3
Neuroimaging markers of cerebral small vessel diseases

3. Neuroimaging markers of cerebral small vessel diseases

According to the classification recently revised in an international working group position paper from the Centres of Excellence in Neurodegeneration under the acronym STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1), neuroimaging markers of SVD include lacunes, recent small subcortical infarcts, WMH, EPVS, MB, and brain atrophy [Wardlaw JM et al, Lancet Neurol 2013].

In the consensus position the hemorrhagic component of SVD is restricted to CMBs, and large ICHs are not contemplated [Wardlaw JM et al, Lancet Neurol 2013].

Moreover, a useful concept when approaching neuroimaging markers of SVD (and hence markers of pathologic consequences on the brain parenchyma), is that their pathogenic mechanisms are probably not uniform, and any given marker may be found in different types of SVD.

In this thesis, I reviewed all neuroimaging markers of SVD, including hemorrhagic markers and nonhemorrhagic markers.

3.1 Non-hemorrhagic manifestations of Small Vessel Disease

Recent small subcortical infarct: neuroimaging evidence of recent infarction in the territory of one perforating arteriole, with imaging features or clinical symptoms consistent with a lesion occurring in the previous few weeks [Wardlaw JM et al, Lancet Neurol 2013].

Lacune of presumed vascular origin: a round or ovoid, subcortical, fluid-filled cavity (signal similar to cerebrospinal fluid) of between 3 mm and about 15 mm in diameter, consistent with a previous acute small subcortical infarct or hemorrhage in the territory of one perforating arteriole [Wardlaw JM et al, Lancet Neurol 2013].

White matter hyperintensity (WMH) of presumed vascular origin: signal abnormality of variable size in the white matter that shows hyperintensity on T2-weighted images such as fluid-attenuated inversion recovery, without cavitation (signal different from cerebrospinal fluid). Lesions in the subcortical gray matter or brainstem are not included in this category unless explicitly stated [Wardlaw JM et al, Lancet Neurol 2013].

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WMH is correlated also with CAA. WMH have been showed to be more severe in CAA patients than in healthy older adults [Reijmer YD et al, J Int Soc Cereb Blood Flow Metab 2015]. Studies using a visual scale or quantitative measure of antero-posterior distribution suggested that patients with CAA may have a higher prevalence of occipital-predominant WMH [Zhu Y-C et al, J Neurol 2012; Thanprasertsuk S et al, Neurology 2014]. Further, the presence of specific visual patterns of WMH such as multiple (typically >10) subcortical spots has been proposed as a novel discriminating marker of CAA-related versus hypertension related deep ICHs [Charidimou A et al, Neurology 2016]. WMH progression appears to be a reasonable biomarker to measure a clinically meaningful aspect of CAA-related brain injury.

Perivascular spaces (also termed Virchow-Robin spaces): fluid-filled spaces that follow the typical course of a vessel as it goes through gray or white matter. The spaces have signal intensity similar to cerebrospinal fluid on all sequences. Because they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel [Wardlaw JM et al, Lancet Neurol 2013].

Perivascular spaces visible on MRI represent another emerging candidate non-hemorrhagic biomarker of CAA [Wardlaw JM et al, Lancet Neurol 2013]. The topography of perivascular spaces appears to differ according to the underlying arteriopathy, with CAA being preferentially associated with high burden of perivascular spaces in the centrum semiovale. [Charidimou A et al, J Neurol Neurosurg Psychiatry 2013]. These spaces were recently shown to be associated with Aβ burden on basis of PET [Ramirez J et al, J Alzheimers Dis JAD 2015], with a potential role in the failure of protein elimination implicated in disease pathogenesis. The interstitial fluid drainage impairment within the perivascular spaces is caused by cumulative leptomeningeal and superficial cortical vascular amyloid-β deposition [Carare RO et al, Neuropathol Appl Neurobiol 2013; Martinez-Ramirez S et al, Neurology 2013].

Cerebral Microinfarcts: tiny infarctions (in the submilimeter to millimeter range), not visible on conventional MR imaging, and only visible on microscopic tissue examination. They are not included in the STRIVE Criteria.

Cerebral Microinfarcts (CMIs) are more common in CAA patients compared to non CAA cases [Soontornniyomkij V et al, Brain Pathol Zurich Switz 2010]. DWI lesions, due to cytotoxic edema accompanying CMIs, are detected in approximately 15% of patients with CAA [Auriel E et al, Neurology 2012; Kimberly WT et al, Neurology 2009] and cortical lesions suggestive of chronic CMIs in up to 100% of CAA patients using ultra-high field strength MRI [van Veluw SJ et al, J Cereb Blood Flow Metab 2014]. These lesions have been found to associate with other SVD markers (WMH, CMBs), but not with conventional vascular risk factors [Auriel E et al, Neurology 2014]. CMIs have a substantial impact on cognitive function and independently contribute to brain atrophy [Launer LJ et al, Ann Neurol 2011; van Veluw SJ et al, Alzheimers Dement J Alzheimers Assoc 2015].

Brain atrophy: reduced brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction; thus, infarction is not included in this measure unless explicitly stated.

The inclusion of brain atrophy as another imaging manifestation of SVD represents a significant change in thinking in the field and highlights the cross-talk between SVD, neurodegeneration, and cognitive impairment [Muller M et al, Neurobiol Aging 2011; Appelman AP et al, Cerebrovasc Dis 2009]. In fact, SVD frequently coexists with neurodegenerative disease (especially Alzheimer's disease), and can exacerbate cognitive deficits, physical disabilities, and other symptoms of neurodegeneration [Wardlaw JM et al2, Lancet Neurol 2013].

3.2 Hemorrhagic manifestations of Small Vessel Disease

Intracerebral hemorrhage (ICH): The spontaneous ICH affecting the lobar regions is the most salient manifestation of CAA, in contrast with deep hemorrhages that are typically associated with hypertensive arteriopathy [Jellinger KA. Ann Neurol 2006].
ICH accounts for approximately 10%–20% of strokes and its clinical importance derives from its high frequency and 30-day mortality, which is close to 50% [O'Donnell MJ et al, The Lancet 2010]. Primary ICH, accounting for 78 to 88 % of cases of ICH, originates from the spontaneous rupture of small vessels [Qureshi AI et al, N Engl J Med 2001]. It has been suggested that the different locations of the hematoma, is related with a different underlying SVD form.
The lobar predominance of CAA related ICHs is driven by the underlying amyloid deposition pattern that favors cortical vessels over deep gray/white matter or the brainstem. CAA related ICHs preferentially affect cortical-subcortical (lobar) regions and have a tendency to cluster in the posterior cortical regions (especially the occipital and temporal lobes), less commonly the cerebellum and rarely deep or brainstem structures [Jellinger KA. Ann Neurol 2006]. CAA related ICH accounts for at least 5-20% of all spontaneous ICH. There is a high risk of recurrence, with rate of about 10% per year in elderly cohorts. Subsequent ICH (which characteristically may cluster over a short period of time (days to weeks) is often much more severe.

Cerebral Microbleeds (CMBs): small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects.
CMBs are one of the common diagnostic markers of the Boston Criteria for CAA (Table 1, pg. 26). Their imaging signature on MRI arises from subclinical oozing of blood products outside the lumen of CAA affected vessels [Shoamanesh A et al, Cerebrovasc Dis Basel Switz 2011]. The subsequent degradation of these components leads to local deposition of hemosiderin, contained within macrophages, whose paramagnetic properties induce a local inhomogeneity in the static magnetic field. As a consequence, hypo-intensity on T2* (Gradient Echo, GRE) or susceptibility weighted (SW) sequences exceeds the physical size of the deposit (*blooming effect*) to an extent that varies with field strength, sequence, and processing method [Boulouis G et al, Semin Neurol 2016]. CMB prevalence is 15.3%-18.7% in population based studies, but has been reported in ranges as wide as 47-80% in ICH patients, 18-71% for ischemic stroke patients and 17-46% for cognitive decline patients (depending on the

imaging parameters) [Martinez-Ramirez S et al, Alzheimers Res Ther 2014]. Also CAA-related CMBs, are typically of lobar distribution with predilection for posterior brain regions. When strictly lobar, they strongly predict CAA pathology, even in patients without ICH method [Boulouis G et al, Semin Neurol 2016]. CMBs appear to be associated with increased risk of both ischemic and hemorrhagic strokes in the general population [Akoudad S et al, Circulation 2015] and they represent a biomarker for disease progression [Akoudad S et al, Cerebrovasc Dis Basel Switz 2014]. Although the exact mechanism of CMBs occurrence in CAA is not well known, they appear to be spatially correlated with areas of amyloid deposition in Positron Emission Tomography studies, suggesting a close relationship to sites of highest CAA severity [Gurol ME et al, Neurology 2012].

Cortical Superficial Siderosis **(cSS)**: a distinct pattern of blood-breakdown product deposition limited to cortical sulci over the convexities of the cerebral hemispheres, resulting in a curvilinear hypointensity pattern following the gyral cortical surface on GRE/SW sequences [Charidimou A et al, Brain J Neurol 2015]. cSS is strongly associated with CAA in the elderly, being found in around 40-60% of cases depending on MRI sequences.

For this reason, cSS and subarachnoid hemosiderosis were proposed as another key hemorrhagic signature of CAA and potentially useful new MR imaging criteria to facilitate the noninvasive diagnosis of CAA [Charidimou A et al, Brain J Neurol 2015].

Even if the exact pathophysiological mechanisms underlying cSS are not yet fully known, observational data indicate that cSS most likely represents blood residues from acute convexity subarachnoid hemorrhages due to rupture of CAA-laden cortical or leptomeningeal vessels [Charidimou A et al, Brain J Neurol 2015]. Depending on the location in the brain these events can be either clinically silent or symptomatic (including transient focal neurological episode, especially if eloquent areas, such as the central sulcus, are affected) [Greenberg SM et al, Neurology 1993].

In a European multicenter cohort of probable or possible CAA, cSS was an independent predictor of time until ICH [Linn J et al, Neurology 2010; Charidimou A et al, Neurology 2013].

3.3 Additional Imaging Modalities and Diffusion Tensor Imaging

Other imaging modalities such as diffusion tensor imaging (DTI) have been used to study cerebral microstructural damage in SVD,

Important changes of diffusion tensor imaging (DTI) metrics (mean diffusivity – MD and fractional anisotropy –FA) have been reported both inside and outside areas of increased signal on T2-weighted or FLAIR images in various white-matter disorders [Molko N et al, Stroke 2001; Kin T et al, AJNR Am J Neuroradiol 2006; Nusbaum AO, AJNR Am J Neuroradiol 2001; Rovaris M et al, Arch Neurol 2002; Tessa C et al, AJNR Am J Neuroradiol 2008; Vrenken H et al, J Magn Reson Imaging 2006].

DTI histogram metrics are correlated with clinical parameters in cerebral SVD. In conditions with diffuse tissue lesions such as hypertension related SVD, a quantitative approach based on whole brain histograms of diffusion was found to reflect the overall disease severity and various DTI histogram parameters (mean value, median value, peak location, peak height, kurtosis, skewness) have been reported to correlate with clinical scores both in cross-sectional and longitudinal studies [Chabriat H et al, Stroke 1999; Stroke 1999 et al, J Neurol Neurosurg Psychiatry 2010; Chua TC et al, Curr Opin Neurol 2008; Della Nave R et al, AJNR Am J Neuroradiol 2007; Mascalchi M et al, Neurology 2002; Nitkunan A et al, Stroke 2008; Nitkunan A et al, Magn Reson Med 2008; Nusbaum AO et al, Neurology 2000; O'Sullivan M et al, Neurology 2004; Rovaris M et al, Radiology 2003; Schmidt R et al, Stroke 2010].

Some DTI metrics were even found more sensitive than clinical scales in detecting the disease

progression over time [Chabriat H et al, Stroke 1999; Nitkunan A et al, Stroke 2008; Molko N et al, Stroke 2002]. In CADASIL, for example, DTI may be abnormal due to subcortical white matter damage [Jang SH et al, BMC Neuro 2015]. In CADASIL, mean value of MD histograms obtained over the whole brain has been previously found to increase before any significant clinical change duringfollow up and to predict disease progression [Molko N et al, Stroke 2002; Holtmannspotter M et al, Stroke 2005].

Chapter 4
Cerebral small vessel diseases and cognition

Cerebral SVD is one of the most important contributors to cognitive impairment in the elderly, contributing to up to 45% of dementias [Bryan RN et al, Radiology 1997; Demchuk AM et al, Cerebrovasc Dis 2008]. The substantial cognitive components of microvascular damage in the brain have been probably overshadowed by neurodegenerative diseases (e.g. Alzheimer's disease).

At present SVD is considered to be among the main causes of vascular cognitive impairment. Vascular cognitive impairment (VCI) itself is a broad term under which all forms of vascular disease that possibly lead to cognitive consequences are grouped [O'Brien JT et al, Lancet Neurol 2003]. Definite classification and criteria for this type of cognitive impairment is not available. This is due to several reasons, of which the heterogeneity of the pathological and clinical aspects of vascular cognitive impairment and the different underlying pathogenic mechanisms and neuroimaging correlates are among the most important [Pantoni L et al, Lancet Neurol 2010].

VCI associated with SVD has more recently received particular attention. It is thought to be a progressive condition from normal cognitive status to frank dementia with progressive course [Pantoni L et al, Cerebrovasc Dis 2009], by contrast with post-stroke dementia, and therefore, it might benefit from prevention [Pantoni L et al, Lancet Neurol 2010] (Figure 6).

VCI is thought to be reasonably homogeneous in clinical and neuroimaging terms [Erkinjuntti T et al, J Neural Transm Suppl 2000; Román GC et al, Lancet Neurol 2002] and, therefore, suitable as a target for implementing studies and therapeutic trials [Inzitari D et al, Ann NY Acad Sci 2000].

4.1 Dementia and vascular cognitive impairment

Dementia is a significant and growing public health problem. Clinic-based and autopsy-based studies show that vascular dementia (VaD) is the second most common cause of dementia, after Alzheimer's disease.

The prevalence and incidence of vascular dementia have been measured in a number of population-based studies conducted in specific geographic regions. Most epidemiological studies showed that VaD and VCI are highly prevalent diseases. In the Italian Longitudinal Study on Aging, VaD accounted for 27% of all incident dementia

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cases in subjects aged 65–84 years, with an incidence rate of 3.3 per 1,000 person-years (6.5in Alzheimer's disease) [Di Carlo A et al, J Am Geriatr Soc 2002].
The frequency of poststroke dementia is about 28% 1.5 years after stroke in patients aged > 70 years, with a relative risk of 4.7 in comparison with controls [Hénon H et al, Cerebrovasc Dis 2006]. The relevance of the problem would be even higher if VCI patients who do not reach the level of dementia were also considered [Pantoni L et al, Cerebrovasc Dis 2009]. Although up to 45% of cases are primarily or partly due to cerebrovascular disease, little is known of these mechanisms or treatments because most dementia research still focuses on pure AD.

The spectrum of dementia due to cerebrovascular diseases is heterogeneous from clinical and pathophysiological aspects [Pantoni L et al, Cerebrovasc Dis 2009] and encompasses: *Subcortical VaD* (caused by SVD), *Multi-infarct dementia, Single strategic infarct dementia*, *Mixed cortical and subcortical damage*, etc.

These various forms have different clinical, neuroimaging, and pathological features [Pantoni L et al, Cerebrovasc Dis 2009]. The most common vascular contributor to dementia is cerebral SVD, a condition that affects perforating vessels and that is already discussed above in the text.

The concept of VCI was introduced in 1993 by Hachinski and Bowler [Hachinski VC et al, Neurology 1993] in reaction to the publication of the NINDS-AIREN criteria, covering a spectrum of cognitive impairment after stroke to cognitive impairment in association with otherwise asymptomatic cerebrovascular disease [Román GC et al, Neurology 1993]. These authors criticized the use of the term VaD, which was considered not appropriate for describing a group of heterogeneous conditions like those affecting cognition as a result of cerebrovascular insults. They stressed the relevance of the concept of 'brain-at-risk', a stage where patients with CVDs and vascular risk factors have no cognitive decline but are at increased risk to which preventive strategies should be applied.

The focus of diagnostic criteria for VaD/VCI, was on the prodromal stages of AD, a condition in which memory deficits are the most prominent disturbances [Dubois B et al, Lancet Neurol 2010 ; Chertkow H, CMAJ 2008].
In VaD/VCI patients other cognitive domains, such as executive functions, attention, motor performance and information processing speed, are mainly affected [Hachinski V et al, Stroke 2006; Sachdev PS et al, Med J Aust 1999; Lamar M et al, Behav Neurol 2010; Pantoni L et al, Lancet Neurol 2010]. Executive functions are defined as 'a set of cognitive skills that are responsible for the planning, initiation, sequencing and monitoring of complex goal-directed behaviour' [Royall DR et al, J Neuropsychiatry Clin Neurosci 2002]. Later, new proposals have been made to create criteria suited for specific VaD subtypes such as subcortical VaD where cognitive together with other clinical and neuroimaging features of the disease are better reflected [Erkinjuntti T et al, J Neural Transm Suppl 2000].

The clinical spectrum of VCI ranges from MCI to dementia [Gauthier S et al, Lancet 2006] and a recent proposal of diagnostic criteria for vascular MCI highlights the need of an objective evidence of decline using validated measures of cognitive functions and giving equal importance to several cognitive domains [Sachdev P et al, Alzheimer Dis Assoc Disord 2014].

4.2 The concept of Mild Cognitive Impairment

Patients with significant vascular lesions in the brain have cognitive deficits, but cannot be considered demented as they are not functionally dependent**.** Similarly to AD, predementia stages of VaD exist [Pantoni L et al, Cerebrovasc Dis 2009]. This is true small-vessel disease cognitive impairment, where the increase in white matter changes and the accumulation of lacunar infarcts may lead to a progressive cognitive decline.

For example, small infarcts detected on MRI are common in the general population [Longstreth WT Jr et al, Arch Neurol 1998]. These infarcts often do not cause clinical acute events and are detected only withMRI scan (so-called 'silent infarcts'), they are associated with subtle cognitive dysfunction [Longstreth WT Jr et al, Arch Neurol 1998] and with an increased risk of developing dementia at follow-up [Vermeer SE et al, N Engl J Med 2003; Vermeer SE et al, Lancet Neurol 2007].

Mild cognitive impairment (MCI) is an intermediate state between normal cognitive status and dementia; it is considered a risk factor for dementia and has become a focus of several clinical and intervention trials. MCI is defined as an abnormal condition defined as an objective cognitive decline (greater than expected for an individual's age and education level) with maintenance of intact global cognitive functioning and autonomy and, therefore, not severe enough to fit the criteria for dementia [Petersen RC et al, Arch Neurol 1999; Dubois B et al, Lancet Neurol 2010]. According to Winblad et al, recommendations for MCI diagnostic criteria include four clinical subtypes: amnestic MCI (single or multiple domain) and nonamnestic MCI (single or multiple domain) [Winblad B et al, J Intern Med 2004]. It has been hypothesized that different MCI subtypes subtend different etiologies [Petersen RC et al, CNS Spectr 2008; Gauthier S et al, Lancet 2006]; amnestic MCI, either single or multiple domain, was considered to have a degenerative etiology, whereas multiple domain MCI, either amnestic or not, a vascular etiology.

Although application of different diagnostic criteria for MCI might affect its prevalence and progression estimates [Stephan BC et al, Alzheimers Res Ther 2009; Matthews FE et al, J Am Geriatr Soc 2008], the frequency of MCI in population-based studies is more than double that of dementia [Panza F et al, Am J Geriatr Psychiatry 2005; Ward A et al, Alzheimers Dement 2012], ranging from 3% to 19% in adults over 65 years [Ward A et al, Alzheimers Dement 2012]. The lack of a universal operational definition of MCI resulted in divergent outcomes in terms of prevalence and progression rates across studies [Salvadori E et al, Alzheimers Dement 2015].

As well as for VaD, the most common cause of MCI of probable vascular origin is SVD, in which lacunar infarcts and white matter changes (WMC) accumulation determines a gradual progression of cognitive impairment, from mild to more severe stages [Pantoni L et al, Neuroepidemiology 2005]. Vascular MCI is theoretically an important MCI subtype to identify as mounting evidence suggests that preventive measures may be undertaken to treat vascular risk factors associated with cognitive deficits [Gorelick PB et al, Stroke 2011].

4.3 Small Vessel Disease neuroimaging markers and cognitive decline

White matter lesions and lacunar infarcts are considered an important substrate for cognitive impairment [Pantoni L et al, Lancet Neurol 2010]. In longitudinal studies white matter lesions have been associated with cognitive decline and dementia in different settings, from hospital-based to population settings [Pantoni L et al, Curr Opin Neurol 2007]. In the Rotterdam scan study, patients with white matter lesions as detected by MRI had an increased risk of developing dementia after a follow-up of 5 years (hazard ratio 1.67, 95% CI 1.25–2.24) [Prins ND et al, Arch Neurol 2004] .These lesions are associated with specific cognitive deficits such as psychomotor retardation, deficits of attention, planning, and set-shifting, and dysexecutive syndrome [Gunning-Dixon FM et al, Neuropsychology 2000; Ferro JM et al, J Neurol Sci 2002]. Moreover, there is a correlation between progression of white matter lesion load and decline in cognitive performance [Schmidt R et al, Stroke 2007].

Lacunar infarcts, especially if strategically located, are associated with cognitive decline and dementia onset since the acute phase of stroke and during follow-up [Tatemichi TK et al, Neurology 1992; Miyao S et al, Stroke 1992; Samuelsson M et al, Stroke 1996; Yamamoto Y et al, Stroke 2002]. Cognitive decline is also associated with silent lacunar infarcts [Vermeer SE et al, N Engl J Med 2003].

Recently CMBs are considered another relevant contributors to cognitive impairment in elderly subjects with SVD. CMBs are associated with executive and speed and attention dysfunction [Charidimou A et al, Neuroradiology 2013; Wu R et al, Med Sci Monit 2014].

It is possible to hypothesize that strategies able to prevent the occurrence (or recurrence) of lacunar infarcts or CMBs and the progression of white matter lesions may be effective in preventing onset (or progression) of cognitive decline in the elderly.

Finally, cerebrovascular disease and neurodegenerative changes are aging-related phenomena and may coexist and both may contribute to cognitive decline in the elderly patients [Pantoni L et al, Cerebrovasc Dis 2009].

In a large sample of over 600 nondisabled aged patients enrolled in the LADIS (Leukoaraiosis and Disability) Study, the presence of both medial temporal lobe atrophy and severe white matter lesions was individually associated with lower scores on the Mini-Mental State Examination. Interestingly, the contemporaneous presence of both lesions was associated with an even lower score [van der Flier WM et al, J Neurol Neurosurg Psychiatry 2005]. These data underline that vascular lesions may have detrimental effects on cognitive performances that are additive to those caused by degenerative mechanisms [Pantoni L et al, Cerebrovasc Dis 2009].

It is a common observation that some patients with pre-existing MCI with a progressive course and without previous cerebrovascular events decline with a steeper course after a stroke [Pantoni L et al, Cerebrovasc Dis 2009]. VaD reflects the global effects of vascular disease on the brain.

In this thesis, we focus on key aspects in the field of SVD: neuroimaging and cognitive perspectives, with particular attention to the hemorrhagic marker of SVD, global SVD-related brain injury on MRI, and microstructural changes evaluated on

DTI. Consequently, the definition criteria of cognitive impairment of probable vascular origin and the consequences of SVD brain parenchyma damages on cognitive features in view of a possible treatment strategy were analyzed.

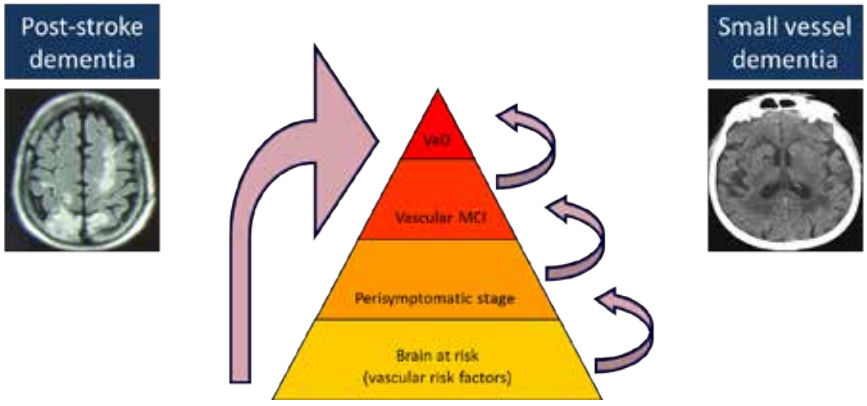

Figure 6. The pyramid concept of VCI (adapted *from Pantoni et al, 2009*).

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Part 2

Experimental section

Objectives and Hypothesis of the research

Objectives: We investigated clinical (neuroimaging and cognitive) biomarkers in the SVD. In particular, we investigated the global burden of SVD neuroimaging markers, with specific attention to subclinical SVD hemorrhagic manifestation and microstructural changes, and their consequences on cognitive features in patients with SVD. After examination of the definition of cognitive impairment of probable vascular origin, a possible treatment strategy were analyzed in detail.

Hypothesis: Our hypothesis is that some specific and subclinical biomarker of SVD, also globally considered, can contribute negatively on manifestations of cerebral SVD, including cognition. Moreover, an evaluation of microstructural changes with modern neuroimaging methods may capture the cumulative effects of microangiopathy burden in patients affected by sporadic SVD.

Consequently, we advance the hypothesis that, considering well-established cognitive definition criteria, a cognitive rehabilitation, primarily directed to achieve functional changes, may reinforce or re-establish previously learned patterns of behavior, or establish new patterns of cognitive activity or compensatory mechanisms. Cognitive rehabilitation could represent a promising approach to prevent VaD or to improve cognitive performances in patients with cerebral SVD.

We tested our hypothesis through a series of analysis from our five study:

- *VMCI-Tuscany: Rischio e determinanti di demenza in pazienti con deterioramento cognitivo lieve ed alterazioni vascolari sottocorticali dell'encefalo. Studio di marker clinici, di neuroimmagini e biologici (Regional Programme for Health Research 2009)*: longitudinal, multicenter, observational study (carried out in the Tuscany region of Italy) investigating predictors of transition from vascular MCI to dementia in a cohort of SVD patients. PI: Domenico Inzitari.

- *Petechial cohort Study*: cross-sectional analysis of data from an ongoing single-centre longitudinal cohort on the natural history of CAA at Massachusetts General Hospital recruited from an outpatient stroke clinic setting. PI: Anand Viswanathan, Steven M. Greenberg.

- *Investigations on MCI: recruitment of a control cohort with neuroimaging, morphological and functional analyses, eye movement and biochemical, molecular and genetic studies Study* [Health Ministry, Finalized Research 2008]: italian, multicenter,

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observational study with the purpose of recruitment of a control cohort with neuroimaging, morphological and functional analyses, and aimed to compare MCI of probable different origin. PI: Domenico Inzitari

➢ *VAScular-COGnitive observational Study*: cross-sectional analysis of data from an ongoing single-center longitudinal cohort on the natural history of SVD at VAS-COG outpatient clinic of SOD Stroke Unit e Neurologia Careggi University Hospital, Florence. PI: Leonardo Pantoni.

➢ *The rehabilitation of attention in patients with mild cognitive impairment and brain subcortical vascular changes using the attention process training-II* [Italian Ministry of Health under Grant Aimed Research Call 2010]: 3-year prospective, single-blinded, randomized clinical trial testing the effect of cognitive rehabilitation in patients with mild cognitive impairment and small vessel disease. PI: Leonardo Pantoni.

Seven analyses will be presented in this thesis divided in 3 conceptually different parts:

- ✓ Studies investigating specific and subclinical neuroimaging features of SVD
- ✓ Studies investigating SVD and relation with cognitive features
- ✓ Study investigating the rehabilitative issues in SVD

- ✓ Three studies investigated specific neuroimaging features in cerebral SVD:

  - The burden and location of CMBs and their association with cognitive performances in a cohort of SVD patients with MCI
  - The biological and clinical significance of a composite score designed to capture the total brain MRI SVD burden in CAA
  - The association between increased burden of SVD injury on MRI and greater connectivity impairments in structural network efficiency in patients with CAA

- ✓ Three studies investigated specific cognitive features and relation with SVD:

  - The evaluation of some clinical, cognitive and imaging features discriminating degenerative MCI on the basis of diagnostic criteria for vascular MCI
  - The assessment of agreement between pragmatic and conventional diagnoses in terms of etiologic subtyping of MCI
  - The visual processing impairment in CAA patients for the posterior cortical predilection of the disease

- ✓ One study investigated rehabilitative issues in SVD:

  - The evaluation of the effect of cognitive rehabilitation in patients with MCI and SVD and alterations in executive/attentional processing.

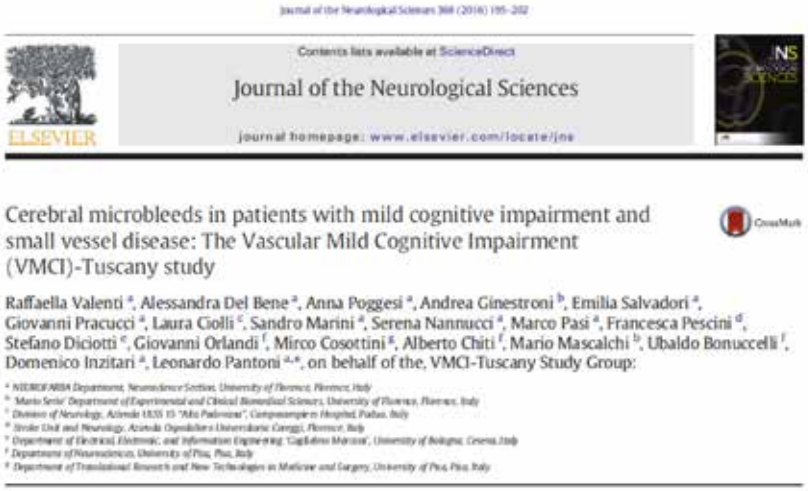
  This topic received a specific separate section in this thesis.

Chapter 1
Cerebral Small Vessel Disease and neuroimaging features

2.1.1 Cerebral microbleeds in patients with mild cognitive impairment and small vessel disease: the Vascular Mild Cognitive Impairment (VMCI)-Tuscany Study

Note: the present study was conducted as part of the Multicenter study "VMCI-Tuscany: Rischio e determinanti di demenza in pazienti con deterioramento cognitivo lieve ed alterazioni vascolari sottocorticali dell'encefalo. Studio di marker clinici, di neuroimmagini e biologici" (Regional Programme for Health Research 2009). The VMCI-Tuscany Study is a longitudinal, multicenter, observational study aimed at evaluating predictors of transition from vascular MCI to dementia. In the study, coordinated by the Neuroscience Section of NEUROFARBA Department, University of Florence, were enrolled 214 patients and were investigated the role of a large set of clinical, cognitive, neuroimaging, and biological markers of SVD as independent predictors of the transition from MCI to dementia in a cohort of patients with SVD.

During this study, I have been participated in the eligible patients' screening phase, enrollment and carried out the acquisition of clinical and neuropsychological data, and managing and data analysis.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Cerebral microbleeds in patients with mild cognitive impairment and small vessel disease: The Vascular Mild Cognitive Impairment (VMCI)-Tuscany study

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Abstract

Background and objectives: Cerebral microbleeds (CMBs) are a neuroimaging expression of small vessel disease (SVD). We investigated in a cohort of SVD patients with mild cognitive impairment (MCI): 1) the reliability of the Microbleed Anatomical Rating Scale (MARS); 2) the burden and location of CMBs and their association with cognitive performances, independent of other clinical and neuroimaging features.

Methods: Patients underwent clinical, neuropsychological (4 cognitive domains), and MRI assessments. CMBs were assessed by three raters.

Results: Out of the 152 patients (57.2% males; mean age±SD: 75.5±6.7 years) with gradient-echo (GRE) sequences, 41 (27%) had at least one CMB. Inter-rater agreement for number and location of CMBs ranged from good to very good [multi-rater Fleiss kappa (95%CI): 0.70-0.95]. Lacunar infarcts and some clinical variables (e.g., hypertension and physical activity) were associated with CMBs in specific regions. Total number of CMBs, and of those in deep and lobar regions, were associated with attention/executive and fluency domains.

Discussion: MARS is a reliable instrument to assess CMBs in SVD patients with MCI. Nearly one third of these patients had at least one CMB. Total CMBs burden was associated with attention/executive functions and fluency domains impairment, lacunar infarcts, and with some potentially modifiable risk factors.

Introduction

Cerebral microbleeds (CMBs) are one of the neuroimaging markers of small vessel disease (SVD) [Pantoni L et al, Lancet Neurol 2010; Wardlaw JM et al, Lancet Neurol 2013]. CMBs are small chronic brain hemorrhages, most likely caused by structural abnormalities of the cerebral small vessels [Greenberg SM et al, Lancet Neurol 2009]. They are radiologically defined lesions on magnetic resonance imaging (MRI) gradient-echo (GRE) T2* weighted or susceptibility-weighted images (SWI), corresponding histopathologically to focal hemosiderin depositions surrounding small vessels [Greenberg SM et al, Lancet Neurol 2009; Schrag M et al, J Stroke Cerebrovasc Dis 2014]. In recent years, the use of the above-mentioned MRI sequences has led to an increased interest in CMBs, which are now increasingly recognized in different populations, might have a role in the clinical course of SVD and potentially prognostic and therapeutic consequences [Charidimou A et al, Neuroradiology 2013; Shoamanesh A et al, Cerebrovasc Dis 2011; Fazekas F et al, AJNR Am J Neuroradiol 1999].

CMBs are frequently observed in community dwelling elderly subjects and their prevalence gradually increases with age [Poels MM et al, Stroke 2010; Sveinbjornsdottir A et al, J Neurol Neurosurg Psychiatry 2008], being around 36% in patients >80 years [Poels MM et al, Stroke 2010]. This prevalence further upsurges in the setting of stroke [Cordonnier C et al, Brain 2007; Werring DJ, Neurology 2005; Kato H et al, Stroke 2002; Yamada S, Eur J Neurol 2012] and in some conditions,

such as cognitive impairment [Cordonnier C, Brain 2011], while patients with no risk factors or known vascular disease may be at lower risk of CMBs [Chowdhury MH et al, J Stroke Cerebrovasc Dis 2011]. The reported prevalence of CMBs in patients affected by mild cognitive impairment (MCI) ranges from 20 to 44%, also according to different MRI sequences used [Yates PA, Front Neurol 2014]. The prevalence is even higher in progressive MCI patients compared to stable MCI [Haller S et al, Radiology 2010]. Evidence from both clinic-pathological correlations and large epidemiological studies supports differing topographic patterns of CMBs distribution according to their etiology. CMBs in deep or infratentorial regions are hypothesized to be associated with hypertensive microangiopathy, while those in lobar regions may be due to cerebral amyloid angiopathy [Greenberg SM et al, Lancet Neurol 2009; Vernooij MW et al, Neurology 2008; Park JH, Ann Neurol 2013; Chiang GC, AJNR Am J Neuroradiol 2015]. Originally thought to be asymptomatic markers of SVD, CMBs have been now considered as relevant contributors to cognitive impairment, both in general elderly populations [Charidimou A et al, J Neurol Sci 2012; Poels MM, Neurology 2012; Yakushiji Y et al, Stroke 2008] and in patients affected by SVD [Werring DJ, Brain 2004; Patel B et al, Stroke 2013], although their specific impact on cognition differs in different cohorts [Charidimou A et al, J Neurol Sci 2012]. Furthermore, the topographic distribution of CMBs may have specific associations with certain cognitive domains [Wu R et al, Med Sci Monit 2014; Martinez-Ramirez S et al, Alzheimers Res Ther 2014].

The reliable rating of CMBs presence, burden (number) and anatomical distribution in the brain using standardized rating scales is an essential prerequisite to investigate their clinical significance. This was also recently recommended in the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) position paper [Wardlaw JM et al, Lancet Neurol 2013], according to which these lesions have to be recorded in terms of number and distribution applying one of the two available standardized visual scores [Wardlaw JM et al, Lancet Neurol 2013; Greenberg SM et al, Lancet Neurol 2009; Gregoire SM et al, Neurology 2009; Cordonnier C et al, Stroke 2009]. The Microbleed Anatomical Rating Scale (MARS) has reported good feasibility [Gregoire SM et al, Neurology 2009; de Laat KF et al, Stroke 2011].

So far, few studies exist that are focused on CMBs and their clinical significance in patients affected by MCI and SVD. The aims of our study were to evaluate in the Vascular Mild Cognitive Impairment (VMCI)-Tuscany Study cohort: 1) the feasibility and reliability of MARS; 2) the presence, number, topographic distribution of CMBs and their possible associations with cognitive performances, independent of their possible associations with other clinical and neuroimaging features.

Methods

Participants

The VMCI-Tuscany Study is a multicenter, prospective, observational study carried out in the Tuscany region, Italy. The study was designed to investigate the effect of a large set of clinical, neuroimaging, and biological markers of SVD in predicting the transition from MCI to dementia [Poggesi A et al, Int J Alzheimers Dis 2012]. The rationale and methodology of VMCI-Tuscany Study have been extensively reported elsewhere [Poggesi A et al, Int J Alzheimers Dis 2012]. In summary, to be included, patients had to be classified as affected by MCI with SVD according to the following criteria: (1) MCI according to Winblad et al. criteria [Winblad B et al, J Intern Med 2004], and (2) moderate to severe degrees of white matter hyperintensities (WMH) on MRI (i.e., score 2 or 3 on the modified Fazekas scale [Poggesi A et al, Int J Alzheimers Dis 2012; Pantoni L et al, Neuroepidemiology 2005]). The local ethics committee approved the study and informed written consent was obtained from all participants. At baseline, each enrolled patient underwent an extensive clinical and neuropsychological assessment and an MRI examination [Poggesi A et al, Int J Alzheimers Dis 2012]. All data collected in each center were entered into a dedicated online database.

MRI assessment

Patients were examined on a 1.5 T (Intera, Philips Medical System, Best, The Netherlands) with 33mT/m gradients strength and a 6-channel head coil technology (Florence center) and a 3 T (Discovery MR750, General Electric Healthcare, Milwaukee) scanner with 50mT/m gradients strength and a 8-channel head coil (Pisa center). Conventional MRI protocol included a sagittal T1-weighted sequence, an axial FLAIR sequence and axial diffusion weighted sequences [Poggesi A et al, Int J Alzheimers Dis 2012].

Visual assessment of neuroimaging was centrally performed by an experienced neurologist blinded to all clinical details and included: 1) WMH on FLAIR sequences according to the modified Fazekas scale; 2) lacunar infarcts, classified as absent, few (1-3), and many (>3); 3) global cortical atrophy (GCA) according to the visual scale of Pasquier et al, in which scores 0–3 represent absent, mild, moderate, and severe cortical atrophy, respectively [Pasquier F et al, Eur Neurol 1996]; 4) medial temporal lobe atrophy (MTA) assessed by means of the Scheltens' scale for which scores 0–4 indicate progressive medial temporal lobe volume loss [Scheltens P et al, J Neurol Neurosurg Psychiatry 1992].

Out of 154 patients enrolled in the VMCI-Tuscany Study, at baseline optional T2*weighted echo planar imaging GRE sequences on MRI were available for 125 patients (Figure 1). In the present study on CMBs, we also considered the 27 patients

excluded from the VMCI Tuscany main study because of mild WMH (modified Fazekas scale score=1) (Figure 1).

Rating of CMBs

CMBs were defined as hypointense signals on T2*-weighted MRI, round or ovoid, blooming, devoid of T1-weighted or T2-weighted hyperintensity, and at least half surrounded by brain parenchyma, according to current consensus criteria [Greenberg SM et al, Lancet Neurol 2009]. MARS was used to assess the presence, number, and location of CMBs [Gregoire SM et al, Neurology 2009]. For this study, we took into account only definite CMBs (small, rounded, well-defined hypointense lesions with clear margins ranging 2-10 mm in size) as defined by MARS [Gregoire SM et al, Neurology 2009]. Lobar MRI landmarks were defined according to Stark and Bradley [Stark DD et al, Magnetic Resonance Imaging, St. Louis, Mosby 1999] and included cortical and subcortical regions; deep regions included the basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter; infratentorial regions included the brainstem and cerebellum [Gregoire SM et al, Neurology 2009]. CMBs mimics (such as sulcal vessel, mineralization in globi pallidi or dentate nuclei, hemorrhages, air-bone interfaces, partial volume artifact, along with choroid plexus and pineal calcifications) were excluded using FLAIR sequences [Greenberg SM et al, Lancet Neurol 2009; Gregoire SM et al, Neurology 2009].

For the purpose of the agreement trial, detection of CMBs was performed by 3 trained raters who recorded the total number and the topographic distributions of lesions. Twenty randomly selected MRI scans were independently assessed by the 3 raters to evaluate inter-rater agreement.

Clinical data and cognitive functions

Vascular risk factors (hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, low physical activity), clinical data (history of stroke, atrial fibrillation, migraine, and main clinical disturbances of SVD, such as memory, urinary and gait disturbances, psychiatric disorders) and drugs in use (ACE-inhibitors, beta blockers, calcium channel blockers, anticoagulants, antiplatelet drugs, statins, oral antidiabetic drugs) were recorded. Detailed criteria are reported elsewhere [Poggesi A et al, Int J Alzheimers Dis 2012].

For the assessment of cognitive performances, we used the VMCI-Tuscany neuropsychological battery [Salvadori E et al, J Alzheimers Dis 2015]. This protocol, extensively reported elsewhere, includes 2 global cognitive functioning tests and 9 second level tests that cover 4 cognitive domains (memory, attention/executive functions, fluency and constructional praxis) [Salvadori E et al, J Alzheimers Dis 2015]. To overcome the problem of standardizing neuropsychological scores, the Equivalent

Score (ES) methodology, a non-parametric norming method, was used [Capitani E et al, J. Clin Exp Neuropsychol 1997]. This is an ordinal 5-point scale (ranging from 0 to 4), where ES=0 represents pathological performances, ES=1 indicates a borderline performance, and ES=2, 3 and 4 represent normal performances [Capitani E et al, J. Clin Exp Neuropsychol 1997]; ES were available for all the tests except for the Mini Mental State Examination (MMSE) and the Symbol Digit Modalities Test [Salvadori E et al, J Alzheimers Dis 2015; Conti S et al, Neurol Sci 2015]. In the previous methodological paper reporting on the psychometric properties of the VMCI-Tuscany neuropsychological battery, confirmatory factor analysis showed a good fit of the 4 theoretically assumed dimension to empirical data, and cognitive compound measures were calculated for each cognitive domain [Salvadori E et al, J Alzheimers Dis 2015].

Statistical analysis

Inter-rater agreement for number and topographic distribution of CMBs was measured using the multi-rater Fleiss kappa measure of agreement [Fleiss JL, Psychological Bulletin 1971]. Results were interpreted as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or very good (0.81–1) agreement according to Landis and Koch [Fleiss JL et al, Statistical methods for rates and proportions, 3rd ed., Hoboken 2003].

The original variables of CMBs (number of CMBs in 3 regions according to MARS) were considered both as continuous variables (mean number of CMBs) and dichotomized into present or absent (deep CMBs, infratentorial CMBs and lobar CMBs). Among other neuroimaging variables considered, mean MTA of the left and right scores was calculated and dichotomized (MTA score 0-2.5 and MTA score ≥3), as previously reported [Salvadori E et al, Alzheimers Dement 2015].

Descriptive and univariate statistical analyses (Pearson's chi-squared test and independent samples t-test for dichotomous and continuous variables, respectively) were used to compare the group with at least 1 CMB (CMBs-positive group) and the group without CMBs (CMBs-negative group) and to characterize the CMBs-positive group in terms of vascular risk factors, demographic, clinical (including current therapy) and neuroimaging features. To evaluate the association between CMBs, vascular risk factors and main clinical data, non-parametric Mann–Whitney U test (dependent variable: CMBs mean number) and chi-square test (dependent variable: CMBs dichotomized as absent or present) were used.

To explore the possible association between neuropsychological performances and mean number of CMBs (total and located in different regions), non-parametric correlation analysis (Spearman's ρ) were performed. Neuropsychological variables included were: compound scores for cognitive domains, ESs for each test and corrected scores for MMSE and Symbol Digit Modalities Test. Non-parametric correlation analysis (Spearman's ρ) was also used to verify a possible correlation between other neuropsychological performances and neuroimaging variables. In case of multiple testing comparison, Bonferroni's correction for multiple comparisons was per-

formed to reduce the probability of a type I error. In particular, we applied Bonferroni's correction to neuropsychological performances (tables 3 and 4), resetting the critical level of significance according to the number of tests included in each cognitive domain ($p<0.0125$ for memory, $p<0.0083$ for attention/executive functions and $p<0.0250$ for fluency).

Other p values, including compound scores for cognitive domains, were two-tailed, and the level of significance was set at $p<0.05$.

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Institute, Inc., Cary, NC) [IBM SPSS Statistics for Windows, IBM Corp 2011].

Results

The study sample included 152 patients (126 examined with 1.5T, 26 with a 3T machine) with a mean(±SD) age of 75.5(±6.7) years; 87 (57.2%) were males (Figure 1). Inter-rater agreement for evaluation of CMBs, in terms of number and location in the three regions of MARS, ranged from good to very good among the three raters [multi-rater Fleiss kappa (95% CI) ranging from 0.70 (0.61-0.79) to 0.95 (0.80-1.11)]. In particular, for total number of CMBs was 0.70 (0.61-0.79), for deep CMBs was 0.95 (0.80-1.11), for lobar CMBs 0.82 (0.68-0.95), and for infratentorial CMBs was 0.81 (0.67-0.95).

Forty-one patients (27%) had at least one CMB and 21 (14%) had multiple CMBs, with a mean number of 3.7±4.8 (range 1-18) (Figure 2). The characteristics of the study sample are reported in table 1. The CMBs-positive and CMBs-negative groups did not differ significantly in terms of demographic, vascular risk factors and clinical features. Among neuroimaging features considered, the presence of lacunar infarcts was significantly associated with CMBs (p=.015) (table 1). In the CMBs-positive group, CMBs were located in deep regions in 21 (51%) patients, in lobar regions in 23 (56%) and in infratentorial regions in 18 (44%). Among patients with deep CMBs, 10 (48%) had also CMBs in lobar regions and 8 (38%) in infratentorial regions. Figure 3 shows the location of CMBs in our sample; 15 patients (36.6%) had CMBs in more than one brain regions.

Among vascular risk factors, history of hypertension was significantly associated with CMBs located in deep regions (p=.049), low physical activity with lobar CMBs (p=.024). Among clinical comorbidities, migraine was significantly related to the presence of infratentorial CMBs (p=.026), while the use of calcium channel blockers to both deep (p=.017) and infratentorial CMBs (p=.049) (table 2). Non-parametric Mann–Whitney U test showed a significant associations between total mean number of CMBs and: migraine (5.4±5.4 vs. 3.0±4.4 in patients with or without migraine respectively, p=.036), history of gait disturbances (5.3±5.9 vs. 1.7±1.3 in patients affected or not by gait disorders respectively, p=.009), use of calcium channel blockers (5.6±5.7 vs. 2.3±3.4 in patients with or without calcium channel blockers therapy respectively, p=.009). These results did not change after additional adjustment for age (data not shown).

Regarding cognitive performances, total number of CMBs was associated with attention/executive (rho=-282, p=.003) and fluency domains (rho=-166, p=.041) (table 3). Considering location of CMBs (table 4), a significant correlation with attention/executive and fluency domains for deep (rho=-.323, p=.001; rho=-.163, p=.045, respectively) and lobar CMBs (rho=-.227, p=.016; rho=-.179, p=.027, respectively) was found. In particular, deep CMBs were associated with MoCA (rho=-.163, p=.047) and, taking into account the second level tests, with selective attention (Stroop-errors) (rho=-.290, p=<.001) (table 4). Lobar CMBs were correlated with MMSE (rho=-.166, p=.041) and with phonemic verbal fluency (rho=-.186, p=.021). These results did not appear to be driven by Fazekas and MTA scores as there was no statistically significant correlation between these neuroimaging variables and cognitive performance (data not shown).

Discussion

This study focused on systematic detection of CMBs in a sample of patients affected by MCI with SVD and on the clinical significance of CMBs in terms of cognitive performances. The main findings of our study are the following. First, MARS proved to be a feasible and reliable instrument to rate the burden and location of CMBs with good-very good inter-rater agreement for number and location of lesions in our specific population setting. These data confirm previous reports in different patient samples [Gregoire SM et al, Neurology 2009]. The systematic application of a standardized rating scale can be thus implemented also in the clinical setting, as suggested in STRIVE recommendations [Wardlaw JM et al, Lancet Neurol 2013]. Second, nearly one-third of patients in our sample had at least one CMB, similarly to other cohorts of patients with MCI (despite the different MRI sequences used [Chowdhury MH et al, J Stroke Cerebrovasc Dis 2011; Yates PA, Front Neurol 2014; Haller S et al, Radiology 2010]) and in those with CMBs, more than one-third had CMBs in multiple regions. Third, the presence of CMBs, independently of other neuroimaging features, influenced attention/executive functions and fluency domains performances.

In recent years, there has been an increasing interest in the relevance of CMBs for cognition [Charidimou A et al, J Neurol Sci 2012]. Our results are consistent with previous studies, although our population is different. The association between CMBs and cognitive dysfunction, with a graded relationship between higher CMBs load and more severe cognitive impairment, was shown in a recent meta-analysis [Wu R et al, Med Sci Monit 2014]. Moreover, in the Rotterdam Scan Study the effect of CMBs on cognition seemed to be independent of vascular risk factors or other concurrent imaging vascular lesions [Poels MM et al, Neurology 2012]. Also our findings do not seem influenced by other concurrent imaging markers (white matter lesions as well as MTA) [Patel B et al, Stroke 2013; Xu X et al, Stroke 2015], suggesting an independent effect of CMBs on cognitive impairment [Wu R et al, Med Sci Monit 2014]. The link between CMBs and worse performances in all cognitive domains except memory, particularly in some specific tests exploring attention and executive functions, is in line with previous studies [Poels MM et al, Neurology 2012; Yakushiji Y et al, Stroke

2008; Werring DJ et al, Brain 2004; van Norden AG et al, Stroke 2011; Yamashiro K et al, Cerebrovasc Dis Extra 2014] and seems to reflect a domain-specific CMBs impairment as suggested in a recent paper investigating the cerebrovascular disease burden on cognition [Xu X et al, Stroke 2015].

In our sample, also the location of CMBs appears important in determining cognitive consequences, as already reported in several population-based studies [Sveinbjornsdottir S et al, J Neurol Neurosurg Psychiatry 2008; Poels MM et al, Neurology 2012]. The correlation between the topographic distribution of CMBs and deficits in specific cognitive domains has been interpreted as direct focal damage of CMBs on the tissue [Wu R et al, Med Sci Monit 2014; Martinez-Ramirez S et al, Alzheimers Res Ther 2014] or as subcortical-cortical disconnection result [Poels MM et al, Neurology 2012; Wu R et al, Med Sci Monit 2014].

Other minor findings of our study, such as the significant association between hypertension and low physical activity with total number and location of CMBs [Uiterwijk R et al, Hypertension 2014; Kim BJ et al, J Stroke 2013], emerged. This may add as recommendation to the control of these potentially modifiable vascular risk factors. Finally, patients who suffered from migraine more commonly had infratentorial CMBs, as already reported [Arkink EB et al, Stroke 2015].

Our study has several limitations. The first is the relatively small sample size; particularly the number of patients with at least 1 CMB is limited and performing multivariate analyses was precluded. The second is the use of machines with different MRI field strengths and the fact that correction for this factor in the analysis was not possible for the limited sample size. Analyses restricted to the larger group of patients examined with the 1.5T magnet however did not show significant differences in the trend of association with clinical and neuroimaging data nor in the correlation of CMBs with cognitive performances when compared with total sample analysis (data not showed). Third, the cross-sectional design of the study could limit the interpretation of the results.

The strengths of our study are the use of one standardized rating scale that can allow the comparability of the results with similar cohorts of patients in accordance with the STRIVE suggestions [Wardlaw JM et al, Lancet Neurol 2013] and the use of a specific and standardized neuropsychological battery.

Conclusions

In conclusion, CMBs load may be considered as an independent contributor to cognitive impairment and their topographic distribution may have specific associations with specific cognitive domains in patients with MCI and SVD. The systematic application of a standardized rating scale can be implemented also in the clinical setting to standardize image interpretation. Longitudinal studies may provide more robust information about the CMBs progression and prognostic significance.

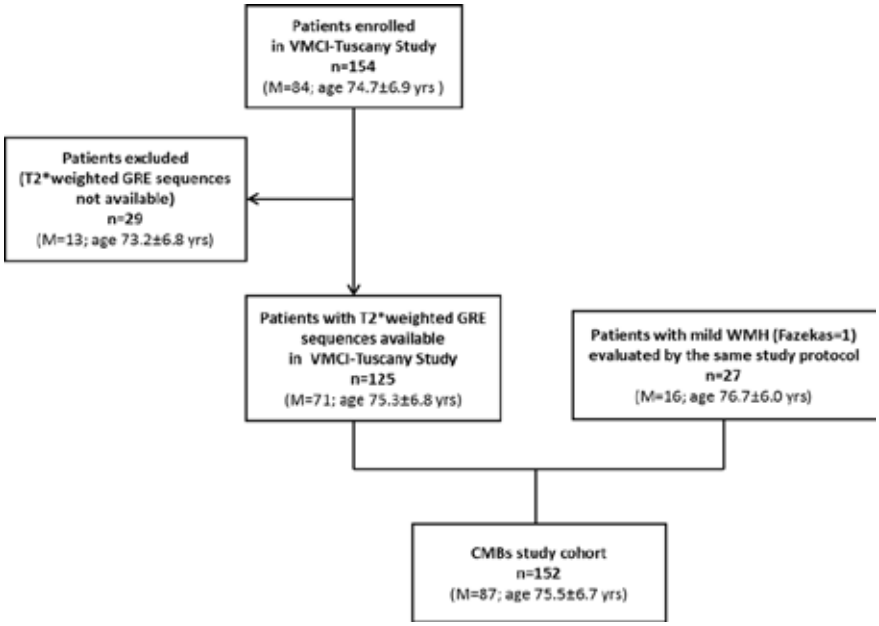

Figure 1. Flow-chart of patients included in the study sample

VMCI: Vascular Mild Cognitive Impairment, M=males, GRE: gradient-echo, WMH: white matter hyperintensities, CMBS: cerebral microbleeds

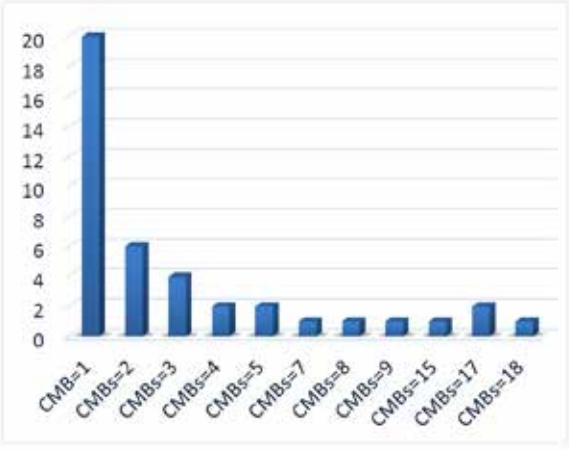

Figure 2. Distribution of number of cerebral microbleeds in patients with at least 1 microbleed sample

CMBs: Cerebral microbleeds

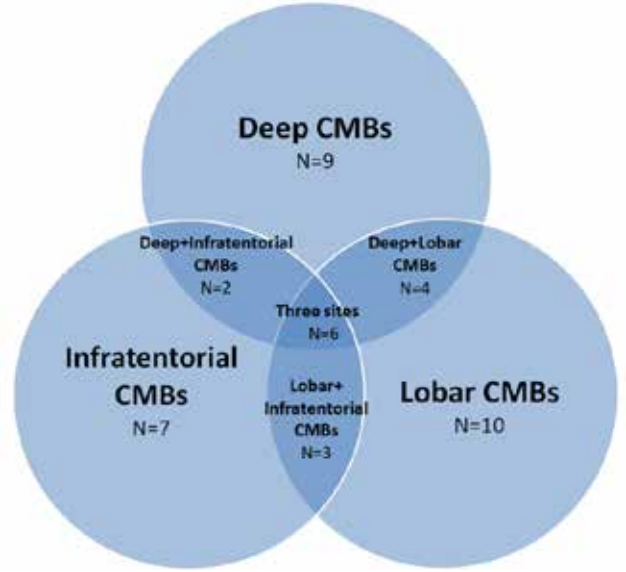

Figure 3. Number of patients with at least 1 microbleed in the 3 different brain regions (according to the Microbleed Anatomical Rating Scale)

CMBs: Cerebral microbleeds

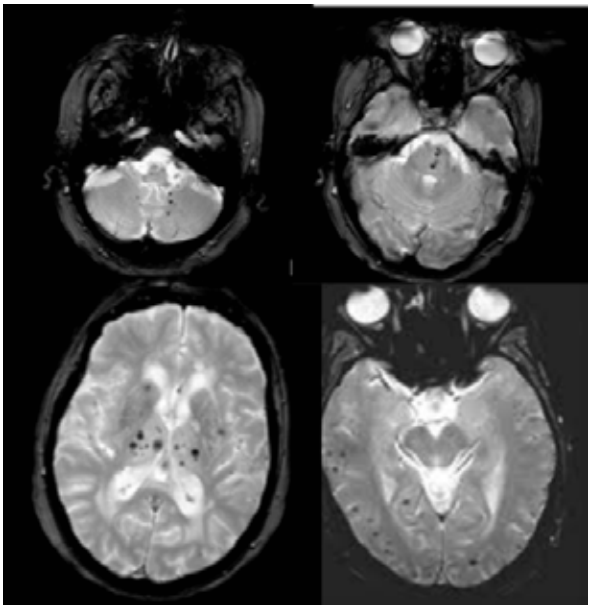

Figure 4. Cerebral microbleeds in infratentorial, deep and lobar regions on T2* GRE MRI sequences of the cerebral microbleeds study sample

			Total sample N=152	CMBs-negative group N=111	CMBs-positive group N=41	P
Demographic, global efficiency features, and depression assessment	Males, N (%)		87 (57.2)	63 (56.8)	24 (58.5)	.844*
	Age, yrs (mean±S.D.)		75.5±6.7	75.6±6.8	75.3±6.4	.818**
	Education, yrs (mean±S.D.)		7.5±6.7	7.4±3.9	7.6±4.7	.789**
	MoCA (mean±S.D.)		21.8±4.5	21.7±4.2	22.1±5.1	.672**
	MMSE (mean±S.D.)		27.4±2.7	27.4±2.8	27.4±2.5	.938**
	GDS (mean±S.D.)		4.3±3.3	4.2±3.0	4.7±3.8	.448**
Vascular risk factors (history of)	Hypertension, N (%)		121 (79.6)	89 (80.2)	32 (78.0)	.772*
	Dyslipidemia, N (%)		94 (61.8)	67 (60.4)	27 (65.9)	.536*
	Diabetes, N (%)		21 (13.8)	17 (15.3)	4 (9.8)	.378*
	Smoking, N (%)		65 (42.8)	45 (40.5)	20 (48.8)	.362*
	Alcohol consumption, N (%)		59 (38.8)	42 (37.8)	17 (41.5)	.684*
	Physical activity (low), N (%)		106 (69.7)	76 (68.5)	30 (73.2)	.575*
Clinical disturbances (history of)	Memory disturbances, N (%)		134 (88.2)	97 (87.4)	37 (90.2)	.629*
	Gait disturbances, N (%)		82 (53.9)	59 (53.2)	23 (56.1)	.747*
	Psychiatric disturbances, N (%)		82 (53.9)	58 (52.3)	24 (58.5)	.490*
	Urinary disturbances, N (%)		96 (63.2)	71 (64.0)	25 (61.0)	.735*
Neuroimaging features	White matter lesions (Fazekas scale)	grade 1	27 (17.8)	21 (18.9)	6 (14.6)	.459*
		grade 2	56 (36.8)	43 (38.7)	13 (31.7)	
		grade 3	69 (45.4)	47 (42.3)	22 (53.7)	
	Lacunar infarcts	absent	52 (34.2)	41 (36.9)	11 (26.8)	.015*
		few	53 (34.9)	43 (38.7)	10 (24.4)	
		many	47 (30.9)	27 (24.3)	20 (48.8)	
	Global cortical atrophy (Pasquier visual scale)	mild	21 (13.8)	18 (16.2)	3 (7.3)	.142*
		moderate	103 (67.8)	76 (68.5)	27 (65.9)	
		severe	28 (18.4)	17 (15.3)	11 (26.8)	
	MTA (dichotomized Scheltens scale)		Total sample N=148	CMBs-negative group N=108 (73%)	CMBs-positive group N=40 (27%)	P
		1-2.5	55 (37.2)	41 (38.0)	14 (35.0)	.740*
		3-4	93 (62.8)	67 (62.0)	26 (65.0)	

Table 1. Characterization of total study sample, cerebral microbleeds-negative and cerebral microbleeds-positive groups in terms of demographic, vascular risk factors, clinical and neuroimaging features

*χ^2 test

** t-test

Statistical analysis refers to comparison between CMBs-negative group and CMBs-positive group.

CMBs: cerebral microbleeds; MoCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; MTA: medial temporal lobe atrophy.

			DEEP CMBs		p*	INFRATENTORIAL CMBs		p*	LOBAR CMBs		p*
			present (CMB≥1) n=21	absent n=20		present (CMB≥1) n=18	absent n=23		present (CMB≥1) n=23	absent n=18	
Vascular risk factors and comorbidities	Hypertension, N (%)		59.4%	40.6%	.049	43.8%	56.3%	.970	59.4%	40.6%	.425
	Dyslipidemia, N (%)		60.7%	39.3%	.074	42.9%	57.1%	.843	60.7%	39.3%	.382
	Smoking, N (%)		40.0%	60.0%	.161	50.0%	50.0%	.443	50.0%	50.0%	.443
	Alcohol consumption, N (%)		47.1%	52.9%	.654	47.1%	52.9%	.732	58.8%	41.2%	.767
	Physical activity (low), N (%)		50.0%	50.0%	.796	43.3%	56.7%	.903	66.7%	33.3%	.024
	Stroke, N (%)		41.2%	58.8%	.279	47.1%	52.9%	.732	64.7%	35.3%	.350
	Migraine, N (%)		46.2%	53.8%	.658	69.2%	30.8%	.026	53.8%	46.2%	.843
	Traumatic brain injury, N (%)		37.5%	62.5%	.387	50.0%	50.0%	.698	75.0%	25.0%	.230
Clinical disturb-ances	Memory disturbances, N (%)		48.6%	51.4%	.317	40.5%	59.5%	.187	59.5%	40.5%	.187
	Psychiatric disturbances, N (%)		62.5%	37.5%	.086	45.8%	54.2%	.767	50.0%	50.0%	.350
	Gait disturbances, N (%)		56.5%	43.5%	.443	56.5%	43.5%	.066	60.9%	39.1%	.486
	Bladder disturbances, N (%)		56.0%	44.0%	.444	52.0%	48.0%	.192	52.0%	48.0%	.509
Neuroimaging features	White matter lesions (Fazekas scale)	grade 1	33.3%	66.7%	.485	16.7%	83.3%	.309	66.7%	33.3%	.852
		grade 2	46.2%	53.8%		53.8%	46.2%		53.8%	46.2%	
		grade 3	59.1%	40.9%		45.5%	54.5%		54.5%	45.5%	
	Lacunar infarcts	absent	45.5%	54.5%	.875	27.3%	72.7%	.317	72.7%	27.3%	.430
		few	50.50%	50.0%		40.0%	60.0%		50.0%	50.0%	
		many	55.0%	45.0%		55.0%	45.0%		50.0%	50.0%	
		mild	33.3%	66.7%	.358	100%	0%	.123	33.3%	66.7%	.641

	Global cortical atrophy (Pasquier visual scale)	mild	33.3%	66.7%	.358	100%	0%	.123	33.3%	66.7%	.641
		moderate	59.3%	40.7%		40.7%	59.3%		55.6%	44.4%	
		severe	36.4%	63.6%		36.4%	63.6%		63.6%	36.4%	
	MTA (dichotomized Scheltens scale)	1-2.5	42.9%	57.1%	.370	28.6%	71.4%	.191	64.3%	35.7%	.524
		3-4	57.7%	42.3%		50.0%	50.0%		53.8%	46.2%	
Drug in use	Beta blockers, N (%)		44.4%	55.6%	.645	33.3%	66.7%	.470	33.3%	66.7%	.470
	Calcium channel blockers, N (%)		72.2%	27.8%	.017	61.1%	38.9%	.049	61.1%	38.9%	.567
	ACE-inhibitors, N (%)		66.7%	33.3%	.080	50.0%	50.0%	.486	61.1%	38.9%	.567
	Diuretics, N (%)		50.0%	50.0%	.920	50.0%	50.0%	.613	50.0%	50.0%	.613
	Antiaggregants, N (%)		51.5%	48.5%	.939	48.5%	51.5%	.230	54.5%	45.5%	.684
	Statins, N (%)		61.1%	38.9%	.262	50.0%	50.0%	.486	55.6%	44.4%	.951

Table 2. Association between presence or absence of cerebral microbleeds for each region and main features

* $\chi 2$ test

CMBs: cerebral microbleeds; MTA: medial temporal lobe atrophy; ACE: angiotensin-converting enzyme

Cognitive domains	Tests (ESs)	N (%)	Total CMBs[§]	p*
Global efficiency	MMSE (corrected score)[#]	152 (100)	-0.57	.487
	MoCA	149 (98.0)	-0.75	.366
Attention/executive functions		112 (73.7)	-.282	.003
	TMT-part A	152 (100)	-.198	.015
	TMT-part B	113 (74.3)	-.129	.174
	Stroop-time	148 (97.4)	-.192	.019
	Stroop-errors	148 (97.4)	-.160	.052
	Visual search	152 (100)	-.134	.101
	SDMT (corrected score)[#]	152 (100)	-.179	.027
Memory		147 (96.7)	.055	.505
	RAVL-immediate recall	152 (100)	-.008	.922
	RAVL-delayed recall	152 (100)	-.003	.969
	Short story	152 (100)	.075	.361
	ROCF-recall	147 (96.7)	.135	.104
Fluency		152 (100)	-.166	.041
	Phonemic verbal fluency	152 (100)	-.134	.100
	Semantic verbal fluency	152 (100)	-.170	.037
Constructional praxis	[ROCF-copy]	149 (98.0)	-.031	.709

Table 3. Correlations between neuropsychological performances (cognitive domains and equivalent scores for each test) and total mean number of cerebral microbleeds

[§]Spearman's rho (non-parametric correlation test)

ESs: equivalent scores; CMBs: cerebral microbleeds; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test; RAVL: Rey Auditory-Verbal Learning Test; ROCF: Rey–Osterrieth Complex Figure; SDMT: Symbol digit modalities test. Stroop indicates Color Word Stroop Test.

[#] no ES available

* The level of significance was set at: $p<0.0083$ for tests exploring attention/executive functions, $p<0.0125$ for memory tests, $p<0.025$ for fluency tests (Bonferroni's corrections), and $p<0.05$ for all the remaining correlations.

Cognitive domains	Tests (ESs)	N (%)	Deep CMBs§	p*	Infra-tentorial CMBs§	p*	Lobar CMBs§	p*
Global effi-ciency	MMSE (corrected score)#	152 (100)	-0.81	.324	-.048	.560	-.166	.041
	MoCA	149 (98.0)	-.163	.047	-.138	.094	-0.82	.321
Attention/executive functions		112 (73.7)	-.323	.001	-.079	.408	-.227	.016
	TMT-part A	152 (100)	-.144	.076	-.029	.721	-.192	.018
	TMT-part B	113 (74.3)	-.227	.016	-.051	.590	-.081	.391
	Stroop-time	148 (97.4)	-.207	.012	-.007	.931	-.154	.062
	Stroop-errors	148 (97.4)	-.290	.000	-.032	.698	-.038	.647
	Visual search	152 (100)	-.199	.014	-.055	.502	-.121	.137
	SDMT (corrected score)#	152 (100)	-.165	.042	-.049	.549	-.201	.013
Memory		147 (96.7)	-.029	.725	.140	.092	-.053	.524
	RAVL-immediate recall	152 (100)	-.039	.637	.114	.163	-.044	.590
	RAVL-delayed Recall	152 (100)	.011	.897	.074	.364	-.070	.392
	Short story	152 (100)	.002	.978	.089	.277	-.046	.573
	ROCF-recall	147 (96.7)	.044	.593	.129	.120	.037	.654
Fluency		152 (100)	-.163	.045	-.133	.103	-.179	.027
	Phonemic ver-bal fluency	152 (100)	-.134	.099	-.117	.150	-.186	.021
	Semantic verbal fluency	152 (100)	-.174	.032	-.131	.108	-.113	.164
Constructional praxis [ROCF-copy]		149 (98.0)	-.060	.467	.002	.981	-.091	.270

Table 4. Correlations between neuropsychological performances (cognitive domains and equivalent scores for each test) and location of cerebral microbleeds (mean number)

§Spearman's rho (non-parametric correlation test)

ESs: equivalent scores; CMBs: cerebral microbleeds; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test; RAVL: Rey Auditory-Verbal Learning Test; ROCF: Rey–Osterrieth Complex Figure; SDMT: Symbol digit modalities test

Stroop indicates Color Word Stroop Test

[#] no ES available

* The level of significance was set at: $p<0.0083$ for tests exploring attention/executive functions, $p<0.0125$ for memory tests, $p<0.025$ for fluency tests (Bonferroni's corrections), and $p<0.05$ for all the remaining correlations

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2.1.2 Biological significance of total small vessel disease MRI burden in cerebral amyloid angiopathy

Note: The next two studies derived from the research that was completed during my time as a Stroke Research Fellow at the Massachusetts General Hospital – J. Philip Kistler Stroke Research Center – Harvard Medical School – Boston Massachusetts during the second year of my PhD program (Supervisor: Professor Steven Greenber; Principal Investigator: Professor Anand Viswanathan).

The protocols for the research described in the next two studies were designed by me with the advice and guidance of my supervisors, principally Professor Anand Viswanathan, Harvard Medical School (Boston, USA). During the fellowship, I have been participated in the study on the association between cognitive impairment in the elderly and characteristic markers of SVD.

Biological significance of total small vessel disease MRI burden in cerebral amyloid angiopathy

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Abstract

Introduction: Cerebral amyloid angiopathy (CAA) is a major cause of lobar intracerebral hemorrhage and cognitive impairment in the elderly. Different neuroimaging markers of CAA are related to distinct biological or clinical aspects of the disease. We investigated the biological and clinical significance of a composite score designed to capture the total brain MRI SVD burden in CAA, by evaluating its correlation with other neuroimaging markers, overall disability, and APOE status.

Methods: We applied the *total MRI small vessel disease (SVD) score* in a prospective cohort of 96 patients with probable/possible CAA (according to Boston criteria). The score, ranging from 0 to 6, considered 4 MRI features: lobar microbleeds, focal or disseminated cortical superficial siderosis, moderate-to severe enlarged perivascular spaces in the centrum semiovale, and moderate-severe white matter hyperintensities (WMH). We explored the association of the score with other MRI markers and clinical variables in adjusted ordinal and linear regression analyses.

Results: The median *total MRI SVD score* was 4.00 (IQR: 3.00-5.00). Higher total MRI SVD score was associated with brain atrophy (OR [95%CI]: 1.57 [1.16-2.12]) and posterior predominance of WMH (OR [95% CI]: 1.65 [1.11-2.46]). The score was related with lower memory performance (coefficient [95% CI]: -0.14 [-0.28 to -0.01]), depressive symptoms (coefficient [95% CI]:1.17 [0.30-2.04]) ApoE_e2 variant (OR [95% CI]: 2.95 [1.26 - 1.87]). No associations with apathy and gait impairment were found.

Discussion: The *total MRI SVD score* might be helpful to capture the cumulative effects of microangiopathy burden in patients affected by sporadic CAA. Larger studies are needed to validate our findings.

Introduction

Cerebral amyloid angiopathy (CAA) represents a common cause of spontaneous lobar intracerebral hemorrhage (ICH) and cognitive impairment in the elderly [Greenberg SM et al, Lancet Neurol 2014]. CAA is associated with a high prevalence of markers of small vessel disease (SVD), including hemorrhagic markers [cerebral microbleeds (CMBs), cortical superficial siderosis (cSS)] and nonhemorrhagic markers [white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), cortical microinfarcts [Greenberg SM et al, Lancet Neurol 2014]. All neuroimaging markers of the CAA may not be individually related with the same biological or clinical aspects of the disease, particularly in early stage. These neuroimaging markers often occur together, but the idea of addressing all features combined as a unitary measure of SVD has only gained attention recently [Staals J et al, Neurobiol Aging 2015; Brenner D et al, J Neurol 2008; Huijts M et al, Front Aging Neurosci 2013; Klarenbeek P et al, Stroke 2013].

A composite score (*total MRI small vessel disease (SVD) score*) was recently developed specifically for CAA patients, based on the key neuroimaging markers of the disease (lobar CMBs, cSS, centrum semiovale (CSO)-EPVS and WMH) [Charidimou A et al, JAMA Neurol 2016]. The score ranged from a minimum of 0 to a maximum of 6 points, creating an ordinal scale representing increasing burden of CAA manifestations on structural brain MRI [Charidimou A et al, JAMA Neurol 2016]. The combined effect of all characteristic neuroimaging markers on specific clinical aspects (such as cognitive performance, gait disorders, depression and apathy) and overall disability have never been studied in CAA and would possibly provide useful information on the effects in CAA patients.

We aimed to investigate the biological significance of the *total MRI SVD score* in patients with a clinical-radiological diagnosis of CAA and its meaning in clinical practice. In particular, we evaluated the possible correlation between *total MRI SVD score* and:

a. other possible neuroimaging markers of the disease

b. overall disability, including depression, apathy, gait disorders and cognitive performance

c. APOE status

Materials and Methods

Study design

This study is a cross-sectional analysis of data from an ongoing longitudinal CAA cohort CAA. We applied the *total MRI SVD score* in a cohort of 96 patients with probable and possible CAA (according to the Boston criteria) [Knudsen KA et al, Neurology 2001]. The Institutional Review Board approved the study and informed consent was obtained from all participants.

Study participants

One-hundred-thirty-two patients with a diagnosis of CAA according to the Boston criteria [Knudsen KA et al, Neurology 2001] were considered for this study. To be included, patients had to be underwent a research brain MRI scan and comprehensive clinical and neurocognitive evaluation between March 2006 and October 2015. According to the inclusion criteria, 36 patients were excluded, because not all data were available. Complete MRI data and neuropsychological data were existing for 96 patients.

Scan protocol

Study participants underwent detailed structural 1.5 T (n=83, 86.5%) or 3 T (n=13, 13.5%) MRI scans (Siemens Healthcare, Magnetom Avanto, Erlangen, Germany) according to study protocol [Reijmer YD et al, Brain: a journal of neurology 2015].

MRI sequences for all subjects included a T1-weighted sagittal multi-echo MPRAGE scan (slice thickness, 1mm; repetition time, 2730ms; voxel size, 1 x 1 x 1mm), a fluid-attenuated inversion recovery (FLAIR) 3D scan (slice thickness, 1mm; repetition time, 6000ms; echo time, 303ms; voxel size, 1 x 1 x 1mm), and a T2*-weighted gradient-echo (GRE) scan (slice thickness, 5mm; repetition time, 763ms;

echo time, 24ms; voxel size, 1 x 1 x 5mm), a high resolution Susceptibility-weighted imaging (SWI) scan (slice thickness, 1.3mm; repetition time, 48ms; echo time, 40ms; voxel size, 0.8 x 0.7 x 1.3mm), using a 12-channel head coil, as previously described in detail [Reijmer YD et al, Brain: a journal of neurology 2015]. MRI were rated blinded to all clinical and neuropsychological data by trained observers, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) [Wardlaw JM et al, The Lancet Neurology 2013]. For patients with multiple MRIs available, the MRI closest to the clinical and neuropsychological assessment was examined.

SVD MRI markers

The rating of images included: presence and number of CMBs according to current consensus criteria and detected using SWI sequences [Greenberg SM et al, The Lancet Neurology 2009], presence and severity of cSS, classified as focal (restricted to ≤3 sulci) or disseminated (≥4 sulci), as previously described [Charidimou A et al, Neurology 2013; Linn J et al, Neurology 2010]. CSO-EPVS were assessed in line with STRIVE definitions and rated on axial T1-weighted MR images, according to a validated 4-point visual scale (0: 0; 1: <10 EPVS in the total WM; 2: >10 EPVS in the total WM or < 10 EPVS in the slice with the greatest number; 3: 10-20 in the slice with the greatest number; and 4: >20 EPVS in the slice with the greatest number of EPVS [Zhu YC et al, Stroke 2010; Martinez-Ramirez S et al, Neurology 2013]. Because in the *total MRI SVD score* the presence of CSO-EPVS was taken into account with rating on axial T2-weighted MR images. On axial T1-weighted MR images in our cohort, based on previous studies, given the clinical significance of the EPVS burden, even statistical grouping, we dichotomized degrees of EPVS into high (score 4) and low (score 1 to 3). The arbitrary cutoff for EPVS detection was chosen to weight the major severity of the EPVS burden and was counted if there were moderate-to-severe (grade 4, i.e. >20) EPVS (one point if present). The intra- and inter-rater Cohen's Kappa agreement for perivascular spaces ranged from 0.90±0.09 and 0.89±0.10, respectively. WMH were rated according to the modified Fazekas rating scale using FLAIR-weighted sequences [Fazekas F et al, AJR American journal of roentgenology 1987]. Additionally, for the frontal-occipital WMH distribution, WMH in the frontal and occipital lobe on axial FLAIR as previously described by Zhu et al. were evaluated [Zhu YC et al, Journal of neurology 2012]. The frontal-occipital gradient (the WMH score in the frontal lobe minus that in the occipital lobe) was calculated (ranging -6 to 6; >0 implies frontal dominance and <0 implies occipital dominance) [Zhu YC et al, Journal of neurology 2012]. Other neuroimaging markers included: presence, number and location of ICH [Kidwell CS et al, Neurology 2009], cerebral global cortical atrophy evaluation on a 4-point Pasquier [Pasquier F et al, Eur Neurol 1996; Harper L et al, J Neurol Neurosurg Psychiatry 2015].

Separately, the ordinal *total MRI SVD score* ranging from 0 to 6, by counting the presence of each of these 4 MRI features, as described above [Charidimou A et al, JAMA Neurol 2016], was calculated. For lobar CMBs a point was awarded if 2-4 CMBs were present and two points for ≥5 CMBs; presence of cSS was awarded with

one point if focal and two points if disseminated; presence of CSO-EPVS was counted if there were moderate-to severe (grade 3–4, i.e. >20)E PVS (one point if present); WMH was defined as either (early) confluent deep (i.e. the region between juxtacortical and ventricular areas) WMH (Fazekas score ≥2) or irregular periventricular WMH extending into the deep white matter (Fazekas score 3) (one point if either present) [Charidimou A et al, JAMA Neurol 2016].

Clinical and neuropsychological evaluation

Demographic information, vascular risk factors and history of ICH were recorded. Patients underwent comprehensive clinical evaluation and standardized neuropsychological assessment as previously described [Reijmer YD et al, Brain: a journal of neurology 2015].

Neuropsychological tests included verbal memory (immediate and delayed memory score of the Hopkins Verbal Learning Test [Brandt J. Clin Neurophysiol 1991]), processing speed (Trail Making Test A [Corrigan J et al, J Clin Psychol 1987] and Symbol Substitution Test [Wechsler D. Wechsler adult intelligence scale - III. Psychological Corporation, 1997]), executive functioning (Trail Making Test B, Digit Span Test backwards [Wechsler D. Wechsler memory scale-revised manual. The Psychological Corporation, 1987]; Verbal Fluency Test [Tombaugh TN et al, Arch Clin Neuropsychol 1999]), and language (Boston Naming Test (short form) [Fastenau PS et al, J Clin Exp Neuropsychol 1998]). Each cognitive test score was transformed into z-scores using the mean and standard deviation (SD) of the whole population and averaged across tests to obtain one average z-score per cognitive domain [Reijmer YD et al, Brain: a journal of neurology 2015]. The neuropsychological evaluation also included depression and apathy scales [Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull, 1988; Starkstein SE et al, J Neuropsych Clin Neurosci 1992. Cognitive data were not available in 4 patients.

To assess the occurrence and severity of gait disturbances, the Short Physical Performance Battery (SPPB) was chosen [Guralnik JM et al, N Engl J Med 1995]. In addition, walking speed was measured by the timed get up and go test [Guttmann CR et al, J Am Geriatr Soc 1991].

APOE genotype was determined by analyzing DNA extracted from blood samples provided by consented participants, in accordance with previously published [Biffi A et al, Lancet Neurol 2011].

Statistical analysis

The associations between vascular risk factors, other neuroimaging markers, and gait disturbances (independent variables) with *total MRI SVD score* (dependent variable) were analyzed using ordinal logistic regression model. For the associations with cognitive domains, depression, apathy, and gait velocity, linear regression analysis

was applied. The associations between *total MRI SVD score* (used as independent variable) with APOE genotype and presence of ICH (dependent variables) were analyzed using ordinal regression analysis.

In the first model, we included age and sex as covariates. In the second model, we additionally included education level, ICH and atrophy. These adjustments were chosen based on the main outcomes used in the models.

Statistical significance level was set at 0.05. The statistical analysis was performed using the SPSS 21 statistical package (IBM Corp., Armonk, NY) and STATA.

Results

The study sample consisted of 96 patients aged (mean, SD) 69.82 (8.26) with CAA. According to Boston criteria, 4 (4.2%) patients were diagnosed with definite CAA, 16 (16.7%) patients with probable CAA (with supporting pathology) and 73 (76.0%) patients with probable CAA; 3 (3.1%) patients had possible CAA. Fifty-six (58.3%) patients had symptomatic ICH and 40 (41.7%) had non-ICH presentation (of these, 5 had dementia). Table 1 shows the main baseline clinical and radiological characteristic of our sample. Among neuroimaging markers of CAA, 41 (42.7%) patients had at least one ICH on MRI and 11 (11.5%) had multiple ICH. The *total MRI SVD score* was (median, quartiles) 4.00 (3.00, 5.00) (Figure 1).

No association between the *total MRI SVD score* and vascular risk factors (age, sex, hypertension, diabetes, hypercholesterolemia, and smoking) were found (data not shown).

Table 2 summarizes the regression models exploring association between *total MRI SVD score* and other neuroimaging markers. Higher *total MRI SVD score* was associated with higher brain atrophy score (OR [95% CI]: 1.57 [1.16 - 2.12], p=0.003), and occipital predominant WMH (OR [95% CI]: 1.65 [1.11 - 2.46], p=0.014). In a sensitivity analysis, the effect estimates were consistent with ICH presence as a further covariate (data not shown).

Concerning the other measures of overall disability, each point increase in the *total MRI SVD score* was associated with higher value on the GDS (coefficient [95% CI]:1.17 [0.30 - 2.04], p=0.009). Among cognitive domains, the linear regression analysis showed an association with memory (coefficient [95% CI]: -0.14 [-0.28 to -0.01], p=0.042) (Table 2). No associations with apathy and gait impairment were found.

Regarding ApoE status (ApoE genotype were available for 73 (76.0 %) patients), ApoE_e2 variant was associated with the increase of the *total MRI SVD score* (OR [95% CI]: 2.95 [1.26 - 1.87], p=0.012) (Table 2).

Discussion

In the current study we investigated the biological and clinical significance of the *total MRI SVD score* in CAA patients. This composite score is based on the four most characteristic neuroimaging signatures associated with CAA and aims to capture the burden of the disease on structural brain MRI [Charidimou A et al, JAMA Neurol 2016].

A higher *total MRI SVD score* was associated with other possible neuroimaging markers of the disease. The association of the atrophy and occipital predominance of WMH with the *total MRI SVD score* may provide that these might be additional promising CAA markers related to CAA severity, as already suggested [Charidimou A et al, JAMA Neurol 2016; 20]. The *total MRI SVD score* was biologically associated with higher score at GDS. Interestingly, the *total MRI SVD score* seemed to not be associated with cognitive domains, except of memory. The lack of clear association between the score and cognitive domains may relate to the small sample size because relatively non-impaired CAA population. Moreover, ApoE_e2 genotypes variant seems to be predictive for *total MRI SVD score*. This specific MRI-visual tool can be used to assess the impact of CAA on vascular physiology and on other neuroimaging and clinical markers of the disease.

Extensive work by two groups have allowed to create the composite scores able to capture the total MRI burden in SVD with a SVD score of overall SVD load by summing some MRI features of SVD [Staals J et al, Neurobiol Aging 2015; Brenner D et al, J Neurol 2008; Huijts M et al, Front Aging Neurosci 2013]. Associations with poorer cognitive function in patients with lacunar stroke and hypertension [Huijts M et al, Front Aging Neurosci 2013], with SVD risk factors [Staals J et al, Neurology 2014], and, more recently, with cognitive ability were found [Staals J et al, Neurobiol Aging 2015].

Our study has several limitations. The multivariate analyses are limited by small sample size. The cross-sectional design precludes us from performing follow-up associations analysis. Moreover, cognitive performances are similar in small different group of patients affected in CAA [Xiong L et al, J Alzheimers Dis 2016].

With the limitations above mentioned, the *total MRI SVD score* may suggest a more comprehensive estimate of microangiopathy burden in the brain of patients affected by sporadic CAA, its impact on vascular pathophysiology damage and on clinical outcomes of CAA and its meaningful effect in clinical practice. The predictive value of the score needs to be confirmed in larger series of CAA patients. If confirmed in larger sample size, the *total MRI SVD score* may allow to stratify vasculopathic changes and clinical severity of CAA patients.

Clinical variables	CAA cohort (N=96)
Age (years), mean (SD)	69.82 (8.26)
Male, N (%)	74 (77.1)
Years of education, mean (SD)	16.74 (3.02)
Hypertension, n (%)	55 (57.3)
Diabetes, n (%)	9 (9.4)
Hypercholesterolemia, n (%)	45 (46.9)
Smoking, n (%)	3 (3.3)
Dementia, n (%)	5 (5.2)
Brain MRI markers	
CMBs, N (%)	89 (92.7)
CMBs > 5, N (%)	76 79.2)
cSS, N (%)	51 (53.1)
Focal cSS, N (%)	20 (20.8)
Disseminated cSS, N (%)	31 (32.3)
CSO-EPVS >20, N (%)	55 (57.3)
WMH [Fazekas score], mean (SD)	1.81 (0.80)
moderate-severe, N (%)	60 (62.5)
Occipital gradient, N (%)	57 (59.4)
Moderate-severe global cortical atrophy [Pasquier scale], N (%)	61 (63.5)
Global disability, cognitive and gait measures	
IQCODE at baseline (79)*, mean (SD)	3.13 (0.24)
mRS (88)*, mean (SD)	0.66 (0.86)
GDS (87)*, median (IQR)	5.00 (2.00, 9.00)
Apathy Scale (80)*, median (IQR)	10.00 (5.25-13.00)
MMSE (91)*, mean (SD)	27.64 (2.37)
SPPB total (53)*, median (IQR)	4..00 (3.00-4.00)
Gait velocity (62)*, m/sec	1.19 (0.35)

Table 1. Characteristics of the study sample

Clinical and radiological characteristics are presented as numbers with percentages, median with interquartile range as appropriate.

* Number of patients with available data

Abbreviations: CMBs=cerebral microbleeds, cSS=cortical superficial siderosis, WMH=white matter hyperintensities, IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly, mRS= modified Rankin Scale, GDS=geriatric depression scale, MMSE=mini mental state examination, SPPB= Short Physical Performance Battery.

Neuroimaging markers	N	OR (95% CI)		p-value	
Cerebral global cortical atrophy	96	1.57 (1.16 - 2.12)		0.003	
ICH presence	96	0.72 (0.35 - 1.48)		0.374	
Occipital predominance WMH	96	1.65 (1.11 - 2.46)		0.014	
Measures of impairment	N	Coefficient (95% CI)		p-value	
GDS	87	1.17 (0.30 - 2.04)		0.009	
apathy	80	0.57 (-0.33 - 1.48)		0.212	
gait velocity	62	- 0.04 (-0.012 - 0.02)*		0.202	
	N	OR (95% CI)		p-value	
LADIS total score	53	- 0.20 (-0.69 - 0.40)		0.520	
Cognitive domains	N	Coefficient (95% CI)**	p-value	Coefficient (95% CI)***	p-value
memory	92	-0.14 (-0.28 to -0.01)	0.042	-0.08 (-0.22 to 0.06)	0.252
speed	92	0.01 (-0.08 to 0.10)	0.795	0.01 (-0.02 to 0.02)	0.774
executive functions	92	-0.05 (-0.14 to 0.05)	0.319	-0.10 (-0.11 to 0.09)	0.813
language	92	-0.10 (-0.25 to 0.05)	0.184	-0.06 (-0.21 to 0.10)	0.471
APOE genotype	N	OR (95% CI)		p-value	
ApoE_e2	73	2.95 (1.26 - 1.87)		0.012	
ApoE_e3	73	0.85 (0.51 - 1.44)		0.556	
ApoE_e4	73	0.73 (0.42 - 1.27)		0.269	

Table 2. Association between total MRI SVD score and neuroimaging markers, clinical outcome measures, cognitive domains and APOE genotype

OR: derived from ordinal logistic regression model adjusted for age and sex

Coefficient derived from linear regression model adjusted for age and sex and ICH

*Derived from linear regression model adjusted for age and sex and education level

** Derived from linear regression model adjusted for age and sex, and ICH

***Derived from linear regression model adjusted for age and sex, education level, ICH and atrophy

Abbreviations: ICH=intracerebral hemorrhage, WMH= white matter hyperintensities, GDS=Geriatric Depression Scale

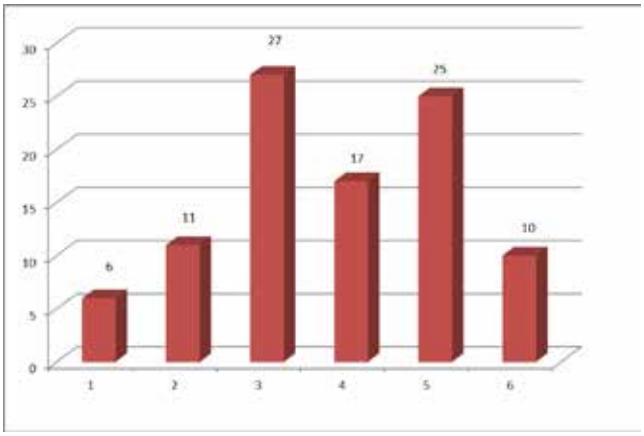

Figure 1. Total MRI small vessel disease score

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2.1.3 Total small vessel disease burden on MRI and impairments in structural brain networks in patients with cerebral amyloid angiopathy

Total small vessel disease burden on MRI and impairments in structural brain networks in patients with cerebral amyloid angiopathy

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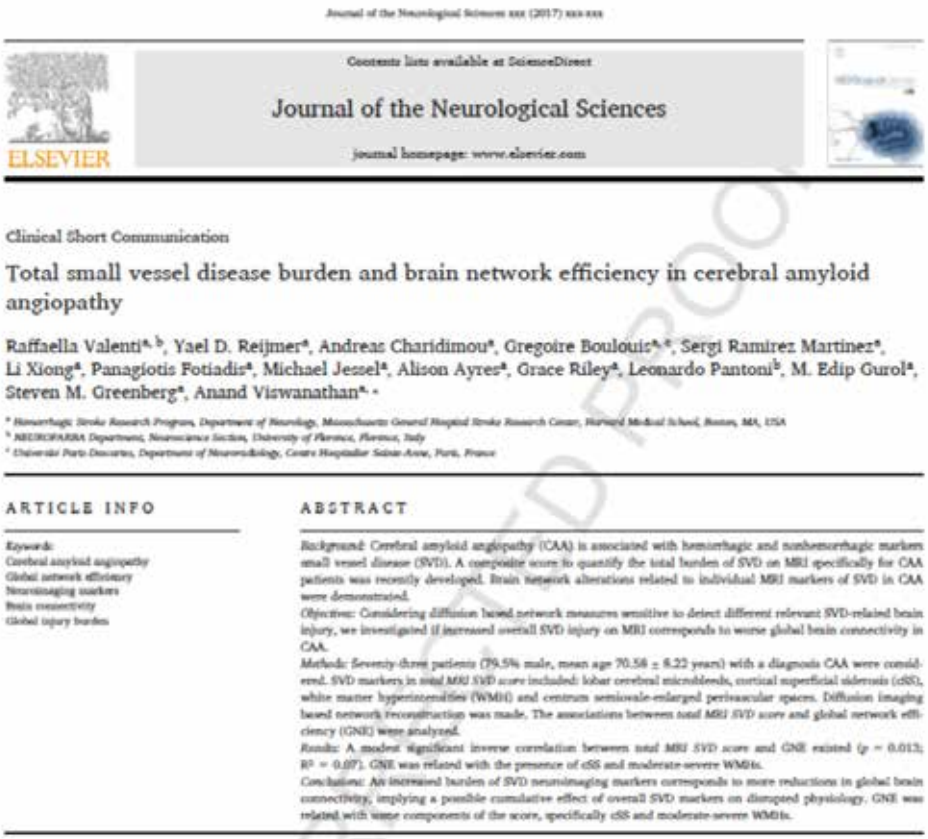

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Clinical Short Communication

Total small vessel disease burden and brain network efficiency in cerebral amyloid angiopathy

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ABSTRACT

Background: Cerebral amyloid angiopathy (CAA) is associated with hemorrhagic and nonhemorrhagic markers small vessel disease (SVD). A composite score to quantify the total burden of SVD on MRI specifically for CAA patients was recently developed. Brain network alterations related to individual MRI markers of SVD in CAA were demonstrated.

Objectives: Considering diffusion based network measures sensitive to detect different relevant SVD-related brain injury, we investigated if increased overall SVD injury on MRI corresponds to worse global brain connectivity in CAA.

Methods: Seventy-three patients (79.5% male, mean age 70.58 ± 6.22 years) with a diagnosis CAA were considered. SVD markers in total *MRI SVD score* included: lobar cerebral microbleeds, cortical superficial siderosis (cSS), white matter hyperintensities (WMH) and centrum semiovale-enlarged perivascular spaces. Diffusion imaging based network reconstruction was made. The associations between *total MRI SVD score* and global network efficiency (GNE) were analyzed.

Results: A modest significant inverse correlation between *total MRI SVD score* and GNE existed ($p = 0.013$; $R^2 = 0.07$). GNE was related with the presence of cSS and moderate-severe WMHs.

Conclusions: An increased burden of SVD neuroimaging markers corresponds to more reductions in global brain connectivity, implying a possible cumulative effect of overall SVD markers on disrupted physiology. GNE was related with some components of the score, specifically cSS and moderate-severe WMHs.

Abstract

Introduction: Cerebral amyloid angiopathy (CAA), a common cause of spontaneous lobar intracerebral hemorrhage (ICH) and cognitive impairment in the elderly, is associated with a high prevalence of markers of small vessel disease (SVD), including hemorrhagic and nonhemorrhagic markers. Brain network alterations related to individual MRI markers of SVD in CAA were recently demonstrated. We investigated if increased overall SVD injury on MRI corresponds to worse global brain connectivity in CAA.

Methods: We applied the *total MRI small SVD score* in a prospective cohort of 73 patients with probable/possible CAA (according to Boston criteria). The score, ranging from 0 to 6, considered 4 MRI features: lobar microbleeds, focal or disseminated cortical superficial siderosis, moderate-to severe enlarged perivascular spaces in the centrum semiovale, and moderate-severe white matter hyperintensities (WMH). The associations between *total MRI SVD score* and global network efficiency (calculated and processed on DTI sequences) were analyzed using ordinal logistic regression model.

Results: The study sample consisted of 73 patients (58 (79.5%) male, mean age 70.58 (SD=8.22). Higher total MRI SVD score was correlated with lower global network efficiency (B coefficient [95% CI]: -0.004 [-0.007 to -0.001], p=0.013). Of the individual SVD components of the total MRI SVD score, presence of cSS and moderate-severe WMHs correlated negatively with global network efficiency (-0.016 ± 0.006, p=0.011 and -0.017 ± 0.005 p=0.002, respectively). No clear dose-response relationship was seen.

Discussion: In this study an increased burden CAA injury on MRI was associated with greater impairments in structural network efficiency, implying a possible cumulative effect of overall SVD markers on disrupted physiology. The association was primarily driven by the presence of moderate-severe WMHs and cSS. Further research are needed.

Background and Objective

Cerebral amyloid angiopathy (CAA) represents a common cause of spontaneous lobar intracerebral hemorrhage (ICH) and cognitive impairment in the elderly [Greenberg SM et al, Lancet Neurol 2014]. CAA is associated with a high prevalence of markers of small vessel disease (SVD), including hemorrhagic and nonhemorrhagic markers [Greenberg SM et al, Lancet Neurol 2014]. These neuroimaging markers often occur together, but the idea of addressing all features combined as a unitary measure of SVD has only gained attention recently [Staals J et al, Neurobiol Aging 2015; Charidimou A et al, JAMA Neurol 2016]. A composite score to quantify the total burden of SVD on MRI was recently developed specifically for CAA patients, based on the key neuroimaging markers of the disease [i.e. lobar cerebral microbleeds (CMBs), cortical superficial siderosis (cSS), white matter hyperintensities (WMH)

and centrum semiovale (CSO)-enlarged perivascular spaces (EPVS)] [Charidimou A et al, JAMA Neurol 2016].

Brain network alterations related to individual MRI markers of SVD in CAA were recently demonstrated [Reijmer YD et al, Brain: a journal of neurology 2015]. Considering diffusion based network measures sensitive to detect different relevant SVD-related brain injury, we aimed to investigate if increased overall SVD injury on MRI (*total MRI SVD score*) corresponds to worse global brain connectivity (evaluated by diffusion imaging based network analysis) in CAA.

Materials and Methods

Cross-sectional data was obtained from an ongoing single-center cohort study on CAA [Xiong L et al, J Alzheimers Dis 2016]. Seventy-three patients with a diagnosis of probable or definite CAA (according to the Boston criteria) [Knudsen KA et al, Neurology 2001] were eligible for the current study. All patients underwent a 1.5 Tesla research brain MRI scan between March 2006 and October 2015, including a diffusion weighted sequence [Reijmer YD et al, Brain: a journal of neurology 2015]. The Institutional Review Board approved the study and informed consent was obtained from all participants. MRI scans were rated for SVD markers by trained observers, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) [Wardlaw JM et al, The Lancet Neurology 2013]. Raters were blinded to all clinical data. SVD markers included: ICH, lobar CMBs and cSS (rated on susceptibility weighted images), WMH (weighted on fluid attenuated inversion recovery images) and (CSO)-EPVS rated on T1 weighted images). More details of markers included in *total MRI SVD score* are described in the paper of Charidimou et al. [Charidimou A et al, JAMA Neurol 2016]. In our cohort, CSO-EPVS were rated on axial T1-weighted MR images, according to a validated 4-point visual scale [Martinez-Ramirez S et al, Neurology 2013]. Based on previous studies, we dichotomized degrees of EPVS into high (score 4) and low (score 1 to 3). The arbitrary cutoff for EPVS detection was chosen to weight severe EPVS burden and was counted if there were moderate-to-severe (grade 4, i.e. >20) EPVS (one point if present). The intra- and inter-rater Cohen's Kappa agreement for perivascular spaces ranged from 0.90±0.09 and 0.89±0.10, respectively.

The total MRI SVD score ranged from a minimum of 0 to a maximum of 6 points, by counting the presence of each of these 4 MRI features, as described [Charidimou A et al, JAMA Neurol 2016].

Total brain volume (TBV) was obtained from T1-weighted multi-echo MPRAGE (MEMPRAGE) scans using the FreeSurfer neuroimaging analysis software's (version 5.3) segmentation algorithm (http://surfer.nmr.mgh.harvard.edu) as previously described [Fotiadis P et al, Lancet Neurol 2016].

Diffusion imaging based network reconstruction: High angular resolution diffusion imaging (HARDI) scans were collected and processed as previously described [Reijmer YD et al, Brain: a journal of neurology 2015]. In brief, whole-brain white

matter tractography was performed using deterministic streamline constrained spherical deconvolution (CSD). The cortical and subcortical gray matter were parcellated into 90 regions and the mean FA of the connection between each pair of brain regions was calculated. To account for the effects of ICH on structural connectivity, we limited our analysis to the network of the ICH-free hemisphere. For each hemispheric network we calculated the global efficiency in accordance to our cross-sectional analysis [Reijmer YD et al, Brain: a journal of neurology 2015]. The global efficiency is calculated as the inverse of the shortest path lengths (i.e. the minimum number of FA-weighted connections between each pair of brain regions) and quantifies how efficiently information is exchanged over the network [Rubinov M et al, Neuroimage 2010].

The associations between *total MRI SVD score* (independent variable) and global network efficiency (dependent variables) were analyzed using ordinal logistic regression model. We additionally assessed the association between each SVD component of the *total MRI SVD score* and global network efficiency with ordinal logistic regression analysis. In the first model, we included age and sex as covariates. In the second model, we additionally included normalized TBV.

Results

The study sample consisted of 73 patients (58 (79.5%) male, mean age 70.58 (SD=8.22). According to Boston criteria, 4 (5.5%) patients were diagnosed with definite CAA and 69 (94.5%) patients with probable CAA. The relative prevalence of neuroimaging markers in this cohort are shown in Table 1. Among neuroimaging markers of CAA, 61 (82.4) patients had more than 5 CMBs, 20 (20.8) had focal cSS and 21 (28.4) disseminated cSS, 45 (60.8) patients were with >20 CSO-EPVS, 51 (68.9) with moderate-severe WMH (49 (66.2) occipital gradient) and 52 (70.3) with moderate-severe global cortical atrophy (Table 1). The total MRI SVD score was normally distributed (mean, SD) 3.9 (1.40) range (min 1-max 6), with score=1 in 4 (5.5%) cases, score=2 in 8 (11.0%), score=3 in 18 (24.7%), score=4 in 12 (16.4%), score=5 in 23 (31.5%), score=6 in 8 (11.0%) (Figure 1).

Figure 2 shows the association between total MRI SVD score and global network efficiency. Higher total MRI SVD score was correlated with lower global network efficiency (B coefficient [95% CI]: -0.004 [-0.007 to -0.001], p=0.013 and coefficient [95% CI]: -0.004 [-0.007 to 0.004], p=0.030 for first model and second model, respectively). Of the individual SVD components of the total MRI SVD score, presence of cSS and moderate-severe WMHs correlated negatively with global network efficiency (-0.016 ± 0.006, p=0.011 and -0.017 ± 0.005 p=0.002, respectively). No clear dose-response relationship was seen.

Conclusion

In the current study we examined whether an increased burden of SVD in patients with CAA was associated with greater impairments in structural network efficiency [Reijmer YD et al, Brain: a journal of neurology 2015]. We showed a modest significant inverse correlation with *total MRI SVD score* and global network efficiency in CAA patients. However, no dose-response relationship was observed. This association was primarily driven by the presence of moderate-severe WMHs and cSS.

We applied the composite SVD score of overall SVD load by summing some MRI features of SVD created by extensive work of two groups [Staals J et al, Neurobiol Aging 2015; Charidimou A et al, JAMA Neurol 2016]. Our results showed more severe CAA injury on MRI corresponds to more reductions in global brain connectivity, implying a possible cumulative effect of overall SVD markers on disrupted physiology [Reijmer YD et al, Brain: a journal of neurology 2015]. However, not every SVD component of the *total MRI SVD score* seemed to significantly contribute to the reduction in network efficiency.

Possible explanations for this finding are: 1. the cut-off score for each SVD marker within the score was not optimal for this sample (e.g. almost all patients have CMBs); 2. a possible ceiling effect due to advanced CAA severity in all patients (mild CAA cases are needed in the future studies); 3. some CAA SVD markers (e.g. cortical microinfarcts, cSS) are markers of cortical brain injury, whereas the network measures may be more sensitive to injury in the subcortical white matter; 4. possibly individual SVD markers do not add up in a synergistic fashion but represent shared diffuse underlying pathology.

An important limitation of our study are the small sample size and the lack of control group. The cross-sectional design precludes us from performing longitudinal analyses.

Further research focused on the association between an increased burden of SVD neuroimaging markers and impairments in structural network efficiency in patients with CAA are needed.

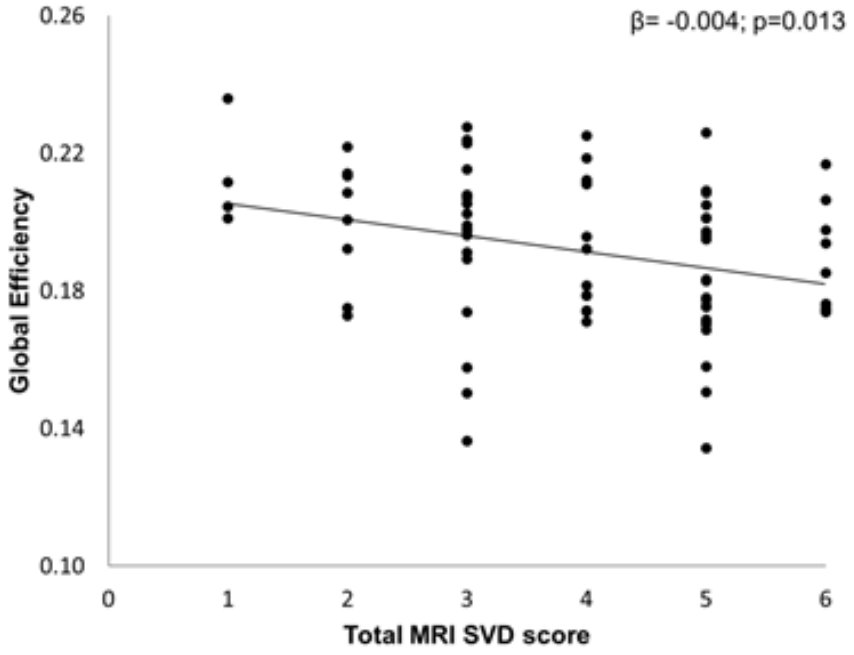

Figure 1. Scatterplot of the association between *total MRI SVD score* and global network efficiency.

Clinical variables	CAA cohort (N=73)
Age (years), mean (SD)	70.58 (8.22)
Male, N (%)	58 (79.5)
Hypertension, n (%)	42 (57.5)
Diabetes, n (%)	5 (6.8)
Hypercholesterolemia, n (%)	33 (45.2)
Smoking, n (%)	3 (4.1)
Dementia, n (%)	5 (6.8)
Brain MRI markers	
ICH	29 (39.7)
CMBs, N (%)	70 (95.9)
CMBs > 5, N (%)	60 (82.2)
cSS, N (%)	39 (53.4)
Focal cSS, N (%)	18 (24.7)
Disseminated cSS, N (%)	21 (28.8)
CSO-EPVS >20, N (%)	45 (61.6)
WMH [Fazekas score], mean (SD)	1.90 (0.73)
moderate-severe, N (%)	50 (68.5)
occipital gradient, N (%)	48 (65.8)
Moderate-severe global cortical atrophy [Pasquier scale], N (%)	51 (69.9)
TBV	1695815,202 (144547,029)

Table 1. Characteristics of the study sample.

Abbreviations: ICH= intracerebral hemorrhage, CMBs=cerebral microbleeds, cSS=cortical superficial siderosis, WMH=white matter hyperintensities,

* Number of patients with available data

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Chapter 2
Cerebral Small Vessel Disease and cognitive features

Note: The next two studies derived from the evidence that application of different diagnostic criteria for different type of cognitive impairment exist. Recent proposal of diagnostic criteria for vascular cognitive impairment highlights the need of an objective evidence of decline using validated measures of cognitive functions and giving equal importance to several cognitive domains [Sachdev P et al, Alzheimer Dis Assoc Disord 2014].

The third one is focused on a specific cognitive deficit in patients affected by CAA, given posterior brain damage predilection of the disease.

2.2.1 Winblad's criteria for differentiating vascular from degenerative mild cognitive impairment. Results from a case-to-case comparison

Winblad's criteria for differentiating vascular from degenerative mild cognitive impairment. Results from a case-to-case comparison

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Abstract

Background: Mild cognitive impairment (MCI) can be subsided by either degenerative or vascular brain changes. Clinical and neuroimaging discriminating factors selective of the two conditions are still undetermined.

Objective: To test whether inclusion criteria established for a study of Vascular MCI (V-MCI) are able to discriminate enough from Degenerative MCI (D-MCI), comparing clinical, cognitive and imaging features commonly associated with either of the two pictures.

Methods: In the Vascular Mild Cognitive Impairment (VMCI)-Tuscany Study the Winblad's et al. clinical definition of MCI, combined with evidence on MRI scan of moderate to severe degree of white matter changes (WMC) were chosen as inclusion criteria. To check for the ability of such criteria to discriminate these patients from those with D-MCI, we compared 30 V-MCI patients with 30 patients with D-MCI. We matched the two groups for age and gender using the propensity score method.

Results: Family history of dementia was more prevalent in the D-MCI group; vascular risk factors, history of stroke, migraine, depression, gait disorders and urinary disturbances were more common in the V-MCI group. Verbal memory was significantly more impaired among D-MCI patients, while divided attention, constructional praxis and phonemic verbal fluency were more common among V-MCI patients. Regarding MRI features, lacunar infarcts were more prevalent among V-MCI patients, while global atrophy and enlarged perivascular spaces in centrum semiovale were more frequent among D-MCI patients. The more discriminating variables between two groups were hypercholesterolemia, gait disorders, constructional praxis, lacunar infarcts and medial temporal lobe atrophy (left hemisphere) for V-MCI and family history of dementia, verbal memory and cortical global atrophy for D-MCI.

Conclusion: The adopted criteria for enrolling patients in the VMCI-Tuscany Study were able to distinguish reliably enough V-MCI from D-MCI, based on current knowledge.

Introduction

Mild cognitive impairment (MCI) is an abnormal condition characterized by cognitive decline (greater than expected for an individual's age and education level) not severe enough to fit criteria for dementia and to affect global functioning and autonomy [Petersen RC et al, Arch Neurol 1999; Dubois B et al, Lancet Neurol 2010]. From population-based studies the frequency of MCI is more than double compared to that of dementia [Ward A et al, Alzheimers Dement 2012], ranging from 3% to 19% in adults over 65 years [Ward A et al, Alzheimers Dement 2012]. Subjects with MCI are considered to be at high risk for developing dementia of Alzheimer's Disease type [Stephan BC et al, Alzheimers Res Ther 2009]. However, application of different diagnostic criteria for defining MCI might affect its prevalence and progression rate [Matthews FE et al, J Am Geriatr Soc 2008]. It is also known that some subtypes of vascular dementia (VaD) are preceded by a prodromal state that can be defined as

vascular-MCI (V-MCI) [Pantoni L et al, Cerebrovasc Dis 2009]. In the Canadian Health and Aging Study 46% of patients with V-MCI developed dementia after 5 years [Wentzel C et al, Neurology 2001]. Progression related mostly to the subcortical VaD type. The determinants of transition from V-MCI to VaD are not fully elucidated, and this was the reason why the Vascular Mild Cognitive Impairment (VMCI)-Tuscany Study [Poggesi A et al, Int J Alzheimers Dis 2012] was designed. This is an ongoing multicenter, prospective, observational study, carried out in the Tuscany region of Italy. A large set of clinical, cognitive, neuroimaging, and biological markers of small vessel disease (SVD) are being investigated as potential predictors of the transition from V-MCI to dementia [Poggesi A et al, Int J Alzheimers Dis 2012].

From neuroimaging point of view, MRI studies have shown that medial temporal lobe atrophy (MTA) and rates of brain loss can predict which subjects with MCI of neurodegenerative type (D-MCI) will progress to AD. On the other side, in subcortical VaD, likely the most frequent VaD subtype, pathological hallmarks are ischemic white matter changes (WMC) and lacunar infarcts, both expression of cerebral SVD. Accumulation over time of both lacunar infarcts and WMC was shown as the main factor of cognitive decline, from mild to more severe stages [Pantoni L et al, Neuroepidemiology 2005]. However MRI studies have also shown that, even in this condition, brain atrophy may contribute to cognitive deterioration [van der Flier WM et al, J Neurol Neurosurg Psychiatry 2005]. Recently, another MRI marker of SVD, i.e. enlarged perivascular spaces (EPVS) has been reported as independent factor of cognitive decline [Doubal FN et al, Stroke 2010; Wardlaw JM et al, Lancet Neurol 2013]. EPVS have been described also in patients with D-MCI and AD [Chen W et al, AJNR Am J Neuroradiol 2011].

The aim of this study was to corroborate inclusion criteria adopted to enroll patients in a study focusing on V-MCI, checking for functional and neuroimaging data commonly considered to discriminate between V-MCI and D-MCI.

Materials and methods

Patients with D-MCI to be compared with the subsample of patients enrolled in the Tuscany VMCI Study were extracted from a series of 80 D-MCI patients enrolled for the prospective MRI study performed by Mascalchi et al. [Mascalchi M et al, AJNR Am J Neuroradiol 2013]. Similar clinical, functional and imaging protocols had been used in the two studies. Thirty D-MCI patients from this series and the 30 with V-MCI, out of the 104 patients enrolled in VMCI-Tuscany Study, were matched for demographic characteristics using propensity score matching.

All patients included were classified as affected by MCI according to original Petersen et al.'s diagnostic criteria [Petersen RC et al, Arch Neurol 1999; Winblad B et al, J Intern Med 2004], as follows: 1) self- or informant-reported cognitive complaint, 2) objective cognitive impairment, 3) preserved general functional abilities, and 4) no dementia.

Moreover, V-MCI patients had moderate to severe WMC on MRI, according to the modified version of Fazekas scale [Pantoni L et al, Neuroepidemiology 2005;

Fazekas F et al, AJR Am J Roentgenol 1987]. D-MCI diagnosis was based on Winblad's clinical criteria for amnestic MCI. In addition, patients had to have at MRI only mild WMC, as rated using the same modified version of Fazekas scale [Fazekas F et al, AJR Am J Roentgenol 1987] (Figure 1).

Both groups had undergone a comprehensive clinical, neuropsychological, laboratory and neuroimaging studies (Table1). Clinical assessment included demographic data, medical history, vascular risk factors profile, neurologic examination (Table1). Functional independence was rated using both ADL (Activities of Daily Living) and IADL (Instrumental Activities of Daily Living) scales; global mental functioning was assessed by the Mini Mental State Examination (MMSE); selective cognitive functions were examined using a standard comprehensive neuropsychological battery including tests of verbal memory, attention, executive functions and language (Table1). Depression was assessed using the Geriatric Depression Scale (GDS) (Table1). For the evaluation of neuropsychological performances, the Equivalent Scores (ES) methodology, a non-parametric norming method overtaking the problem of standardizing neuropsychological scores, was applied. The ES methodology is an ordinal 5-point scale (ranging from 0 to 4), in which ES = 0 represents pathological performances, ES = 4 indicates an optimal performance, proposed by Capitani and Laiacona [Poggesi A et al, Int J Alzheimers Dis 2012; Capitani E et al, J Clin Exp Neuropsychol 1997; Salvadori E et al, J Alzheimers Dis 2015].

All patients had a brain MRI study performed on a 1.5 T scanner (Intera, Philips Medical System, Best, The Netherlands), and using a standard protocol including T1-weighted and Fluid Attenuated Inversion Recovery (FLAIR) images. We reviewed all MRI scans, blind to clinical data and recorded the followings imaging features: a) deep WMC classified on FLAIR sequences as mild, moderate or severe degree according to the modified Fazekas' scale [Fazekas F et al, AJR Am J Roentgenol 1987]; b) presence and number of lacunar infarcts categorized into none, few (1-3 lacunes) and many (≥3 lacunes) [van der Flier WM et al, J Neurol Neurosurg Psychiatry 2005]; c) global cortical atrophy using the scale of Pasquier et al. that considers opening of sulci and narrowing of gyri (scores 0–3 representing absent, mild, moderate, and severe cortical atrophy, respectively) [Pasquier F et al, Eur Neurol 1996]; d) MTA measured by means of the Scheltens' scale on T1- coronal weighted images (range from 0 to 4 on the left and right hemisphere indicating progressive medial temporal volume loss; mean MTA of the bilateral scores was calculated and dichotomized (MTA score 0-2.5 and MTA score ≥3) [Scheltens P et al, Eur Neurol 1997]. Moreover, we assessed the presence of EPVS defined as ≤3 mm round or linear cerebrospinal fluid-isointense lesions appearing hypointense on T1/FLAIR sequences. EPVS were rated in the basal ganglia, centrum semiovale and midbrain using a published visual rating scale [Doubal FN et al, Stroke 2010]. We dichotomized basal ganglia and centrum semiovale EPVS into 0 (EPVS score 0,1) and 1 (EPVS scores 2,3,4) reflecting mild versus moderate to severe EPVS as used in previous studies [Potter GM et al, Int J Stroke 2015]. Inter-rater agreement on assessment of each single MRI change ranged from good to very good for lacunar infarcts (weighted Cohen's kappa 0.82), WMC (weighted Cohen's kappa 0.91), MTA (weighted Cohen's kappa 0.87), cortical global atrophy (weighted Cohen's kappa 0.62), and EPVS (Intraclass Correlation Coefficients 0.72 for basal ganglia and 0.93 for centrum semiovale).

Statistical analysis

After a preliminary analysis about demographic data, the two groups (104 V-MCI and 30 D-MCI) resulted different in regard to age, gender and education level. A univariate analysis, purposing adjusting for the demographic variables, was not correctly applicable because of the small sample of D-MCI group. Thus, considering demographic characteristics of D-MCI sample, we created two groups of patients, matched for age, sex and educational level by the propensity score method obtaining 30 patients with V-MCI and 30 with D-MCI. Propensity score matching was obtained by means of PSMATCHING3 extension of R in SPSS20 with algorithm "Nearest Neighbor" [Thoemmes F et al, Multivariate Behavioral Research 2011].

Descriptive analyses were used to briefly characterize the baseline sample in terms of demographic, clinical and neuroimaging features. For neuropsychological data mean ES was used to compare performance's distributions across two different groups [Salvadori E et al, J Alzheimers Dis 2015].

For dichotomous and categorized variables Pearson χ^2 test and for continuous variables nonparametric Mann–Whitney *U* test were used. To classify in order of importance the variables discriminating the two groups, logistic regression analysis was used. All *p* values were two-tailed, and the level of significance was set at $p < 0.05$.

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Institute, Inc., Cary, NC) [IBM Corp (2011) IBM SPSS Statistics for Windows, Version 757 20.0. IBM Corp, Armonk, NY].

Results

After the equivalence of demographic characteristics between the two groups achieved using the PS matching, the cognitive reserve turned out to be not dissimilar between the two groups: in fact IQ score estimated by intelligence short test was 29.27 vs. 28.70, among D-MCI and V-MCI patients respectively (p=0.898).

Patients' characteristics are summarized in Table 2 and in Table 3. Family history of dementia was more prevalent in the D-MCI group (p=0.009), while family history of stroke did not differ between the two groups (Table 2). Regarding vascular risk factors, hypertension, hypercholesterolemia and alcohol intake were more common in the V-MCI group (p=0.007, p<0.001, p=0.007, respectively) (Table 2). Moreover, heart disease (p=0.026), migraine (p=0.008) severe depression (p<0.001), gait disorders (p<0.001) and urinary disturbances (p=0.003) were more prevalent in the V-MCI patients (Table 2). Neurological examination showed no statistically significant differences between the two groups.

Concerning neuropsychological data, global mental functioning was similar for D-MCI and V-MCI patients (p=0.203); functional autonomy was equally preserved in the two groups (p=0.149) (Table 3). Attentive and executive functions, in particular tests evaluating selective attention and psychomotor speed did not significantly differ between the two groups (Table 3). Verbal memory assessed using the Short Story recall test was significantly more impaired in D-MCI than V-MCI (p=0.001), while

abnormal performances in divided attention (Trail Making Test, Part B (TMT-B), constructional praxis (Rey-Osterrieth Complex Figure (ROCF) for immediate copy) and phonemic verbal fluency, were significantly more frequent in the V-MCI group than in the D-MCI group ($p=0.002$, $p<0.001$, and $p=0.014$, respectively) (Table 3).

Regarding MRI features, lacunar infarcts were ten times more frequent among V-MCI than among D-MCI patients ($p<0.001$), while global cortical atrophy was more than ten times more frequent in the D-MCI group ($p<0.001$) (Table 3). There were no statistical differences regarding MTA, slightly more represented among V-MCI patients in both hemispheres, and in the number and location of EPSV located in the basal ganglia; in contrast, EPSV in centrum semiovale were more prevalent in the D-MCI than in the V-MCI group ($p=0.004$) (Table 3). By logistic regression model we achieved a ranking in order of importance of the discriminating variables for V-MCI and D-MCI. Regarding clinical variables, the more predictive variables were hypercholesterolemia, gait disorders and family history of dementia; among neuropsychological variables were constructional praxis and verbal memory; and among MRI features, MTA (left hemisphere), lacunar infarcts and cortical global atrophy (data not shown).

Discussion

Our results show that the adopted criteria for enrolling patients in a study aiming to investigating biomarkers of V-MCI progression, i.e. Winbland's et al. clinical criteria combined with MRI WMC evidence of moderate or severe degree according to the Fazekas scale, were substantially reliable for discriminating V-MCI from MCI on degenerative basis, assuring enough homogeneity of thus defined patients' samples to be used for V-MCI studies. Such conclusions are based on a significantly greater prevalence of family history of dementia in the D-MCI group, the greater deficit of episodic memory among patients with D-MCI, and the impairment of divided attention, constructional praxis and phonemic verbal fluency among patients with V-MCI, on cognitive grounds; the greater prevalence of global cortical atrophy and EPVS in centrum semiovale among patients with D-MCI and lacunar infarcts with V-MCI, on brain imaging grounds. The cognitive study confirmed the relevance of memory disorders in MCI of neurodegenerative type (also defined 'amnestic MCI'); however it has to be underlined that episodic memory was assessed in D-MCI patients using the Short Story recall test, that is a different test in respect to that used for the V-MCI Tuscany inclusion criteria. On the other side, the V-MCI group resulted characterized by the multi-domain profile, involving attentive and executive functioning, such as divided attention, visuo-constructional abilities and phonemic verbal fluency [Salvadori E et al, J Alzheimers Dis 2015].

On brain imaging, as expected, global cortical atrophy was typical of patients with impairments on degenerative basis, even in the earlier stages. In our sample, however, bilateral MTA resulted slightly more frequent in V-MCI patients. In the LADIS study significant correlation between the presence of severe WMH and MTA was found [van der Flier WM et al, J Neurol Neurosurg Psychiatry 2005; Korf ES et al, Diabet

Med 2007]. Regarding EPVS, they have been recently identified as a potential MRI marker of the presence and severity of SVD [Doubal FN et al, Stroke 2010; Wardlaw JM et al, Lancet Neurol 2013]. EPSV have been reported to be associated with increasing age, lacunar stroke subtype and WMC [Potter GM et al, Int J Stroke 2015]. In our sample, basal ganglia EPVS were found also in D-MCI group, despite the much lower prevalence of hypertension or diabetes. Mechanisms that are supposed to possibly underlie enlargement of perivascular spaces include increased permeability of the arterial wall, brain atrophy, and impaired perivascular drainage [Adachi M et al, Neuroradiology 1998], all plausibly connected with the degenerative pathology.

In summary definition of vascular MCI based on Winbland's et al criteria combined with the MRI evidence of Fazekas' moderate or severe WMC appears reliably good for discriminating V-MCI from D-MCI, making more homogeneous study samples to be used for clinical studies in this disease setting.

Clinical assessment	Method/Scale
Clinical history	Standard
Family history	Standard
Vascular risk factors	Standard
General physical examination	Standard
Neurological examination	Standard
Functional assessment	Activities of Daily Living Instrumental Activities of Daily Living
Depressive symptoms	Geriatric Depression Scale
Neuro-psychological evaluation	**Method/Scale**
Global cognitive functioning	Mini-Mental State Examination, IQ estimated
Verbal Memory	Short story recall test
Constructional praxis	Rey-Osterrieth Complex Figure, copy
Selective attention	Color Word Stroop Test (short form)
Divided attention and psychomotor speed	Trail Making Test (part A, part B)
Language	Phonemic verbal fluency
Neuroimaging evaluation (MRI)	
White matter lesions severity	Fazekas Scale (FLAIR and T2-weighted sequences)
Lacunar and non-lacunar infarcts	T1-weighted and proton density sequences with evaluation of number and location
Cortical atrophy	Visual rating scale (Pasquier Scale)
Medial temporal lobe atrophy	Coronal T1-weighted sequences (Scheltens' Scale)

Table 1. Protocol for the clinical, neuroimaging and neuropsychological assessment.

* For the protocol's details see Poggesi A, Int J Alzheimers Dis 2012.

	D-MCI (30) (n, %)	V-MCI (30) (n, %)	p (χ^2)
Mean age (years ± SD)[a]	71.1 ± 5.9	71.3 ± 6.9	0.859[a]
Gender (female)	20 (66.7)	19 (63.3)	1.000
Education level (years ± SD)[a]	8.6 ± 4.4	8.9 ± 4.3	0.623[a]
Family history			
Family history of dementia	20 (66.7%)	9 (30.0%)	0.009*
Family history of stroke	10 (33.3%)	17 (56.7%)	0.119
Vascular risk factors			
Hypertension	13 (43.3%)	24 (80.0%)	0.007*
Hypercholesterolemia	4 (13.3%)	22 (73.3%)	<0.001*
Diabetes	4 (13.3%)	6 (20.0%)	0.731
History of smoke	7 (23.3%)	11 (36.7%)	0.399
Alcohol intake	3 (10.0%)	13 (43.3%)	0.007*
Clinical characteristics			
Heart disease	1 (3.3%)	8 (26.7%)	<0.026*
Migraine	7 (23.3%)	18 (60.0%)	0.008*
Thyroid disorders	6 (20.0%)	8 (26.7%)	0.761
Gait disorders	3 (10.0%)	18 (60.0%)	<0.001*
Urinary disturbances	6 (20.0%)	18 (60.0%)	0.003*
Psychiatric disorders	12 (40.0%)	18 (60.0%)	0.196
Mood disorders	9 (32.1%)	16 (53.3%)	0.120
Severity of depression	1 (3.6%)	13 (43.3%)	<0.001*

Table 2. Baseline demographic and clinical characteristics.

[a] Anova univariate analysis

	D-MCI (30)	V-MCI (30)	p[a]
Mean MMSE	28.4 ± 1.8	27.4 ± 2.5	0.203
IADL (preserved number of items)	7.1 ± 1.8	7.1 ± 1.0	0.149
Cognitive assessment			
	D-MCI (30) ES (mean)	V-MCI (30) ES (mean)	p [a]
TMT-A[d] (abnormal performance)	2.9 ± 1.6	2.2 ± 1.6	0.107
TMT-B[d]	3.0 ± 1.4	1.6 ± 1.7	0.002*
TMT-B-A[d]	3.3 ± 1.1	2.6 ± 1.4	0.088
ROCF-immediate copy[d]	3.0 ± 1.6	0.9 ± 1.5	<0.001*
ROCF –delayed copy[d]	2.6 ± 1.5	2.2 ± 1.4	0.314
Story Recall Test[d]	1.3 ± 1.4	2.5 ± 1.3	0.001*
Stroop Test: Time[d]	2.7 ± 1.6	1.7 ± 1.7	0.076
Stroop Test: Error[d]	3.4 ± 1.3	3.2 ± 1.2	0.315
Phonemic fluency[d]	3.2 ± 0.9	2.3 ± 1.4	0.014*
Neuroimaging features			
	D-MCI	V-MCI	p [b]
Lacunar infarcts	2 (6.7%)	20 (66.7%)	<0.001*
Cortical global atrophy (severe)	14 (46.7%)	1 (3.3%)	<0.001*
MTA dx (severe)	20 (66.7%)	21 (70.0%)	0.931
MTA sx (severe)	20 (66.7%)	22 (73.3%)	0.711
EPVS Basal Ganglia (severe)	9 (32.1%)	15 (53.6%)	0.105
EPVS Centrum Semiovale (severe)	26 (92.9%)	17 (60.7%)	0.004*
EPVS Midbrain	14 (50.0%)	16 (57.1%)	0.592

Table 3. Neuropsychological and neuroimaging features of the two groups

IADL: Instrumental Activities of Daily Living; MMSE: Mini Mental State Examination; TMT: Trail Making Test; ROCF: Rey–Osterrieth Complex Figure; MTA: medial temporal lobe atrophy; EPVS: enlarged perivascular spaces.

[a] nonparametric Mann–Whitney U test

[b] Pearson χ^2 test

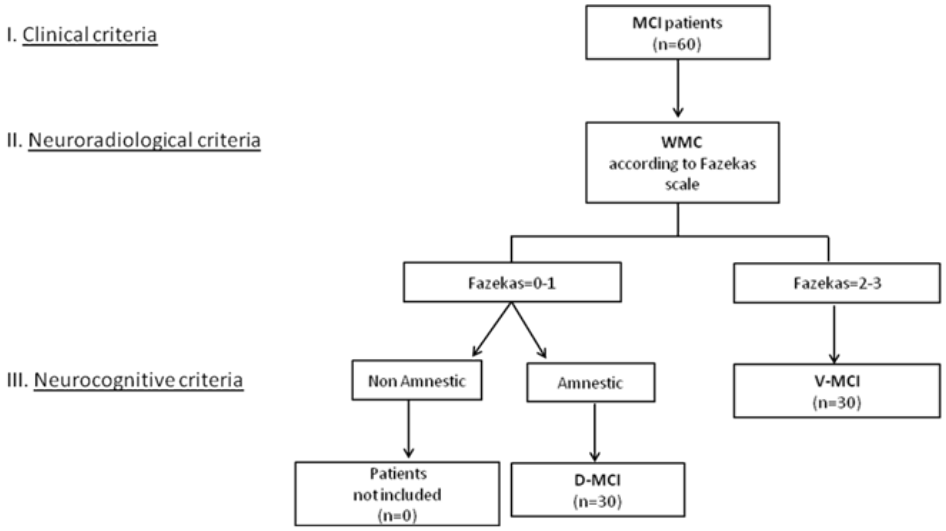

Figure 1. Post-hoc flow-chart of selected patients

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2.2.2. Mild cognitive impairment etiologic subtyping using *pragmatic* and *conventional criteria*: preliminary experience in the Florence VAS-COG clinic

Mild cognitive impairment etiologic subtyping using *pragmatic* and *conventional criteria*: preliminary experience in the Florence VAS-COG clinic

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ORIGINAL ARTICLE

Mild cognitive impairment etiologic subtyping using *pragmatic* and *conventional criteria*: preliminary experience in the Florence VAS-COG clinic

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Abstract

Background: Mild cognitive impairment (MCI) is an abnormal condition defined by the presence of cognitive decline not severe enough to fit dementia criteria. According to Winblad et al.'s criteria, he clinical distinction of MCI subtypes (amnestic/non-amnestic, single/multiple domain) is based on the cognitive profiling (*conventional diagnosis*) and infers possible different MCI etiologies. MCI rodromic of vascular dementia (Vasc-MCI) is thought to be characterized by a multiple domain profile. In our outpatient clinic (the "Florence VAS-COG clinic"), the diagnosis of MCI and of its different subtypes (vascular, degenerative, mixed) is based on a comprehensive evaluation of clinical and neuroimaging features (*pragmatic diagnosis*).

Aims: To compare the pragmatic and conventional diagnoses in terms of etiologic subtyping of MCI.

Methods: We retrospectively assessed the agreement between the two diagnoses in 30 MCI patients. Agreement was considered present when degenerative MCI was of the amnestic type (single or multiple domain) and Vasc-MCI was of the multiple domain type (amnestic or non-amnestic MCI).

Results: In 15/30 (50%) patients, the diagnoses were in disagreement: 5/9 (56%) patients diagnosed with a degenerative MCI type presented a non-amnestic cognitive profile (4 single domain and 1 multiple domain); 10/21 (48%) Vasc-MCI were classified as non-amnestic single domain.

Conclusions: The application of MCI etiologic subtyping using pragmatic or conventional diagnoses leads to different results. In our setting, not all the Vasc-MCI patients have a multiple domain profile. Our preliminary study suggests that the cognitive profile of Vasc-MCI is more heterogeneous than previously suggested.

Introduction

Mild cognitive impairment (MCI) is an abnormal condition defined as an objective cognitive decline (greater than expected for an individual's age and education level) with maintenance of intact global cognitive functioning and autonomy and, therefore, not severe enough to fit the criteria for dementia [Petersen RC et al, Arch Neurol 1999; Dubois B et al, Lancet Neurol 2010]. Although application of different diagnostic criteria for MCI might affect its prevalence and progression estimates [Stephan BC et al, Alzheimers Res Ther 2009; Matthews FE et al, J Am Geriatr Soc 2008], the frequency of MCI in population-based studies is more than double that of dementia [Panza F et al, Am J Geriatr Psychiatry 2005; Ward A et al, Alzheimers Dement 2012], ranging from 3% to 19% in adults over 65 years [Ward A et al, Alzheimers Dement 2012].

The original Petersen et al.'s diagnostic criteria for MCI included: subjective complaint of memory loss; memory impairment on brief cognitive or neuropsychological testing; decline from previously normal level of function; present basic daily functioning unchanged; no medical, neurologic or psychiatric explanation for memory loss; and, cognitive impairment not meeting the criteria for dementia [Dubois B et al,

Lancet Neurol 2010; Chertkow H et al, CMAJ 2008]. The focus of these criteria was on the prodromal stages of Alzheimer disease (AD), a condition in which memory deficits are the most prominent disturbances [Dubois B et al, Lancet Neurol 2010; Chertkow H et al, CMAJ 2008]. Also in the more recent clinical criteria for individuals with MCI, memory is the most common and the typical involved domain among patients who subsequently progress to AD [Albert MS et al, Albert MS 2011].

It is assumed that also some subtypes of vascular dementia (VaD) are preceded by a prodromal state that can be defined as vascular-MCI (Vasc-MCI) [Hachinski VC et al, Neurology 1993; Pantoni L et al, Cerebrovasc Dis 2009; O'Brien JT et al, Lancet Neurol 2003]. In the Canadian Health and Aging Study, 46% of patients with Vasc-MCI developed dementia after 5 years [Rockwood K et al, Neurology 2000; Wentzel C et al, Neurology 2001]. Unlike degenerative dementia, not all forms of VaD (e.g., post-stroke dementia) are preceded by MCI [Pantoni L et al, Cerebrovasc Dis 2009]. The most common cause of Vasc-MCI is small vessel disease, in which lacunar infarcts and white matter changes (WMC) accumulation determines a gradual progression of cognitive impairment, from mild to more severe stages [Pantoni L et al, Neuroepidemiology 2005]. Vasc-MCI is theoretically an important MCI subtype to identify as mounting evidence suggests that preventive measures may be undertaken to treat vascular risk factors associated with cognitive deficits [Gorelick PB et al, Stroke 2011].

The clinical classification of MCI proposed by Winblad et al. [Winblad B et al, J Intern Med 2004] is based on the cognitive profiling and implies possible different etiologies of MCI (*conventional diagnosis*). According to these authors, MCI is classified into amnestic and non-amnestic forms, depending on whether a memory deficit is present or not [Winblad B et al, J Intern Med 2004]. In the non-amnestic form of MCI the decline is in domains not related to memory (e.g., attention, language, or visuospatial skills). This subtype is considered the forerunner of dementias that are not related to AD, such as VaD, frontotemporal lobar degeneration, or dementia with Lewy bodies [Winblad B et al, J Intern Med 2004]. In both amnestic and non-amnestic forms, a further subdivision is made according to the presence or absence of deficits in different domains (single or multiple domain amnestic MCI, single or multiple domain non-amnestic MCI) [Winblad B et al, J Intern Med 2004; Petersen RC et al, CNS Spectr 2008]. According to this classification, Vasc-MCI is characterized by a multiple domain profile, either amnestic or non-amnestic [Winblad B et al, J Intern Med 2004; Petersen RC et al, CNS Spectr 2008].

Although many studies have referred to the Petersen et al.'s criteria to diagnose MCI [Panza F et al, Am J Geriatr Psychiatry 2005], it has been recently observed that the specific operational definitions often differed [Clark LR et al, J Int Neuropsychol Soc 2013; Stephan BC et al, BMJ Open 2013], while some authors have pointed out that the heterogeneity of MCI subtypes is not reflected in conventional criteria [Delano-Wood L et al, J Int Neuropsychol Soc 2009; Edmonds EC et al, Alzheimers Dement 2014].

In our out-patient service dedicated to the psycho-cognitive and behavioral consequences of cerebrovascular diseases (the "Florence VAS-COG" clinic) [Ciolli L et al, Neurol Sci 2012]), the diagnosis of MCI and of its different etiological subtypes is

based on a global evaluation of clinical, neuropsychological and neuroimaging aspects (*pragmatic diagnosis*).

We performed a retrospective study to compare the etiologic subtyping of MCI using daily clinical *pragmatic diagnoses* and *conventional diagnoses* according to the original Winblad's criteria.

Methods

We retrospectively reviewed the clinical, neuropsychological and neuroimaging data of non-demented patients with possible MCI afferent to our VAS-COG clinic.

The diagnosis of MCI, according to the VAS-COG clinic protocol, was obtained after a detailed personal history, general and neurological examinations, functional, behavioral and psychiatric assessments, and neuroimaging evaluation (table 1) [Ciolli L et al, Neurol Sci 2012]. Neuroimaging (MRI or, in case of MRI contraindications, CT*)* plays an important role in our clinical work-up and the following parameters are visually appraised: WMC severity, infarcts, both lacunar and non-lacunar, assessed in terms of number and location, and cortical atrophy, medial temporal lobe atrophy (table 1). Each patient is assessed by means of an extensive neuropsychological battery focused on the evaluation of different cognitive domains especially those affected in patients with vascular lesions such as attention and executive functions, in addition to domains more typically impaired in the early stages of AD (as memory, semantic knowledge) [Salvadori E, J Alzheimers Dis 2014] (table 1).

Pragmatic diagnostic criteria used in the VAS-COG clinic [Ciolli L et al, Neurol Sci 2012] were the following: degenerative-MCI was defined as MCI according to Petersen et al.'s criteria in the absence of significant vascular lesions, i.e., presence of any of the following: 1) moderate to severe WML evaluated with the modified Fazekas scale; 2) lacunar infarcts >3 or at least one in a strategic site; 3) non-lacunar infarct; Vasc-MCI, is defined by consensus as the presence of MCI that does not involve exclusively memory domains and with neuroimaging evidence of significant vascular lesions and/or clinical history or signs of stroke; mixed MCI is defined, by consensus, in 2 different instances: a. MCI fitting Petersen's criteria and presence of significant vascular lesions on neuroimaging or b. MCI with clinical history or signs of cerebrovascular events and with neuroimaging features of a neurodegenerative process (moderate-to-severe diffused or lobar cortical atrophy including medial temporal lobe atrophy).

For *conventional diagnosis* (according to Winblad et al.'s criteria) diagnostic criteria are the following: if a memory deficit is present, the patient is classified as having amnestic MCI; if the memory domain is intact, the patient is classified as having non-amnestic MCI. Then, if there are deficits in a number of different domains, the patient is considered as having multiple domain MCI, otherwise as single domain MCI.

The agreement between the two kinds of MCI etiologic subtyping was considered present when degenerative MCI was of the amnestic form (single or multiple domain), and Vasc-MCI was of the multiple domain (amnestic or non-amnestic MCI).

We evaluated 46 patients for a suspicion of MCI; the diagnosis of MCI was confirmed in 42 (91%) patients. The neuropsychological evaluation did not confirm the presence of cognitive impairment in 4 patients (9%), and they were consequently diagnosed as affected by subjective memory impairment secondary to mood disorders.

Out of the 42 patients, 12 were diagnosed as affected by mixed MCI and thus excluded from the present analysis. The remaining 30 patients (17 males had a mean age of 75.9 years ±SD 7.4, and a mean education level of 7.6 years ± SD 4.6) and were classified according to *pragmatic diagnosis* as follows: 9/30 (30%) patients degenerative MCI, 21/30 (70%) Vasc-MCI (table 2).

The agreement between *pragmatic diagnoses* and *conventional diagnoses* was described in a contingence table, and the association between the two diagnoses assessed by means of Pearson chi-square test using SPSS version 20.0 for Windows (SPSS Institute, Inc., Cary, NC).

Results

The comparison between *pragmatic diagnoses* and *conventional diagnoses* is reported in table 2. In 15/30 (50%) patients the diagnoses were in agreement: 4/9 (44%) degenerative MCI patients presented an amnestic cognitive profile (all multiple domain); 11/21 (52%) Vasc-MCI patients had a multiple domain profile, amnestic (n=9) and non-amnestic (n=2). In 15/30 MCI patients the comparison of *pragmatic* and *conventional diagnoses* was discordant: 5/9 degenerative MCI patients presented a non-amnestic cognitive profile, 4 single domain and 1 multiple domain; 10/21 Vasc-MCI were classified as non-amnestic single domain. There was no patient with amnesic single domain MCI. Regarding Vasc-MCI patients, 11/21 patients were classified as multiple domain, amnestic (n=9) and non-amnestic (n=2) and 10/21 were single domain (non-amnestic).

The chi-square test did not show an association between two kinds of compared diagnoses. The frequency of MCI subtypes according to conventional diagnoses was similar in degenerative MCI and Vasc-MCI.

Discussion

In this retrospective study on MCI patients, we compared *pragmatic diagnoses* derived from clinical practice and *conventional diagnoses* for MCI etiologic subtyping according to Winblad et al.'s criteria and found that half of patients diagnosed with degenerative MCI presented a non-amnestic cognitive profile and almost half of those Vasc-MCI patients had a single domain cognitive profile. Our study has to be seen as a first and preliminary experience to test whether the assumptions made by Winblad et al. are confirmed once a clinical-based diagnosis is applied in clinical practice.

The disagreement between pragmatic and conventional MCI diagnoses might have several explanations. We used a neuropsychological battery more specifically set to explore in detail a large number of cognitive domains and developed for Vasc-MCI. With particular reference to Vasc-MCI, unexpectedly not all cases had a multiple domain profile as proposed by Winblad et al. It is important to note that the single domain Vasc-MCI patients have a non-amnestic profile. Our data suggest an unforeseen high number of Vasc-MCI patients classified as non-amnestic single domain (in our experience mainly deficits in attention functions) [Winblad B et al, J Intern Med 2004; Busse A et al, Neurology 2006; Busse A et al, Psychol Med 2003]. Some authors suggested that single domain MCI are misdiagnosed because of normal variability in cognitive test performance [Ward A et al, Alzheimers Dement 2012; Sachdev PS et al, Am J Geriatr Psychiatry 2012].

As recently observed [Clark LR et al, J Int Neuropsychol Soc 2013; Stephan BC et al, BMJ Open 2013], the specific operational definitions used for diagnosis of MCI and its subtyping are often different and various methods have been applied for operationalizing MCI criteria and neuropsychological profiles varied depending on the criteria used to define MCI [Salvadori E, J Alzheimers Dis 2014]. Several factors involved in the definition of MCI may differ across settings [Clark LR et al, J Int Neuropsychol Soc 2013; Stephan BC et al, BMJ Open 2013].

Of note, *conventional diagnoses* are biased toward the detection of memory deficits [Winblad B et al, J Intern Med 2004; Busse A et al, Neurology 2006; Busse A et al, Psychol Med 2003]. In fact, Winblad's criteria are hierarchically based on the presence or absence of significant memory impairment. Consequently, patients with mild memory deficits and concomitant severe deficits in other domains are classified as amnestic. However, a dichotomous "amnestic" or "non-amnestic" scheme that collapse together all individuals with non-memory deficits may obscure groups with important patterns of impairment and, therefore, not adequately capture the heterogeneity of MCI [Matthews FE et al, J Am Geriatr Soc 2008]. Concerning to degenerative MCI, National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed a definition of MCI due to AD as "objective evidence of impairment in one or more cognitive domains, typically including memory", trying to overcome the hierarchical view of Winblad et al.' criteria but still focusing on memory as the guiding domain [Albert MS et al, Albert MS 2011].

Finally, because the lack of a universal operational definition of MCI and the use of different assessment protocols among clinicians [Ganguli M et al, Arch Neurol 2011; Manly JJ et al, Ann Neurol 2008; Jak AJ et al, Am J Geriatr Psychiatry 2009; Luck T et al, Dement Geriatr Cogn Disord 2010], the standard test correction rules may change the results, depending on whether a test was considered in the normal range or at the borders of normality. There are inconsistencies in the instruments and methodology used to diagnose MCI and this concept highlights the urgent need for a standardized approach to map MCI (degenerative MCI and Vasc-MCI) [Stephan BC et al, BMJ Open 2013]. Regarding MCI due to AD or preclinical AD, the NIA-AA new diagnostic procedures and task force on designing clinical trials in early predementia suggests the need of a more complete procedure considering biomarkers of Aβ deposition (cerebrospinal fluids (CSF) Aβ42 and positron emission tomography (PET) amyloid imaging) and biomarkers of neuronal injury (CSF tau/phosphorylated-

tau, hippocampal volume or medial temporal atrophy, FDG-PET and SPECT perfusion imaging) to identify brain changes that precede the development of symptoms of dementia [Albert MS et al, Albert MS 2011; Aisen PS et al, Neurology 2011]. In this view, our study takes into account the presence of neuroimaging biomarkers, specifically related to SVD.

We recognize the several limitations of our retrospective study. First, the very small sample of patients. Another potential shortcoming is the possible higher predisposition of physician in our centre towards a diagnosis of Vasc-MCI, especially considering that our pragmatic diagnoses were obtained "by consensus". Also the neuropsychological evaluation used in our center deserves some comments. Our battery appears quite unbalanced towards an evaluation of attentive and executive functions rather than memory tests. On the other side, the absence in our sample of patients with a cognitive profile characterized by an amnesic single domain could underline the need of a neuropsychological battery to consider a large number of cognitive domains in MCI patients. Last, in this study we did not have biomarkers data as brain PET and CSF biomarkers to support the identification of neurodegenerative dementia, as recommended by recent task force particularly in early predementia AD [Albert MS et al, Albert MS 2011; Aisen PS et al, Neurology 2011].

With the limitation of the small patient sample, this study confirms that MCI must not be treated as a unitary disorder, also for prevention and therapeutic programs [Sachdev PS et al, Am J Geriatr Psychiatry 2012], and suggests that the cognitive profile of Vasc-MCI is more heterogeneous than previously recommended and might include non-amnestic single domain; moreover, it outlines the need for a standardized criteria for Vasc-MCI and MCI subtypes. Our preliminary results needs to be confirmed in larger series of MCI patients such as those currently enrolled in ongoing studies [Poggesi A et al, Int J Alzheimers Dis 2012].

Clinical assessment	Method/Scale
Clinical history	Standard
General physical examination	Standard
Neurological examination	Standard
Functional assessment	ADL[33] IADL[34]
Depressive symptoms	Geriatric Depression Scale [35]
General cognitive profile	Clinical Dementia Rating Scale [36]
Neuroimaging evaluation	
White matter lesions severity	CT: van Swieten Scale [37] MRI: Fazekas Scale [38] (FLAIR and T2-weighted sequences)
Lacunar and non-lacunar infarcts	T1, T2-weighted and proton density sequences with evaluation of number and location number and location
Cortical atrophy	Visual rating scale
Medial temporal lobe atrophy	Coronal T1-weighted sequences Scheltens' Scale [39]
Neuro-psychological evaluation	**Method/Scale**
Global cognitive functioning	Mini-Mental State Examination [40]
Verbal Memory	Rey Auditory Verbal Memory Test [41] (immediate and delayed recall)
Focused and sustained attention	Digit Cancellation Test [42, a]
Visuo-spatial sustained attention	Symbol Digit Modalities Tests [43, a]
Selective attention	Stroop Test (Short Form) [44, a]
Divided attention	Trail Making Test [45, a]
Language	Phonemic and semantic verbal fluency [46,a]
Visuo-spatial abilities	Clock drawing test [47, a]
Neuro-psychiatric disturbances	Neuro-psychiatric Inventory [48, a]
Subjective memory complaint	MAC-Questionnaire [49]
Self-referred attention complaint	Attention Questionnaire [50]

Table 1. VAS-COG clinic protocol for the clinical, neuroimaging and neuropsychological assessment.

[a] For these tests we used normative values validated on an Italian population.

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Pragmatic diagnoses		Conventional diagnoses			
N, %		Amnestic		Non-Amnestic	
		Single Domain	Multiple Domain	Single Domain	Multiple Domain
Degenerative MCI	(9)	0	4 (44%)	4 (44%)	1 (11%)
Vasc-MCI	(21)	0	9 (43%)	10 (48%)	2 (9%)

Table 2. Comparison of pragmatic diagnosis and conventional diagnosis in 30 MCI patients (in bold cases of disagreement between diagnoses) [for disagreement definition, see text].

chi-square test p=0.984

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2.2.3 Visuospatial functioning in Cerebral Amyloid Angiopathy

Visuospatial functioning in Cerebral Amyloid Angiopathy: a pilot study

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Short Communication

Visuospatial Functioning in Cerebral Amyloid Angiopathy: A Pilot Study

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Abstract

Background: Cerebral amyloid angiopathy (CAA) is an important contributor to cognitive impairment in the elderly. According to the hypothesis, not been previously tested, that CAA's posterior cortical predilection would cause visual processing impairment, we systematically evaluated visuospatial abilities in CAA patients.

Methods: Twenty-two non-demented patients with probable CAA according to the Boston criteria, had standardized neuropsychological evaluation including the Benton Facial Recognition Test (BFRT) and Benton Judgment of Line Orientation Test (BJLO). We investigated the association between visuospatial impairment and neuroimaging markers of CAA (intracerebral hemorrhage, lobar cerebral microbleeds (CMBs), cortical superficial siderosis, white matter hyperintensities (WMH) volume and anterior-posterior distribution, as well as total brain volume) and performances in other cognitive domains (attention and executive function, processing speed and episodic memory) and apathy/depression.

Results: Neurocognitive evaluation demonstrated visuoperceptual impairment (23% on BFRT and 13.6% on BJLO), without other significant cognitive deficits. In correlation analysis, BFRT was inversely correlated with WMH volume ($p=0.015$) and BJLO with parietal CMBs ($p=0.015$).

Conclusions: This pilot study highlights the possible presence of visual processing deficits in CAA. In our sample the visual processing functions seem to be more affected than other cognitive skill. The impairment could be related to global disease severity in addition to local brain injury, even in the absence of focal ICH lesions. It thus may be important to focus more clinical attention on visuospatial functioning deficits in patients with the disease.

Background and Purpose

Cerebral amyloid angiopathy (CAA) is an important contributor to cognitive impairment in the elderly [Case NF et al, Stroke 2016; Xiong L et al, J Alzheimers Dis 2016] and is characteristically associated with a high prevalence of characteristic markers of small vessel disease, including white matter hyperintensities (WMH) and strictly lobar cerebral microbleeds (CMBs) [Smith EE et al, Stroke: a journal of cerebral circulation 2009]. Individuals with moderate-to-severe CAA pathology have lower performance in specific cognitive domains, most notably executive dysfunction processing speed and memory [Xiong L et al, J Alzheimers Dis 2016; Arvanitakis Z et al, Annals of neurology 2011]. MRI studies have demonstrated an occipital predilection of neuroimaging markers of CAA [Thanprasertsuk S et al, Neurology 2014], in line with the distribution of CAA pathology [Vinters HV et al, Stroke 1983]. Posterior lesions can be associated with lower performance on tasks assessing visuospatial abilities [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994], but the specific effects of CAA on visuospatial function has not been explored.

A variety of tests designed to probe the visuospatial functioning has been developed for neuropsychological assessment. The Benton Facial Recognition Test (BFRT) [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994; Benton AL et al, Benton Facial Recognition: Stimulus and Multiple Choice Pictures. Lutz, FL, U.S.A: PAR: Psychological Assessment Resources, Inc.;1983] and the Benton Judgment of Line Orientation Test (BJLO) [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994; Benton AL et al, Judgment of Line Orientation, Form H. Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1983] are two well validated and widely used tests with available normative data that respectively probe visuoperceptual discrimination of unfamiliar faces and judgment of spatial relationships. The posterior regions predominantly serving these functions include the parietal, parietal-occipital and occipito-temporal regions, especially in the right hemisphere [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994].

In the current study we sought to systematically evaluate visuospatial abilities in CAA patients, given the known posterior predilection of CAA neuroimaging markers. In particular, we aimed to: (a) investigate the frequency of visual processing deficits in this patient population and explore if visual processing is more affected than other cognitive skills; and (b) investigate if visual processing deficits are related to local brain injury or global disease severity based on neuroimaging markers.

Materials and Methods

Patients

This study is a cross-sectional analysis of data from an ongoing longitudinal cohort study of CAA at Massachusetts General Hospital recruited from an outpatient stroke clinic setting. Twenty-two non-demented patients fulfilling the Boston criteria [Knudsen KA et al, Neurology 2001] for probable or definite CAA who underwent research MRI (July 2014-July 2015) were eligible for the current study. Blind persons (n=1) and patients with a Mini-Mental State Examination (MMSE) $\leq$24 (n=1) were excluded. The Institutional Review Board approved the study and informed consent was obtained from all participants.

Clinical and neuropsychological evaluation

Demographic information, vascular risk factors and history of intracerebral haemorrhage (ICH) were recorded. Patients systematically underwent standardized neuropsychological assessment as previously described [Reijmer YD et al, Brain: a journal

of neurology 2015], including assessment of functions as well as verbal memory, processing speed, attention and executive functioning. Available published normative data were used for comparison and corrected score or Z-scores (with percentiles) for each cognitive test were calculated.

The neuropsychological evaluation also included apathy and depression self-report scales [Yesavage JA, Psychopharmacol Bull 1988; Starkstein SE et al, J Neuropsych Clin Neurosci 1992], a brief vision screening interview (e.g., screening for prior vision injury, macular degeneration, glaucoma, cataracts, etc.), the BFRT (short form) [Benton AL et al, Benton Facial Recognition: Stimulus and Multiple Choice Pictures. Lutz, FL, U.S.A: PAR: Psychological Assessment Resources, Inc.;1983] and the BJLO [Benton AL et al, Judgment of Line Orientation, Form H. Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1983]. The short form of the BFRT has 27 possible points; on each item, subjects were presented with a target face above six test faces, and they were asked to indicate which of the six images match the target face [Benton AL et al, Lutz, FL, U.S.A: PAR: Psychological Assessment Resources, Inc.;1983]. Corrected long form scores were obtained according to the standardized transformation approach [Benton AL, Annual review of psychology 1994; Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994]. For BJLO, subjects were asked to match two angled lines to a set of 11 lines arranged in a semicircle and separated 18 degrees from each other [Benton AL, Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1983; Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994]. Corrected scores for BFRT and BJLO were classified according to the standard approach in the Benton clinical manual [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994] to separate intact and impaired performances [Benton AL, Annual review of psychology 1994; Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994]. Corrected scores in or above the low average range were defined as intact and scores falling below the low average range (borderline/impaired ranges) were defined as impaired [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994]. For both tests we used scores for borderline performances to be broadly inclusive for the "impaired" groups, specifically scores ≤ 40 (corresponding to the $<16^{th}$ %ile) for BFRT and <20 ($<21^{st}$ %ile) for BJLO [Benton AL, Annual review of psychology 1994; Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994].

As an additional screening of visuospatial ability, Mini-Mental State Examination (MMSE) pentagon drawings were used and scored according to an established qualitative scoring method (QSPT) [Caffarra P et al, Behav Neurol 2013].

MRI protocol and neuroimaging evaluation and analysis

Study participants underwent detailed structural 1.5 T (n=13) or 3 T (n=9) (on the basis of time of enrolment) MRI scans (Siemens Healthcare, Germany) according to study protocol [Reijmer YD et al, Brain: a journal of neurology 2015]. There were no differences between 1.5T and 3T subjects, particularly in visual discrimination impairment. Imaging for all patients included T1-weighted, FLAIR, both T2*-gradient echo (GRE) and susceptibility-weighted imaging (SWI) as previously defined [Reijmer YD et al, Brain: a journal of neurology 2015]. MRI were reviewed blinded to all clinical and neuropsychological data by trained observers, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) [Wardlaw JM et al, The Lancet Neurology 2013]. MRI scanning were conducted in the same day as neuropsychological tests (n=18), while 4 patients underwent tests less than 2 months after MRI.

The presence, number and location of intracerebral hemorrhages (ICH) [Kidwell CS et al, Neurology 2009] was recorded.

Total number of lobar cerebral microbleeds (CMBs) was detected by the previously described semiautomatic method based on the radial symmetry transform using susceptibility-weighted imaging (SWI) sequences [Kuijf HJ et al, PloS one 2013]; each CMB was subsequently reviewed by an experienced reader blinded to clinical data (according to current consensus criteria) [Greenberg SM et al, The Lancet Neurology 2009] and registered to the native T1-weighted space of each subject and allocated to 34 anatomical regions of interest (ROIs) per hemisphere, using the cortical parcellation algorithms provided by FreeSurfer, as previously described [Desikan RS et al, NeuroImage 2006]. Total number of CMBs, Single anatomical regions and united parieto-occipital regions were considered for statistical analysis.

Cortical superficial siderosis (cSS) was defined as previous described [Charidimou A et al, Neurology 2013], and classified as focal or disseminated [Linn J et al, Neurology 2010], scored separately for each hemisphere [Charidimou A et al, Neurology 2013].

White matter hyperintensities (WMH) volumes were measured, excluding infratentorial regions, on FLAIR sequences using a semiautomated segmentation method on MRIcroN (http://www.mricro.com) as previously described [Gurol ME et al, Neurology 2006]. For the anterior-posterior (AP) distribution of WMH, the AP center of WMH was calculated using the quantitative and semiautomated method according to previously established methodology (higher values indicate a more anterior distribution of WMH, and lower values more posterior distribution) [Reijmer YD et al, Brain: a journal of neurology 2015].

Total brain volume (TBV) was obtained from T1-weighted multi-echo MPRAGE (MEMPRAGE) scans using the FreeSurfer neuroimaging analysis software's (version 5.3) segmentation algorithm (http://surfer.nmr.mgh.harvard.edu) [Fischl B et al Proceedings of the National Academy of Sciences of the United States of America 2000], and included the brain tissue within the cranium, excluding the brainstem, ventricles, cerebrospinal fluid analysis and choroid plexus, as previously reported [Gurol ME et

al, Neurology 2006] and were expressed as a percentage of the estimated total intracranial volume, taking into account differences in subjects' head size [Reijmer YD et al, Brain: a journal of neurology 2015].

Statistical Analysis

Discrete variables are presented as count (%) and continuous variables as mean (SD) or median (25%, 75% quartiles) as appropriate. A correlation analysis between neuropsychological tests and neuroimaging variables was performed using non-parametric correlation tests (Spearman's rho).

For comparisons on demographic characteristics, neuropsychological features, neuroimaging markers between the group of patients with and without BFRT impairment, the independent samples Mann-Whitney U test and Pearson Chi-square test were applied to non-normally distributed continuous variables and to categorical variables, respectively. In this comparison analysis, we applied Bonferroni's correction for multiple comparisons, resetting the critical level of significance according to the number of variables considered ($p<0.0015$).

Other statistical significance level was set at 0.05 05 and all tests of significance were two-tailed.

The SPSS 21 statistical package was used for statistical analysis (IBM Corp., Armonk, NY).

Results

Our cohort consisted of 22 non-demented patients with probable CAA. Mean age was 69.9±6.0 years and 18 (81.8%) patients were males. The mean number of CMBs was 123.45±175.50 (ranging 0-715). Based on neuropsychological evaluation, the patients exhibited a cognitive profile in the normal range in all domains, except in one executive function test (on Trails B z-score = -3.1±4.9, $<1^{st}$ percentile) and in visuospatial function as measured by the BFRT and BJLO (Table 1). The mean BFRT score was 44.64±6.26 (52^{th}, 33rd-59th percentile) and mean BJLO score 25.8±6.3 ($<60^{th}$ percentile). Five (22.7%) patients showed impairment on the BFRT test ($\leq 11^{th}$ percentile) and 3 (13.6%) showed impairment on the BJLO test ($\leq 9^{th}$ percentile). Of these, there were 2 patients (without significant eye problems) who were impaired on both tests. Figure 1 is an illustrative example of CMB distribution in one patient with severely impaired performance on the BFRT (BFRT$<1^{st}$ percentile). Table 2 provides details on the clinical symptoms of the CAA patients. Two subjects with impairment in BFRT and BJLO, as clinical presentation, reported to miss-identify the names of person; for one of these, abstraction deficit and spatial disorientation were recorded (an episode with loss of his sense of direction, as a driver, and with difficulty "to recognize the way without global positioning system" was reported). Among patients with facial identify deficit, one suffered from left side neglect after ICH and another one received a diagnosis of inflammatory CAA.

In correlation analysis between visuospatial function and neuroimaging markers, the BFRT score showed an inverse moderate correlation with WMH volume (Spearman's rho=-0.513, p=0.015). No correlation with focal ICH lesions (presence, number and location), total CMBs counts and cSS, age and visual processing tests was found. The BJLO score was associated with lower total lobar parietal CMBs counts (Spearman's rho=-0.513, p=0.015). There is a trend (but not statically significant) for correlation between BJLO score and total brain volume (TBV) (rho=0.417, p=0.054).

Comparing patients with and without visuoperceptual discrimination impairment, there were no statistically significant differences, particularly regarding ICH and other main neuroimaging characteristics and other cognitive tests (including pentagon drawings) and behavior/mood factors (Table 3).

Discussion

We evaluated visuospatial abilities in non-demented patients with CAA, a clinical feature not previously specifically investigated in patients with the disease. Visuoperceptual impairment was present in 23% of patients, without other significant cognitive deficits. This is slightly higher than previously reported in neurological patients with focal brain damage in right, left or both hemispheres [Tranel D et al, Journal of clinical and experimental neuropsychology 2009]. Although our neuropsychological tests are not directly comparable because different normative data used, the visual processing impairment appears more affected than other relatively spared cognitive skills, because tests evaluating verbal memory, processing speed, and attention resulted in the normal range.

We found that the lower performance on a visual discrimination test correlated with the burden and topographic distribution of select neuroimaging markers of CAA and not with focal occipital intracerebral hemorrhage. Specifically, WMH volume and CMBs in parietal were inversely correlated with BFRT and BJLO scores, respectively. We can speculate that the visual processing impairment is due to global disease severity (e.g. measurable by total neuroimaging lesion burden or WMH volume), in addition to local brain injury in structures important for processing visual information (e.g. parietal areas). Low visuospatial discrimination test performances were also slightly related with TBV (in line with previous literature suggesting atrophic brain changes may contribute to worse visual discrimination in normal adults [Schretlen DJ et al, Neuropsychology 2001] and Alzheimer's disease patients [Smits LL et al, Alzheimers Dement 2014]).

Interestingly, because the group with visual discrimination impairment was comparable in terms of cognitive profile with the group without visual discrimination impairment, these findings suggest that visual discrimination deficits may develop in a subgroup of patients with CAA.

Our study has several limitations. The main one is the small sample size, because it is a specific and exploratory study. This precludes us from performing multivariate analyses that could demonstrate an independent association between CAA neuroimaging markers and visuospatial deficits. Secondly, because we lack a control group, it

is uncertain whether these visual discrimination deficits are present at the same rate in non-CAA populations. However, comparison with age-adjusted normative scores would suggest that patients with CAA have increased impairment in visual discrimination abilities compared to healthy individuals [Benton AL et al, Contributions to Neuropsychological Assessment: Clinical Manual. New York: Oxford University Press, 1994; Tranel D et al, Journal of clinical and experimental neuropsychology 2009]. Thirdly, it is possible that differing MRI field strengths used in a subgroup of patients could lead to bias in our results. However, comparison of patients undergoing 3T versus 1.5T scan did not show differences in visual discrimination impairment between groups.

This pilot study suggests that visuospatial deficits in patients with CAA are both present and measureable. Visuospatial deficits may have clinical importance in identifying cognitively normal CAA patients with increased CAA-related small vessel disease burden.

	CAA patient (N=22)
MMSE	28.32±1.62 (50th)
QSPT	11.68±1.39
BNT§	0.08±1.15 (53rd)
HVLT-R Total Recall§§	45.05±12.91 (30th)
HVLT-R Delayed Recall§§	42.59±13.21 (21st)
HVLT-R Retention§§	44.00±13.75 (27th)
HVLT-R Recognition§§	45.25±10.66 (30th)
Digit Symbol§§§	8.64±3.05 (32nd)
Trail A§	-1.25±2.28 (10th)
Trail B§	-3.10±4.95 (<1st)
Digit Span Forward§	-0.07±0.74 (45th)
Digit Span Backward§	-0.04±1.46 (47th)
Total Switching§§§	8.27±3.73 (27th)
Category Switching§§§	8.59±3.43 (30th)
Category Fluency (Animal Naming)§	-0.26±0.90 (39th)
Verbal Fluency-COWAT (FAS)§	-0.41±0.72 (32nd)
BFRT§§§§	44.64±6.26 (52th)
BJLO§§§§	25.77±6.26 (60th)
GDS	6.09±5.34
Apathy Scale	9.73±5.45

Table 1. Cognitive test profile in the study sample.

MMSE=Mini Mental State Examination, QSPT=Qualitative Scoring MMSE Pentagon Test, BNT=Boston Naming Test (short form), HVLT-R=Hopkins Verbal Learning Test-Revised, Trail A=Trail Making Test A, Trail B= Trail Making Test B, COWAT=Controlled Oral Word Association Test, BFRT= Benton Facial Recognition Test, BJLO= Benton Judgment of Line Orientation Test, GDS=Geriatric Depression Scale.

The scores are shown as mean ± SD (percentiles).

§ z-scores

§§ T-scores

§§§ scaled scores

§§§§ corrected scores

	CAA patient (N=22)
ICH	12 (54.5)
TFNE	3 (13.6%)
TIA	2 (9.1%)
SAH	0 (0%)

Table 2. The main clinical symptoms of the CAA patients.

ICH= Intracerebral hemorrhage

TFNE=Transient focal neurological episodes

TIA=Transit Ischemic Attack

SAH=Subarachnoid Hemorrhage

	Patients with BFRT impairment (N=5)	Patients without BFRT impairment (N=17)	p value
Age (years)	72.60 (61.80, 76.88)	68.50 (65.45, 75.55)	0.762
Sex (female/male)[#]	1/4	3/14	0.905
Education level (years)	18.50 (15.00, 19.75)	18.00 (14.00, 19.50)	0.880
MMSE[§17]	.77 (-1.16, 1.74) [77th (12th, 96th)]	.00 (-.42, .39) [50th (32nd, 63rd)]	0.283
MMSE pentagon copy test deficit[#]	2/5 (40%)	6/17 (35.3%)	0.848
QSPT[6]	12.00 (10.50, 13,00)	12 (10.50, 13,00)	0.940
BNT[§]	-.83 (-1.73, 0.98) [19th (4th, 82nd)]	.53 (.00, 0.83) [68th (50th, 79th)]	0.493
HVLT-R Total Recall[§§18]	51.00 (23.00, 59.50) [54th (<1st, 82nd)]	44.00 (37.50, 57.00) [27th (10th, 76th)]	0.940
HVLT-R Delayed Recall[§§18]	48.00 (24.00, 53.50) [42nd (<1st, 62nd)]	45.00 (37.00, 52.50) [31st (10th, 58th)]	0.880
HVLT-R Retention[§§18]	43.00 (32.00, 55.00) [24th (4th, 69th)]	48.00 (37.50, 51.00) [42nd (10th, 54th)]	0.820
HVLT-R Recognition[§§18]	47.00 (36.50, 58.00) [38th (8th, 79th)]	45.00 (36.00, 56.00) [31st (8th, 73rd)]	0.735
Digit Symbol[§§19]	8.00 (5.50, 11.50) [25th (6th, 68th)]	10.00 (6.00, 11.00) [50th (9th, 63rd)]	0.649
Trail A[§20]	-.96 (-5.46,.27) [16th (<1st, 61st)]	-.87 (-1.62,.39) [18th (5th, 63rd)]	0.493
Trail B[§20]	-1.32 (-2.70, .42) [9th (<1st, 66th)]	-2.43 (-6.44, .56) [1st (<1st, 70th)]	0.750
Digit Span Forward[§21]	-.43 (-.81,- .08) [32nd (19th, 45th)]	.10 (-.77, .74) [53rd (21st, 77th)]	0.283
Digit Span Backward[§21]	-.46 (-.91, .45) [32nd (18th, 66th)]	-.43 (-.89, .81) [32nd (18th, 79th)]	0.649
Total Switching[§§]	5.00 (3.00, 10.50) [5th (1st, 55th)]	9.00 (7.00, 11.50) [37th (16th, 68th)]	0.283
Category Switching[§§]	5.00 (2.50, 10.00) [5th (1st, 50th)]	9.00 (7.00, 11.50) [37th (16th, 68th)]	0.101
Category Fluency (Animal Naming)[§22]	-.79 (-1.35, .67) [21st (8th, 75th)]	-.29 (-.76, .18) [37th (21st, 55th)]	0.543
Verbal Fluency-COWAT (FAS)[§22]	-.21 (-.91, .81) [39th (18th, 79th)]	-.63 (-.77, -.21) [25th (21st, 39th)]	0.401
BJLO[§§]	26.00 (14.00, 29.50) [56th (22nd, 86th)]	28.00 (24.00, 30.00) [7nd (56th, 86th)]	0.401
GDS	6.00 (4.50, 11.00)	3.00 (2.00, 8.00)	0.218
Apathy Scale	8.00 (6.00, 10.50)	11.00 (5.00, 15.00)	0.543
ICH presence[#]	3/5 (60.0%)	9/17 (52.9%)	0.781
parieto-occipital ICH[#]	1/3 (33.3%)	5/9 (55.5%)	0.505
right ICH[#]	2/3 (40.0%)	5/8 (62.5%)	0.898
Total lobar CMBs	234.00 (12.50, 341.50)	34.00 (6.50, 124.50)	0.283
parieto-occipital CMBs	76.00 (9.50, 179.50)	23.00 (4.00, 86.50)	0.359
cSS presence[#]	3/5 (60.0%)	7/17 (41.2%)	0.457
disseminated right cSS	3/5 (60.0%)	4/17 (23.5%)	0.124
WM Volume	16.13 (3.41, 43.84)	10.38 (3.52, 17.70)	0.446
AP WM distribution	22.63 (4.65, 32.81)	16.63 (12.82, 21.00)	0.595
TBV	.62697 (.56670, .63614)	.60747 (.57053, .64760)	0.940

Table 3. Comparison of demographic, neuropsychological and neuroimaging characteristics between patients with and without visual discrimination impairment.

MMSE=Mini Mental State Examination, QSPT=Qualitative Scoring MMSE Pentagon Test, BNT=Boston Naming Test (short form), HVLT-R=Hopkins Verbal Learning Test-Revised, Trail A=Trail Making Test A, Trail B= Trail Making Test B, COWAT=Controlled Oral Word Association Test, BFRT= Benton Facial Recognition Test, BJLO= Benton Judgment of Line Orientation Test, GDS=Geriatric Depression Scale, ICH= Intracerebral hemorrhage, CMBs=cerebral microbleeds, cSS=cortical superficial siderosis, WM=white matter, AP=anteroposterior distribution, TBV=total brain volume.

Variables with not normal distribution are shown as median (25%, 75% quartiles) [(percentiles)].

[§] z-score

[§§] corrected-score

Independent Samples Mann-Whitney U Test.

[#] Pearson Chi-square.

* The significance level (Bonferroni's corrections) is $p<0.0015$.

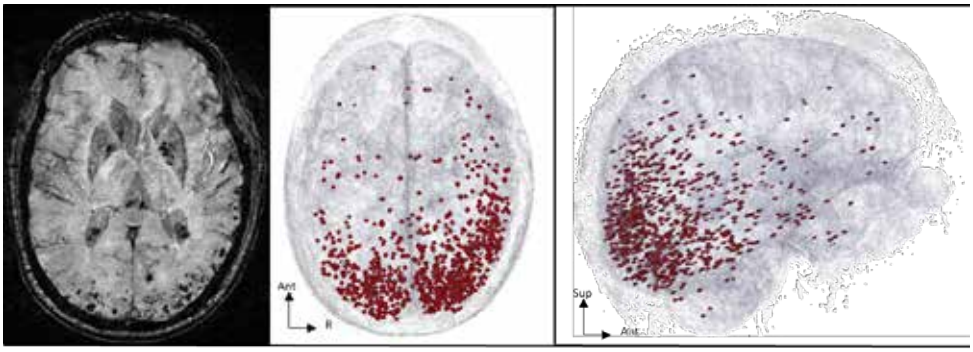

Figure 1. Representative example of the topographic distribution of multiple lobar CMBs in a patient with severe visual discrimination impairment (BFRT=34). Visualization obtained using 3D Slicer version 4.4 -http://www.slicer.org

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Part 3

Rehabilitative issues in Small Vessel Disease

Chapter 3
Rehabilitative issues in Small Vessel Disease

3.1 Rehabilitation of attention in patients with mild cognitive impairment and brain subcortical vascular changes using the Attention Process Training-II. The RehAtt Study

During my PhD I have been participating to the management of the project "The rehabilitation of attention in patients with mild cognitive impairment and brain subcortical vascular changes using the Attention Process Training-II. The RehAtt Study" aiming to study the effectiveness and impact of cognitive rehabilitation on functional abilities and quality of life in patients with MCI and SVD.

In the Canadian Health and Aging Study 46% of patients with VMCI developed dementia after 5 years. Progression applies mostly to the subcortical Vascular Dementia (VaD) type whose core features are alterations in executive/attentional processing. At present, no drug treatment is available to prevent VaD or to improve cognitive performances in patients with VMCI. Cognitive rehabilitation was primarily directed to achieve functional changes by reinforcing or re-establishing previously learned patterns of behavior, or establishing new patterns of cognitive activity or compensatory mechanisms. The RehAtt Study is an observational study which enrolled 40 patients carried out at the VAS-COG outpatient clinic of SOD Stroke Unit e Neurologia Careggi University Hospital, Florence.

The RehAtt study is funded by Tuscany region and Health Ministry (Bando Ricerca Finalizzata 2010, Grant number: RF-2010-2321706, Trial registration: NCT02033850 (ClinicalTrials.gov Identifier), PI Leonardo Pantoni).

Abstract

Background: Patients with mild cognitive impairment (MCI) and small vessel disease (SVD) have a high risk of progressing to dementia. We tested the effect of cognitive rehabilitation in these patients using the Attention Process Training-II (APT-II) program in a single-blinded, randomized clinical trial.

Methods: Patients with MCI and SVD were randomized to APT-II program (40 hours total treatment) or standard care. All patients were evaluated at baseline with

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extensive functional, quality of life, and cognitive tests, and MRI. Patients were re-evaluated after 6 and 12 months.

Results: Forty-six patients were enrolled and 43 (65% males, mean±SD age 75.1±6.8) completed the study. No change was seen in the primary outcomes (functional status and quality of life) between treated and non-treated patients. Considering secondary cognitive end-points, the Rey Auditory-Verbal Learning Test immediate recall showed a statistically significant improvement in the APT-II group compared to standard care group (6 vs. 12 months: 1.8±4.9 and -1.4±3.8, p=.021; baseline vs. 12 months: 3.8±6.1 and 0.2±4.4, p=.032, respectively). More patients had a stable or better evaluation in the treatment group compared to standard care group for the Visual search test (6 vs. 12 months: 95% vs. 71%, p=.038, respectively) and the Rey–Osterrieth Complex Figure immediate copy (6 vs. 12 months: 95% vs 67%, p=.027, respectively).

Conclusion: Treatment of MCI patients with SVD with APT-II program does not produce significant effects in quality of life or functional status. APT-II program seems to produce some improvement in focused attention and working memory.

Trial registration: NCT02033850 (ClinicalTrials.gov Identifier).

3.1.1 Introduction

Dementia is one of the most disabling conditions affecting older people and it is expected that the number of demented patients will increase substantially in the future due to the aging of the population. The most frequent cause is Alzheimer's disease (AD) which is attributed to brain degeneration. One third of dementia cases are due to vascular dementia (VaD), an entity that encompasses a few subtypes, among which subcortical VaD, consequent to brain small vessel disease (SVD), is the most frequent [Di Carlo A et al, J Am Geriatr Soc 2002].

The term mild cognitive impairment (MCI) defines a transitional state between normal aging and dementia, and is thought to anticipate dementia [Gauthier S et al, Lancet 2006]. Subjects with MCI, compared to those without, progress to AD at a rate ten times greater [Stephan BC et al, Alzheimers Res Ther 2009]. Pre-dementia stages of VaD are also recognized [Pantoni L et al, Stroke 2011]. In the Canadian Health and Aging Study, 46 % of patients with MCI developed dementia after 5 years, and progression relates mostly to the subcortical VaD type [Wentzel C et al, Neurology 2011].

In patients with subcortical VaD, ischemic lesions are particularly located in the subcortical white matter (WM) underlying the prefrontal cortex [Cummings JL et al, Arch Neurol 1993]. This damage of the frontal lobe is reflected in the fact that alteration in executive and attentional processing seems to be the core feature of subcortical VaD; these patients are grossly slowed up with poor information retrieval and problems with tasks that require mental flexibility and shifting of attention [Sachdev PS et al, Med J Aust 1999]. Executive and attentional abilities are critical to the daily functioning and have important consequences on the patient's social adjustment and

maintenance of independence in a complex society [Salvadori E et al, Neurol Sci 2016].

At present, no drug is available to prevent VaD in patients with MCI or to improve cognitive performance in this group of patients. In recent years, there has been an increasing demand of rehabilitation, which originated from an extended life span, a lower incidence of mortality in the acute phase of illness, and a higher incidence of cognitive impairment and dementia in the elderly [Salvadori E et al, Neurol Sci 2016].

Cognitive rehabilitation is primarily directed to achieve functional changes by reinforcing, strengthening, or reestablishing previously learned patterns of behavior, or establishing new patterns of cognitive activity or compensatory mechanisms for impaired brain circuitries [Salvadori E et al, Neurol Sci 2016].

While systematic reviews of literature have been published about rehabilitation of attention for patients with acquired acute brain damage including traumatic brain injury (TBI) or stroke [Sohlberg MM et al, J Med Speech Lang Pathol 2003; Cicerone KD et al, Arch Phys Med Rehabil 2011; Cappa SF et al, Eur J Neurol 2005; Loetscher T et al, Cochrane Database Syst Rev 2013], cognitive rehabilitation in chronic cerebrovascular diseases, such as SVD, has been neglected [Salvadori E et al, Neurol Sci 2016].

The Academy of Neurologic Communication Disorders and Sciences Committee concluded that there was evidence of improvement in attention-based skills with direct training (defined as the repeated stimulation of attention via graded exercises) and recommended use of direct attention training in conjunction with metacognitive training (feedback, self-monitoring, strategy use) for post-acute or mildly impaired patients with intact vigilance [Sohlberg MM et al, J Med Speech Lang Pathol 2003]. The Brain Injury interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, and the European Task Force on Cognitive Rehabilitation of the European Federation of Neurological Societies concluded that there is substantial evidence to support attention training in the post-acute phase after TBI (respectively, as 'practice standard' and 'grade A recommendation') [Cicerone KD et al, Arch Phys Med Rehabil 2011; Cappa SF et al, Eur J Neurol 2005]. The Brain Injury interdisciplinary Special Interest Group pointed out that remediation of attention should include direct attention training and metacognitive training, to promote development of compensatory strategies and foster generalization to real-world tasks. In a Cochrane review, Loetscher and Lincoln concluded there was some evidence that the training may have a short-term effect on attentional abilities, but future studies need to assess the persisting effects and measure attentional skills in daily life [Loetscher T et al, Cochrane Database Syst Rev 2013].

These systematic reviews have generally found some evidence to support the effectiveness of rehabilitation of attention after TBI or stroke, but have also recognized the need for better specification of treatment effects and increased methodological accuracy. In more recent psychological and neuropsychological theorizing, attention is not considered to be a unitary function. Most of the studies that have examined the possibility to actively rehabilitate attention pointed out that a variety of attentional processes concur in producing the overall behavioral outcome, and it is now widely accepted that attention refers to a class of processes, dealing with the intensity and

selectivity components of attention. The proponents of the present study uphold a hierarchical clinical model of attention that proposes five sub-categories (Figure 1): (1) focused attention, the ability of an individual to focus gaze on an object; (2) sustained attention, the ability to maintain the focus on the object; (3) selective attention, the ability to sustain attention in the presence of distractors; (4) alternating attention, the ability to change mental-set as signaled by some type of cue; (5) divided attention, the ability to simultaneously process two pieces of information at once [Raskin SA et al, Handbook of neuro rehabilitation 1994; Van Zomeren AH et al, Clinical neuropsychology of attention 1994].

3.1.2 APT-II program

The APT-II program consists of a group of hierarchically organized tasks aimed at exercising different components of attention (focused, sustained, selective, alternating, and divided attention) [Sohlberg M et al, Association for Neuropsychological Research and Development 1996].

The hierarchical clinical model of attention has also been used to create a rehabilitation program, namely the Attention Process Training-II (APT-II) program [Sohlberg M et al, Association for Neuropsychological Research and Development 1996]. The APT-II stresses specific principles: (1) the program is hierarchically constructed; (2) the concept of hierarchical functioning allows basic skills to be constantly stimulated, while newer, more complex skills are targeted and exercised; (3) repetition could sensitize cortical responses and expedite the establishment of new neural organization; (4) generalizability of cognitive improvement to daily activities; (5) improvement of overall quality of life. The APT-II program effectiveness has been demonstrated in TBI and post-stroke rehabilitation [Park NW et al, Neuropsychol Rehabil 2005; Sohlberg M et al, J Clin Exp Neuropsychol 2000; Niemann H et al, J Consult Clin Psych 1990; Barker-Collo SL et al, Stroke 2009], but there is an increasing interest in the study of rehabilitation of attention in those disease processes that evolve over time, such as chronic SVD.

Considering that the APT-II contains specific exercises to facilitate generalization to daily life, the skills learned by each patient during the training are expected to generalize to daily activities. In addition, the improvement of cognitive skills should also improve patient's overall quality of life because these learned skills are applicable to real-life situations.

The purposes of the RehAtt study were to investigate: (1) the effectiveness of the APT-II program in the rehabilitation of attention in individuals affected by MCI with SVD; (2) the effect of the possible cognitive improvement in real life, for example in terms of functionality in daily activities and quality of life; (3) the impact of the attention training on brain activity at rest, and the possibility of achieving a training-induced cognitive plasticity effect [Salvadori E et al, Neurol Sci 2016].

3.1.3 Methods

Study design

The RehAtt (Rehabilitation of Attention) study is a 3-year prospective, single-blinded, randomized clinical trial. The rationale and methodology of the RehAtt study were reported in detail by Salvadori E et al. and published [Salvadori E et al, Neurol Sci 2016]. The study was carried out at the VAS-COG clinic of the Careggi University Hospital, Florence, Italy, in accordance with the Helsinki Declaration [Salvadori E et al, Neurol Sci 2016].

The study was approved by Local Ethics Committee and each patient gave a written informed consent [Salvadori E et al, Neurol Sci 2016].

Inclusion and exclusion criteria

To be included in the RehAtt study, patients followed in the VAS-COG clinic of the Careggi University Hospital (Florence, Italy) [Poggesi A et al, J Alzheimers Dis 2014], had diagnosis of MCI, with an attentional deficit, and SVD according to the following criteria: (1) MCI defined according to Winblad et al. criteria [Winblad B et al, J Intern Med 2004] and operationalized according to Salvadori et al. [Salvadori E et al, Alzheimers Dement 2015]; (2) evidence of impairment across attention neuropsychological tests (at least one score borderline among attention/executive functions tests included in the specifically developed neuropsychological battery [Salvadori E et al, J Alzheimers Dis 2015]); (3) evidence on MRI of subcortical vascular lesions: moderate to severe age-related white matter hyperintensities (WMH) on T2 weighted Fluid Attenuated Inversion Recovery (FLAIR) sequence according to a modified version of the Fazekas scale [Pantoni L et al, Neuroepidem 2005]. The degree of WMH severity was rated on FLAIR sequence taking into account only deep and subcortical white matter lesions. The modified Fazekas scale is a visual scale based on a categorization into three severity classes: grade 1 (mild WMH) = single lesions below 10 mm, areas of 'grouped' lesions smaller than 20 mm in any diameter; grade 2 (moderate WMH) = single lesions between 10 and 20 mm, areas of 'grouped' lesions more than 20 mm in any diameter, no more than 'connecting bridges' between individual lesions; grade 3 (severe WMH) = single lesions or confluent areas of hyperintensity 20 mm or more in any diameter [Salvadori E et al, Neurol Sci 2016].

Exclusion criteria are: (1) inability or refusal to undergo brain MRI; (2) inability to give an informed consent; (3) age<18 years.

Clinical assessments

At baseline, according to the study protocol [Salvadori E et al, Neurol Sci 2016], each enrolled patient underwent an extensive clinical, functional, and neuropsychological assessment carried out by one neurologist, and an MRI examination (Table 1) [Salvadori E et al, Neurol Sci 2016].

Clinical assessment: Social background and medical history, standard cardiovascular and neurological examinations.

Functional, quality of life and mood assessment

• Functional status measured by means of the Activities of Daily Living scale (ADL) [Katz S et al, JAMA 1963], Instrumental Activities of Daily Living scale (IADL) [Lawton MP et al, Gerontologist 1969], and Disability Assessment in Dementia scale (DAD) [Gélinas I et al, Am J Occup Ther 1999].

• Quality of life measured by means of the 36-Item Short Form Health Survey (SF-36) [Ware JE et al, Med Care 1992], EuroQol [Rabin R et al, Ann Med 2001], and Attention Questionnaire (AQ) [Sohlberg M et al, Association for Neuropsychological Research and Development 1996].

• Geriatric Depression Scale (GDS) for the assessment of mood [Yesavage JA, Psychopharmacol Bull 1988].

Extensive neuropsychological assessment

Each patient is assessed with an extensive neuropsychological evaluation according to a test battery specifically developed for patients with MCI and SVD, namely the VMCI-Tuscany neuropsychological battery [Salvadori E et al, J Alzheimers Dis 2015]. The development and psychometric properties of the VMCI-Tuscany neuropsychological battery have been extensively reported [Salvadori E et al, J Alzheimers Dis 2015]. The battery includes two global cognitive functioning tests (Montreal Cognitive Assessment test, MoCA; Mini Mental Status Examination test, MMSE), as well as tests for the memory domain (Rey Auditory-Verbal Learning Test immediate and recall, Short story, Rey–Osterrieth Complex Figure recall), for attention and executive function (Trail Making test part A and B, Visual search, Symbol Digit Modalities test, Color Word Stroop Test), for language (phonemic and semantic verbal fluency), and constructional praxis (Rey–Osterrieth Complex Figure copy). In the previous methodological paper reporting on the psychometric properties of the VMCI-Tuscany neuropsychological battery, a confirmatory factor analysis showed a good fit of the four cognitive domains model (memory, attention/executive functions, language, and constructional praxis), and was used to derive compound measures for each cognitive dimension [Salvadori E et al, J Alzheimers Dis 2015]. Compound measures corresponded to the arithmetic mean of the equivalent scores obtained in each test included

in the correspondent dimension, and those synthetic indexes will be used to analyze cognitive performances within and between groups.

MRI protocol

All the MR examinations are performed on a 1.5 T system (Magnetom Aera, Siemens Medical Solutions, Erlangen, Germany) equipped with a 20-channel head and neck coil. The gradients have maximum strength of 45 mT/m and slew rate of 200 mT/m/ms. After scouts, the examination protocol includes high-resolution sagittal contiguous 3D T1-weighted images with 1-mm isotropic voxels which were obtained with a Turbo Spin Echo SPACE (Sampling Perfection with Application optimized Contrasts using different flip angle Evolution) sequence [repetition time (TR) = 600 ms, echo time (TE) = 7 ms, slice thickness = 1 mm, no inter-slice gap, field of view (FOV) = 232 mm (phase) X 256 mm (frequency), acquisition matrix = 232 X 256, turbo factor = 36, number of excitations (NEX) = 1, GRAPPA acceleration factor = 2, number of slices = 176], axial T2- weighted images, which were obtained with a FLAIR sequence [TR = 9000 ms, TE = 112 ms, inversion time (TI) = 2500 ms, slice thickness = 3 mm, 0.6 mm inter-slice gap, FOV = 187 mm (phase) X 230 mm (frequency), acquisition matrix = 260 X 320, turbo factor = 16, NEX = 2, number of slices = 35], and T2* weighted FLASH (Fast Low Angle SHot) [TR = 907 ms, TE = 25 ms, flip angle = 20°, slice thickness = 5 mm, 0.5 mm interslice gap, FOV = 208.4 mm (phase) X 230 mm (frequency), acquisition matrix = 205 X 256, interpolated to 464 X 512, NEX = 1, number of slices = 25].

Diffusion tensor imaging (DTI) is performed using a single shot echo-planar imaging (EPI) sequence (TR = 10,800 ms, TE = 87 ms, acquisition matrix = 106 X 106, slice thickness = 2.4 mm, FOV = 256 mm X 256 mm, 2.4-mm isotropic voxels, no inter-slice gap, NEX = 3, GRAPPA acceleration factor = 2, number of slices = 67, diffusion sensitizing gradients applied along 30 non-collinear directions using b value of 0 and 1000 s/mm^2). Finally, patients are evaluated with resting state functional MRI (rsfMRI) using a T2*-sensitive EPI sequence (TR = 2.520 s, TE = 50 ms, flip angle = 90°, field of view = 256 mm 9 256 mm, acquisition matrix = 64 9 64, GRAPPA acceleration factor = 2, no interslice gap, number of slices = 32) and with perfusion imaging using a pulsed arterial spin labeling (PASL) approach (Siemens PICORE Q2T) (TE = 12 ms; TR = 2500 ms; TI = 1800 ms; flip angle = 90°; bolus duration = 700 ms; Inversion Array size = 1; Flow limit = 100 cm/s; FOV = 256 mm X 256 mm; acquisition matrix = 64 X 64, slice thickness = 8 mm, 2 mm inter-slice gap, number of slices = 9).

The study protocol comprises 2 follow-up visits (at 6 and 12 months). During the follow-up visits clinical, functional, and neuropsychological assessment were performed according to the baseline study protocol.

The MRI assessment was performed at baseline and then repeated at 1-year follow-up, at the end of the study.

Procedures

The study included an intervention group ('attention training') and a control group ('standard care'). After baseline assessment, participants were randomly assigned to the intervention group ('attention training') or the control group ('standard care') according to a stratified randomization detailed in the methodological paper [Salvadori E et al, Neurol Sci 2016]. Stratified minimization randomization was used to ensure the balance for possible prognostic factors (age, gender, and WMH degree) across the groups (Table 2). To dichotomize age and to balance groups' sizes, the median age of the basal cohort of the VMCI-Tuscany study (N = 200) was applied (cut-off = 75.58). The neurologist who collected clinical, functional and neuropsychological data was blind to the intervention conditions. Participants were informed that the study aimed to compare cognitive training and standard care, and could not be kept blind to the intervention conditions. However, they were asked not to reveal their group membership during follow-up assessments to ensure that the neurologist remained blind to training allocation for the entire study duration [Salvadori E et al, Neurol Sci 2016].

Neuropsychological rehabilitation program

The APT-II program is a widely used cognitive rehabilitation program designed to remediate attention deficits [Sohlberg M et al, Association for Neuropsychological Research and Development 1996]. The APT-II consist of a group of hierarchically organized tasks that exercise different components of attention, including: focused, sustained, selective, alternating, and divided attention.

The APT-II exercises have a common structure. Before each task is given, the requirements are briefly explained. Some tasks are subject-paced while others are experimenter-paced, but in both cases, exercises typically take 2 or 3 min to complete. The program tasks place increasing demands on complex attentional control and working memory systems, but do not have a heavy memory load and usually require the participant to classify stimuli. Examples of exercises include auditory attention tapes such as listening to descending number sequences, alphabetizing words in an orally presented sentence, detecting targets with the presence of distracter noise or complex semantic categorization tasks requiring switching sets. A number of tasks combine auditory and visual activities. Feedback about accuracy and speed of performance is provided after each exercise. Other aspects of performance such as patterns of errors are also discussed. As the program proceeds participants are educated about different types of attention, and parallels between difficulties of daily living and problems performing particular APT-II exercises are pointed out.

All APT-II sessions have been administered by one clinical neuropsychologist. Participants in the intervention ('attention training') group were scheduled to receive 40 hours (2-hour weekly sessions for a total of 20 weeks) of individual attention process training by means of the APT-II program. All cognitive training sessions were administered by the same clinical neuropsychologist. Participants in the control

('standard care') group did not receive cognitive training interventions, were instructed to have a usual lifestyle, and were conventionally provided of medication and clinic consultations as usually needed.

Outcome measures

Primary outcomes

The primary outcomes of this study were the improvement of functionality in activities of daily living and quality of life in treated (with intervention training) patients compared to non-treated (control) patients. Since this was a pilot study, we decided to assess each outcome with more than one scale.

Functional status was measured by means of three widely known scales (ADL, IADL, and DAD) that were administered to the caregiver.

- ADL: a measure of participant's skill level on six basic functional domains. We took into account the number of preserved items, and summed them into a global score ranging from 0 (completely dependent) to 6 (completely autonomous) [Katz S et al, JAMA 1963].
- IADL: a measure of participant's skill level on eight complex functional domains. We took into account the number of impaired items, and summed them into a global score ranging from 0 (completely autonomous) to 8 (completely dependent) [Lawton MP et al, Gerontologist 1969].
- DAD: a measure of participant's skill level on several basic, instrumental and leisure activities. DAD scale includes 40 dichotomous items summed into a total score that is then converted into a percentage (higher scores represent less disability) [Gélinas I et al, Am J Occup Ther 1999].

Quality of life was measured by three questionnaires tools administered to the patient and comprise two generic questionnaires on perceived health status and/or cognitive status (SF-36 and EuroQol), and a self-report questionnaire specifically developed to rate the occurrence of different attention problems in everyday life (AQ):

- SF-36: a 36-item self-reported survey of patients' own general health and well-being. The SF-36 consists of eight basic health dimensions (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health) and 2 higher-order summary scores (Physical Component Summary, PCS; and Mental Component Summary, MCS). Summary scores are transformed into a 0-100 scale (lower scores represent more disability), and t scores are calculated using national norms [Ware JE et al, Med Care 1992].
- EuroQol (EQ): a self-reported health-related quality of life measure composed of a descriptive section (the respondent classifies his/her health according to five dimensions) that can be converted into a single summary index, and a visual analogue scale used as a quantitative measure ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [Rabin R et al, Ann Med 2001].

- AQ: a 12-item self-reported questionnaire specifically developed to rate the occurrence of different attention problems in everyday life. AQ supplies a total score ranging from 0 (absence of attention problems) to 36 (highest presence of attention problems) [Sohlberg M et al, Association for Neuropsychological Research and Development 1996].

Geriatric Depression Scale: is a 15-item self-reported questionnaire used to identify depressive symptoms in the elderly. The Geriatric Depression Scale supplies a total score ranging from 0 (absence of depressive symptoms) to 15 (severe depressive symptoms) [Yesavage JA, Psychopharmacol Bull 1988].

Considering that the APT-II contains specific exercises to facilitate generalization to daily life, the skills that are learned by each patient during the rehabilitation program are expected to generalize to daily activities. In addition, the improvement of cognitive skills should also improve patient's overall quality of life because these learned skills are applicable to real-life situations.

Secondary outcomes

Secondary outcomes included:

1) improvement in cognitive performance in any of 14 scores deriving from the 11 neuropsychological tests included in the VMCI-Tuscany neuropsychological battery [Salvadori E et al, Alzheimers Dis 2015], more specifically: two global cognitive functioning tests (Montreal Cognitive Assessment test; Mini Mental Status Examination test), and tests for the memory domain (Rey Auditory-Verbal Learning Test immediate and recall, Short story, Rey–Osterrieth Complex Figure recall), attention and executive functions (Trail Making Test part A and B, Visual search, Symbol Digit Modalities Test, Color Word Stroop Test), language (phonemic and semantic verbal fluency), and constructional praxis (Rey–Osterrieth Complex Figure copy). Cognitive performance of each patient was classified as 'normal', 'borderline' (an age and education adjusted score between the outer and inner confidence limits for the 5th centile of the normal population), or 'abnormal' (an age and education adjusted score below the 5th centile of the normal population) based on the non-parametric equivalent score methodology for all the tests except for the Symbol Digit Modalities Test for which the national parametric norms were used because equivalent scores were not available.

Cognitive performance of each patient was classified as 'normal', 'borderline' (an age and education adjusted score between the outer and inner confidence limits for the 5th centile of the normal population), or 'abnormal' (an age and education adjusted score below the 5th centile of the normal population) based on the non-parametric equivalent score methodology for all the tests except for the Symbol Digit Modalities Test for which the national parametric norms were used because equivalent scores were not available. Equivalent score (ES) methodology was available for all the tests included in the battery except for the symbol digit modalities test. ES methodology is a non-parametric norming method based on percentiles, and allows to convert age and education adjusted scores into an ordinal fivepoint scale (ranging from 0 to 4), where

ES = 0 represents an abnormal performance (below the 5th centile of the normal population), ES = 1 indicates a borderline performance (an adjusted score between the outer and inner confidence limits for the 5th centile of the normal population), and ES = 2, 3 and 4 represent a normal performance. Symbol digit modalities test performance was classified as abnormal when the adjusted score was below the 5th centile of the normal population, otherwise it was considered normal. As stated before, compound cognitive measures corresponds to the arithmetic mean of the equivalent scores obtained in each test included in the correspondent domain.

2) reduction of the term risk of transition to dementia. Data collected during the 1-year follow-up visit were used to evaluate the occurrence of a transition from MCI to dementia for each patient. Dementia diagnosis was made according to DSM-V criteria [American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing 2013].

3) improvement in long-term brain activity at rest evaluated by means of functional MRI, as a result of a training-induced cognitive plasticity, evaluated six months after the end of the cognitive rehabilitation period.

The APT-II program should sensitize cortical responses and promotes the establishment of new neural organization. The present study is using arterial spin labeling (ASL) and rsfMRI to assess whether the attention training have an impact on brain perfusion and functional changes associated with MCI and SVD [Mozolic JL et al, Front Hum Neurosci 2010].

MRI protocol, detailed in the methodological paper [[Salvadori E et al, Neurol Sci 2016], included the following sequences: i) High-resolution sagittal contiguous 3D T1-weighted images with isotropic voxels (Turbo Spin Echo SPACE sequence); ii) Axial T2-weighted images (FLAIR sequence); iii) T2* weighted FLASH; iv) Diffusion tensor imaging (DTI) (single shot EPI sequence); v) Resting state functional MRI (rsfMRI) (T2*-sensitive EPI sequence); vi) Perfusion imaging (pulsed arterial spin labeling, PASL).

Statistical analysis

Sample size was a priori determined taking into account data from previous studies, as well as feasibility and timing, and a foreseen target of 40 patients was established.

According to the study chronogram, administration of the neuropsychological rehabilitation program lasted 18 months, and 20 treated patients corresponded to a total of 800 h of individual attention process training, and to approximately 45 h of rehabilitation activities in a month.

This workload was in line with the availability of dedicated space, setting, and personnel [Salvadori E et al, Neurol Sci 2016].

Collection of baseline and follow-up clinical, neuropsychological, functional, and MRI data in a dedicated database was made. Data are checked and controlled for consistency in real time during collection. Post processing of neuroimaging acquired at baseline and at 1 year was performed.

Descriptive analysis were used to illustrate the baseline total sample characteristics (demographics, vascular risk factors, global cognitive and functional status). In order to verify if the 'attention training' and 'standard care' groups were not different in baseline characteristics not included in the stratified randomization, independent sample t tests and chi square tests were used to compare the two groups according to demographics, vascular risk factors, and global cognitive and functional status.

Primary outcomes and cognitive secondary outcomes were analyzed according to two different approaches:

Changes in scores (Δ) approach. Delta scores (Δs) were calculated by computing the difference between the scores obtained in two evaluations (baseline vs. 6 months; 6 months vs. 12 months; baseline vs. 12 months) for each patient. All Δs were calculated in order that a positive score indicates an improvement, while a negative score indicates a worsening. Delta scores were analyzed using independent sample t tests with treatment (*attention training* vs. *standard care*) as the only independent variable.

Clinically significance approach. The availability of *t* scores for the SF-36 summary scores (Physical Component Summary and Mental Component Summary) allowed us to classify each patient evaluation as 'normal well-being' (*t* score > 40) or 'reduced well-being' (*t* score ≤ 40) at each visit. As previously stated, the availability of parametric and non-parametric national norms for the cognitive variables, allowed us to classify each patient's performance as 'normal', 'borderline' or 'abnormal' at each visit. Variations in performance categories over time (baseline vs. 6-month; 6-month vs. 12-month; baseline vs. 12-month) was evaluated for each person and dichotomized as: 'stable or better evaluation' or 'worst evaluation'. Variations in performance categories were analysed using chi square tests for a 2x2 contingency table.

Chi quare test for a 2x2 contingency table was used to compare patients who became demented at 1-year follow-up visit with those who did not, in the two treatment groups.

Analysis of data was performed using SPSS 18.

3.1.4 Results

Recruitment procedures

Participants' selection and evaluation of eligibility started by data collected in both the VMCI-Tuscany study and the VAS-COG clinic of the Careggi University Hospital. The VMCI-Tuscany study is a multicenter, prospective, observational study aimed at evaluating predictors of the transition from MCI with SVD to dementia [Poggesi A et al, Int J Alzheimers Dis 2012]. The outpatient VAS-COG clinic is entirely dedicated to assess and follow-up patients affected by cognitive, psychiatric, and behavioral disturbances caused or associated with cerebrovascular diseases, and it is active since January 2006 [Poggesi A et al, J Alzheimers Dis 2014]. Participants

were also referred from other neurologic or geriatric units of the Careggi University Hospital [Salvadori E et al, Neurol Sci 2016].

The enrolment activities started on October 1, 2013 and were completed on April 30, 2015. To reach the foreseen number of 40 patients, we evaluated 175 potentially eligible patients [Salvadori E et al, Neurol Sci 2016]. Out of these 175 referred patients, 46 (26 %) were enrolled and completely assessed according to the study protocol. One hundred twenty-nine (74 %) patients were excluded after assessment. As shown in Figure 1, main reasons for non-enrolment were: refusal (n = 45), not fitting the cognitive criteria (n = 28 cognitively normal, n = 15 demented), contraindications for the MRI examination (n = 20), not fitting the MRI criteria (n = 15).

Patient baseline characteristics

Out of the 46 enrolled patients, one patient dropped-out before randomization because of the occurrence of cerebral hemorrhage, and 2 dropped-out after the allocation to the treatment group: one interrupted the treatment after 4 hours of treatment for a gastrointestinal perforation that required emergency surgery and a long hospitalization, and one other interrupted the treatment after 30 hours, and refused to undergo the 6-month follow-up; he consented to be contacted for the 12-month follow-up visit but deceased in the meanwhile for metastatic liver cancer (Figure 1).

Despite this minimal loss, the study enrolment reached and slightly exceeded the foreseen target (40 patients). Thus, the final baseline RehAtt cohort includes 43 patients affected by MCI with SVD. Twenty-two were randomly assigned to the 'standard care' group, and 21 to the 'attention training' group. All these patients completed the protocol, were re-assessed at 6 and 12 months, and repeated the MRI exams (Figure 1).

As shown in Table 3, 65% (n=28) of the total basal sample were males. The mean (±SD) age and years of education were 75.1±6.8 and 8.2±4.3, respectively. Concerning vascular risk factors distributions, it is that typical of a cohort of patients with SVD (table 3). Out of the 43 patients: 38 (88%) had hypertension, 31 (72%) hypercholesterolemia, 7 (16%) diabetes, 18 (42%) reported smoking habits, 17 (40%) had history of stroke, and 19 (44%) of alcohol consumption.

Regarding neuropsychological aspects, the cognitive and functional tests profile were those expected in a sample of MCI with SVD. The tests that resulted in an elevated percentage of abnormal performance were those that specifically assessed attention and executive functions. Percentage distributions of normal, borderline, and abnormal performances in cognitive tests in the total baseline sample are shown in Figure 2. MMSE resulted largely normal in our sample, while MoCA resulted abnormal in 24 % of patients, and borderline in 12 %. The immediate copy of the Rey–Osterrieth Complex Figure resulted the most difficult test, with an abnormal performance in 70 % of patients. Other tests that resulted in an elevated percentage of abnormal performance were those that specifically assessed attention and executive functions, namely the symbol digit modalities test (52 %), Part B of the trail making test (43 %), and the stroop test (50 %).

Comparisons between 'attention training' and 'standard care' groups showed that there were not statistically significant differences in baseline demographics, vascular risk factors, and global cognitive and functional status (Table 3), and this evidence assured the 'ceteris paribus' basal condition.

Results for the primary functional outcomes are shown in Tables 4 and 5. Considering both the Δs and the clinically significance approaches, the 'attention training' and 'standard care' groups did not differ significantly in any of the functional or quality of life measures after 6 or 12 months.

Results for the cognitive secondary outcomes are shown in Tables 6 and 7. Using the Δs approach (Table 6), we found a statistically significant difference between treated and non-treated patients in favor of treated patients in the Δs of the Rey Auditory-Verbal Learning Test immediate recall (working memory) when comparing 6 months vs. 12 months (1.8±4.9 and -1.4±3.8, p=.021, respectively) and baseline vs. 12 months (3.8±6.1 and 0.2±4.4, p=.032, respectively). Both results showed a statistically significant improvement in working memory in treated patients compared to non-treated ones. Considering the clinically significance approach (Table 7), we found that percentages of patients that resulted in a stable or better evaluation were significantly higher in treated patients compared to non-treated ones both in the Visual search test (95% vs 71%, p=.038, respectively) and in the Rey–Osterrieth Complex Figure immediate copy (95% vs 67%, p=.027, respectively), but only in the 6 months vs. 12 months comparison.

Out of the 43 enrolled patients, 8 (19%) were diagnosed as demented at 1-year follow-up visit according to DSM-V criteria, 34 (79%) remained MCI, and 1 (2%) reverted to normal cognitive function. The chi square test for the association between treatment and dementia diagnosis was not statistically significant. Distributions of patients who became demented or not between the treated and non-treated groups were as follows: patients diagnosed as demented were 3 (14%) and 5 (23%), respectively; patients who remained MCI were 17 (81%) and 17 (77%), respectively; the only patient who reverted to normal cognition was in the 'attention training' group**.**

3.1.5 Discussion

To the best of our knowledge, Rehatt this study is the first-ever randomized trial using cognitive training to improve cognitive performances and outcome of patients affected by MCI with SVD. Rehatt Study is the first attempt to reduce attention deficits in patients with MCI and SVD and as such it has to be intended as a pilot study [Salvadori E et al, Neurol Sci 2016]. The study results represent an essential methodological background for designing and sample sizing other multicenter, prospective, doubleblinded, randomized and controlled clinical trials. Moreover, results from the study may provide both health systems and professionals with a useful tool for tailoring the appropriate preventive strategy in individual patients, improving their quality of life and reducing the risk of transition to dementia.

Feasibility of cognitive rehabilitation in clinical practice may be an issue. Approximately one-quarter of our eligible patients refused to adhere to the study because

they were dependent on the availability of a caregiver in transport and logistics management, and because they considered the required commitment highly demanding. On the other hand, the patients who accepted to be enrolled in the study showed a good compliance, and the trained ones reported great satisfaction, and appreciated the possibility to receive an intense training and to continuously interact with a trained specialist in a specifically dedicated setting.

Concerning representativeness of our sample, distributions of vascular risk factors, clinical features and cognitive profile of the basal cohort were consistent with data reported in the literature from similarly defined patients'populations. Distribution of cognitive performances confirmed that attention-executive dysfunction is one of the prominent features of subcortical vascular cognitive impairment (VCI) [Cummings JL et al, Arch Neurol 2003; Sachdev PS et al, Med J Aust 1999; O'Brien JT et al, Lancet Neurol 2003]. Impairment in high level visuo-constructional abilities was also observed in our sample. On one hand, this evidence was in line with previous reports about complexity of neuropsychological profile in VCI patients [Pantoni L et al, Cerebrovasc Dis 2009], but on the other hand it may be related with the growing evidence that the Rey–Osterrieth Complex Figure test, commonly used to assess visuoconstructional skills, involves also executive functioning [Eslinger PJ et al, J Clin Exp Neuropsychol 1990; Freeman RQ et al, Neuropsychology 2000]. Most of our patients with mild degree of cognitive impairment were cognitively normal on MMSE, a screening tool designed to detect moderate/severe cognitive impairment. As expected, MoCA resulted more sensitive to mild cognitive deficits in our sample, and this preliminary evidence further support its specificity for VCI [Koski L, Cerebrovasc Dis 2013].

To establish reliable and validated intervention practices, the field of cognitive rehabilitation needs evidencebased guidelines, supported by well-controlled studies that systematically evaluate outcome and effectiveness of specific interventions. On the other hand, clinical practice in cognitive rehabilitation suggests that individuals respond to different interventions in different ways and at different times, and an individualized approach could be more effective. In this study, the lack of an individualized approach might result in a limitation, and reduce the possibility to demonstrate the effectiveness of the treatment. Considering this possible limitation, the choice of the APTII has been mainly due to its flexible structure that offers to the trainer the possibility to use a large variety of training tasks, to develop a training able to deal with several deficits, and to tailor the rehabilitation treatment on the specific cognitive profile of each patient. The rationale of the APTII is based on a hierarchical concept of attention, sequencing attentional trainings according to a pre-established model of intervention, and clearly states that specific attention deficits call for specific training procedures [Sohlberg M et al, Association for Neuropsychological Research and Development 1996].

We believe that this approach minimizes the chance of leaving important areas of attention untreated, reduces the gap between a standardized and a person-oriented approach, and allows to create customized trainings within a standardized procedure.

As other cognitive rehabilitation studies, the RehAtt study faces the difficulties related to the type of alternative treatment that would have to be assigned to the control group. The use of an active placebo treatment could reduce the patients' compliance

in the study, because the request of weekly visits for 5 months would be very demanding and, most importantly, questionable under ethics viewpoint. As a result in the ReHAtt study the control group did not receive any intervention, and had a usual lifestyle; however, all participants were clearly instructed to immediately communicate any change regarding medications or activities focused on cognition [Salvadori E et al, Neurol Sci 2016].

Another possible limitation, that the Rehatt study shares with several studies on cognitive rehabilitation, is the limited sample size. As reported in recent Cochrane reviews on cognitive rehabilitation [Bahar-Fuchs A et al, Cochrane Database Syst Rev 2013; Chung CS et al, Cochrane Database Syst Rev 2013; Loetscher T et al, Cochrane Database Syst Rev 2013], the most part of the evaluated randomized controlled trials (RCTs) included relatively small sample sizes (N<50). In a realworld hospital setting, planning and organization of a cognitive rehabilitation treatment is highly demanding in terms of feasibility, availability of dedicated space and personnel, and timing. Furthermore, despite the need of robust and well-controlled studies to guarantee enough tatistical power, the lack of prior studies with similar sample population, intervention, and outcome measures did not allow an a priori power analysis. In line with this important issue, methodology and results of the present pilot study will contribute to increase the scientific knowledge that will be essential for future RCTs.

Despite the high prevalence of MCI in the elderly and the increased risk of developing dementia in these patients compared with the general population, research on cognitive rehabilitation in chronic SVD has been relatively underdeveloped. Considering also that, at present, no drug treatment is available to prevent dementia in patients with MCI, a prevention strategy based on cognitive rehabilitation could be of great importance. Knowledge about effectiveness and impact of cognitive rehabilitation on functional abilities and quality of life in patients with MCI and SVD is essential to the identification of potential preventive targets, contributing to reduce the burden of disability and social discomfort in the elderly. This represents one of the greatest challenges for social and health systems in our aging society.

We were unable to detect a favorable effect of the APT-II program (as implemented in this study for a total of 40 hours) on strong outcomes such as functional status and quality of life in our elderly sample. We saw instead some moderate effects on a few cognitive tests evaluating attention and working memory domains.

Overall, the trial has therefore to be considered negative. The main possible reason for this failure is obviously the inefficacy of the treatment. One could alternatively hypothesize that the same program implemented for longer periods could have a better effect.

Of note, in our study the control group remained quite stable overall in functional and cognitive performances. This may in part explain the lack of efficacy of this treatment. This behavior appears quite different from the natural history of the disease where an overall decline is usually seen; for example, in the V-MCI Tuscany study patients with MCI and SVD decline on the average about 2 points per year on the MoCA [unpublished data]. In this study, patients in the APT-II groups had improving scores on the MoCA over time, while those of the standard care group were stable. This behavior might have attenuated the differences between treated and non-treated

patients. Of note, this behavior of the placebo groups has been seen also in other trials in similar patients [Black S et al, Stroke 2003].

Changes in cognitive performances over time suggest that practice, by repeating the assessment tasks every six months, may play a role in improving performance in both treatment groups. The presence of practice effects is significant for methodological reasons: it highlights both the importance of controlling for these effects when designing studies to evaluate training efficacy, and the difficulties of drawing firm conclusions about treatment effectiveness from studies with limited sample sizes.

One last point concerns the mean age of our population that is quite old. Whether the same approach could have different effect in younger age-groups of patients with MCI and SVD remains to be explored.

Few considerations related to this type of treatment can be made. First, the APT-II program is demanding in terms of patient compliance. This notwithstanding, the rate of drop-out was extremely low in our study. On the other hand, these cognitive training approaches can be proposed only to well motivated patients and this is reflected by the high selection rate recorded in our study in which a not negligible number of patients refused to take part.

Finally, as typical of cognitive training approaches, the APT-II program places increasing demands on working memory systems and complex attentional control. The lack of efficacy of treatment in our study may be also due to the fact that a direct attention cognitive training could be a challenging approach for elderly MCI patients, thus reducing possibility to achieve a stable or generalizable effect. Future trials on elderly MCI patients should verify the efficacy of less demanding and more ecological cognitive interventions, such as cognitive rehabilitation approaches based on meta-cognitive strategies' learning. Despite the null effect on primary outcomes, the APT-II treatment induced beneficial, although limited, effects on some cognitive measures.

3.1.6 Conclusion

In conclusion, cognitive training of patients with MCI and SVD with APT-II program produces only minimal improvement in some cognitive performances without producing an effect in terms of functionality and quality of life. It remains to be tested in future trials whether focusing on the rehabilitation of more specific domains could result in different results.

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Part 4

Discussion

Chapter 4
Discussion

Sporadic cerebral SVD has a crucial role in stroke, cognitive impairment, and functional loss in elderly persons. Modern neuroimaging has revolutionized our understanding of the consequences of SVD. In this thesis we analyzed neuroimaging and cognitive features in two main different types of SVD (or age- and hypertension-related SVD arteriolosclerosis) and cerebral amyloid angiopathy, a particular chronic degenerative disease characterized by progressive deposition of amyloid-β (Aβ) in the media and adventitia of small arteries and arterioles. We focused particular attention on hemorrhagic manifestation of these forms of SVD.

A natural step was to try to combine the different manifestations of SVD on structural imaging, to gauge total brain SVD severity. Recently, the approach of assessing total MRI SVD burden into a score has been developed and validated in patients at high risk for ischemic small vessel damage, including lacunar or non-disabling cortical stroke. This comprehensive framework should also be evaluated in other types of SVD and in different clinical cohorts, as it has potential advantages over individual markers. A total MRI SVD score may better stratify the impact of microangiopathy-related damage on clinical outcomes (such as disability and cognition) and ultimately be used as a composite endpoint in clinical trials. Another key area of need is the identification of neuroimaging biomarker dynamic progression over time and determination as to whether this captures clinically relevant changes.

In this thesis we investigated in particular the hemorrhagic manifestation, global neuroimaging burden and microstructural changes in CAA, and their specific consequences on cognitive features in patients with SVD and CAA. ''Invisible'' on conventional clinical MRI SVD-associated changes may contribute substantially to abnormalities of clinical function.

We also examined the definition of cognitive impairment of probable vascular origin and its possible treatment strategy.

The main findings of our studies are the following.

1. The total burden of CMBs, one of the neuroimaging marker of SVD, was associated with attention/executive functions impairment, lacunar infarcts, and with some potentially modifiable risk factors in a cohort of patients with MCI and SVD. This confirm an independent effect of CMBs on cognitive impairment, with a graded relationship between higher CMBs load and more severe cognitive impairment, as already shown in the literature.
2. The total MRI SVD score might be helpful to capture the cumulative effects of microangiopathy burden in the brain of patients affected by sporadic CAA, given

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the correlation between the score and brain atrophy, posterior predominance of WMH, memory deficit, depressive symptoms and ApoE_e2 variant genotype in our cohort.

3. Increased burden CAA injury on MRI was associated with greater impairments in structural network efficiency (evaluated by DTI) in our study, implying a possible cumulative effect of overall SVD markers on disrupted physiology. In our study the association was primarily driven by the presence of moderate-severe leukoencephalopathy and siderosis. Even if the network measures are more sensitive to injury in the subcortical white matter and not to other SVD markers, we considered DTI measures useful for the detection of diffuse underlying pathology in SVD.

4. Based on current knowledge, some clinical and imaging features are able to distinguish reliably MCI of vascular from degenerative origin. Interestingly, global atrophy was demonstrated to be a marker of SVD, in line with the inclusion of brain atrophy as another imaging manifestation of SVD in the STRIVE Criteria. SVD frequently coexists with neurodegenerative disease.

5. Not all the vascular MCI patients have a multiple domain profile but they could show a more heterogeneous cognitive profile, overlapping with neurodegenerative cognitive features.

6. Given the demonstrated posterior brain predilection of neuroimaging markers of CAA, more clinical attention on visuospatial functioning in patients with CAA could be important. The impairment in visuospatial functioning shown in our study seemed related to global disease severity.

7. A specific separate section in this thesis was dedicated to the RehAtt Study. Rehatt this study is the first-ever randomized trial using cognitive training to improve cognitive performances and outcome of patients affected by MCI with SVD. Despite the high prevalence of MCI in the elderly and the increased risk of developing dementia in these patients compared with the general population, research on cognitive rehabilitation in chronic SVD has been relatively underdeveloped. Considering also that, at present, no drug treatment is available to prevent dementia in patients with MCI, a prevention strategy based on cognitive rehabilitation could be of great importance.

A favorable effect of the APT-II program on strong outcomes (such as functional status and quality of life in our elderly sample) was not found, but some moderate effects on a few cognitive tests evaluating attention and working memory domains (visual search test and in the Rey–Osterrieth Complex Figure immediate copy) were demonstrated.

Knowledge about effectiveness and impact of cognitive rehabilitation on functional abilities and quality of life in patients with MCI and SVD is essential to the identification of potential preventive targets, contributing to reduce the burden of disability and social discomfort in the elderly. This represents one of the greatest challenges for social and health systems in our aging society.

Part 5

Conclusions

Chapter 5
Conclusions

In conclusion, in our opinion:

- ✓ Sporadic cerebral SVD is a complex "micro-world", to be globally considered
- ✓ Even if marker on MRI may be found in different types of SVD, given the frequent coexistence of different forms of SVD, all the relevant lesion types and SVD neuroimaging burden should be taken into account
- ✓ The cumulative effects of microangiopathy burden in the brain of patients affected by SVD is crucial
- ✓ SVD frequently coexists with neurodegenerative disease
- ✓ The systematic application of a standardized rating scale can be implemented also in the clinical setting to standardize image interpretation
- ✓ Cognitive rehabilitation could represent a promising approach to prevent VaD or to improve cognitive performances in patients with cerebral SVD

Longitudinal studies may provide more robust information about progression and prognostic significance of our findings.

A depth knowledge of the total lesion neuroimaging burden, stratified for different subtypes of SVD, may have important consequences in the future also from therapeutic point of view.

Moreover, future trials focusing on the rehabilitation of more specific domains would be tested in patients with SVD, for example in patients affected by CAA and CADASIL. These trials could result in different results.

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