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SMALL VESSEL VASCULAR COGNITIVE IMPAIRMENT: NATURAL HISTORY, NEUROPSYCHOLOGICAL PROFILE AND ECONOMIC ANALYSIS

DETERIORO COGNITIVO DE ORIGEN VASCULAR: HISTORIA NATURAL, PERFIL NEUROPSICOLÓGICO Y ANÁLISIS ECONÓMICO

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"SMALL VESSEL VASCULAR COGNITIVE IMPAIRMENT: NATURAL HISTORY, NEUROPSYCHOLOGICAL PROFILE AND ECONOMIC ANALYSIS"

CERTIFY:

That this work has been performed by Ciro Ramos Estébanez under our supervision, and possesses the requirements of originality needed to be presented as a Doctoral Thesis in order to apply for the Cantabria University Ph.D. Degree.

José Luis Hernández Hernández Jesús González Macías

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"Every man can, if he so desires, become the sculptor of his own brain"

Santiago Ramón y Cajal

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Summary / Resumen

Vascular cognitive impairment (VCI) is a prevalent condition with an undefined natural history. VCI may happen in the context of small or large vessel disease and progress to vascular dementia (VaD). The epidemiological features, natural history, and economic impact of VCI and VaD are studied.

A sample of 314 patients admitted to a teaching tertiary center during a 13-year period with a diagnosis of stroke, or neuroradiological vascular disease, or VCI, or VaD met our criteria for VCI or VaD (lacunar state, Binswanger's disease, pure cortical VaD, corticosubcortical, or strategic infarctions). There were a retrospective (n = 88), and a prospective arm (n=226) of the study. Prospective neuropsychological assessment was performed in individuals with VCI (n=141). Additionally, we report a cost-description retrospective analysis of community dwellers inpatient expenses in a prospective subset of the sample (n= 122).

An unrecognized diagnosis of VCI was related with a clinical onset with cognitive impairment (not stroke), age < 85, and taking prophylactic medication for stroke. A VCI onset without stroke happened in patients with silent ischemia, Binswanger's disease, no ischemic events during their VCI stage, and lengthier VCI periods. Executive dysfunction was a distinct deficit found in small vessel patients meeting Binswanger's disease or lacunar state criteria. Gait disturbances with frontal features were also frequent in the Binswanger's group. VCI presenting with stroke conveys loftier expenses than a VCI onset without stroke. Thus, patients with large-vessel disease incurred larger costs during the VCI stage. Care became more onerous at an advanced VaD period in all groups. Once VaD developed, Binswanger's disease expenditure per-capita was significantly higher and eventually counterbalanced the initially lower costs seen during the VCI phase.

El deterioro cognitivo leve de perfil vascular (DCV) es una entidad prevalente con una historia natural mal definida. Puede deberse a una enfermedad de gran vaso o de pequeño vaso y progresar a demencia vascular (DaV). El presente estudio analiza las características epidemiológicas, la historia natural y el impacto económico del DCV y la DaV. Se estudiaron 314 pacientes ingresados en un hospital universitario de tercer nivel en un período de 13 años con diagnostico de ictus, patología vascular radiológica, DCV, o DaV y que cumplían nuestros criterios de DCV o DaV (estado lacunar, enfermedad de Binswanger, DaV cortical, córtico-subcortical, o infarto estratégico). Se analizaron 88 pacientes retrospectivamente y 226 de forma prospectiva. Dentro del último grupo, en 141 pacientes con DCV se realizó una evaluación neuropsicológica. Además, se realizó un análisis retrospectivo del gasto sanitario durante la hospitalización, en una muestra de122 pacientes.

El diagnóstico no reconocido de DCV se correlacionó con un inicio con deterioro cognitivo no ictal, con una edad < 85 años, y con el empleo de medicación preventiva frente al ictus. El inicio del DCV sin ictus sucedió en individuos con isquemia silente, con enfermedad de Binswanger, con DCV sin eventos isquémicos y con periodos prolongados de DCV. La presencia de disfunción ejecutiva fue característica de los pacientes con enfermedad de Binswanger o con estado lacunar. El DCV iniciado con un ictus tuvo un gasto mas elevado que los casos de DCV que se iniciaron sin eventos isquémicos. Por este motivo la atención a los pacientes con enfermedad de gran vaso resultó más costosa durante la fase de DCV. El gasto generado por todos los grupos fue mayor en el período de DaV avanzada. Sin embargo, el coste individual en pacientes con enfermedad de Binswanger fue más elevado y eventualmente compensó el menor gasto durante la etapa de DCV.

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Introduction

2.1. General Introduction to Cognitive Behavioral Neurology

The cerebral cortex has been recognized as the key neural substrate in human cognition. The distinct cytoarchitecture of each cortical area determines functionally characteristic domains. Many of those neuronal populations are unimodal, yet some groups exhibit multimodal properties. These neuronal groups operate within networks that drive perception, action, and amongst other capabilities, abstract thought.

2.1.2. Lesion studies

Indeed, many lesion studies and virtual lesion paradigms have yielded fruitful information concerning the role of different anatomical areas and neuronal populations in behavior. John Harlow's initial description of Phineas Gage (1868), which was enriched with subsequent contributions (Damasio et al 1994; Ratiu et al, 2004); Broca's aphasia descriptions (Broca, 1861 (a, b, c); Domanski, 2013), and Wernicke's work (1874) are classical examples that provide a link between anatomy and behavior. Finally, Oppenheim described the neuropsychological correlates of orbitofrontal and mesial frontal lesions (Oppenheim 1890; 1891).

2.1.3. The dawn of modern neuroscience

As previously described, gray matter centers had been the focus of lesion studies. However, this situation was about to change, for Dejerine described some of the major cortical association tracts and cortico-subcortical loops during the XIX century (1895). From the pathological perspective, Otto Binswanger, Emil Kraepelin, and Alois Alzheimer had provided a quantum leap

in the understanding of diverse dementia syndromes. Some of these conditions involved a pervasive white matter disease (i.e. Binswanger's disease).

2.1.4. Contemporary cognitive neurology theory

The physiological involvement of these networks was described well in the XX century. Anatomical connections between diverse domain-specific cortical areas or concerning cortical and subcortical areas are now known to drive complex behaviors (Alexander et al, 1986; Alexander et al, 1990, Alexander & Crutcher, 1990; Geschwind 1965a,b; Goldman-Rakic & Porrino, 1985, 1988; Goldman-Rakic & Selemon 1990; Jones and Powell, 1970; Mesulam, 1981, 1986, 1990, 1998, 2000; Nauta, 1964; Pandya and Kuypers, 1969; Naeser et al, 1982; Ungerleider and Mishkin, 1982; Pandya and Yeterian, 1985). Indeed, the theory of networks interacting and modulating behavior was established. Thus, the concept of metacognition with higher hierarchical management of information developed (Shimamura, 2000). In addition, cognitive research has recently started to draw promising data about the role of behavioral control at genetic level in animal (Gardfield et al, 2011; Weber et al, 2013) and human models.

Thus, it is in the context of the recent advances in cognitive behavioral neurology that we embraced the uncharted territory of cognitive decline in a white matter chronic ischemia model.

2.2. Historical Background

Generic descriptions of stroke, lacunae, aging, cognitive decline, and dementia have been a present in literary, medical, and philosophical writings throughout history. We will proceed to provide a historical background about the

development of the aforementioned concepts during the XIX and XX Centuries. We shall reference philosophy and science. In Lakatos's words (1970), while paraphrasing Kant, 'philosophy of science without history of science is empty; history of science without philosophy of science is blind'.

2.2.1. Philosophical & scientific background

During the XVII century reductionism (Descartes, 1637) had helped to connect illness with an altered physical state. However, the XIX century hailed a new concept of disease influenced by empiricism and based on the Francis Bacon's mechanistic ideas. Besides, the nervous system became the ontological model central to human economy (Jackson, 1970).

Advances in the understanding of disease opened the route toward the development of modern medical concepts and definitions. For example, Cullen described delirium with and without pyrexia. Within the latter, he further described 'amentia', 'oneirodynia', 'melancholia', and 'mania' (Cullen, 1827). Critically, he further elaborates on 'amentia' and separated traumatic brain injury from mental retardation and senile dementia (Cullen, 1827).

As the new concept of dementia spreads throughout Europe, Philippe Pinel followed Cullen's lead in France and described four types of insanity in his 'Memoirs of madness' in 1794 (Weiner, 1992): moral insanity, monomania or partial derangement of the understanding, mania or raving madness, incoherence or dementia. Amongst his merits shines his definition of 'madness' as a disease, thereby not to be prosecuted by the law, but bound to receive 'moral therapy'.

Plato's initial concept of Associationism, later popularized by Aristotle, became matter of debate. Hume, Locke, and Hartley updated their views, while Hartley attempted to describe the physiological basis for this theory. For example, in reference to recent memory decline, Hartley posed: 'The dotage of old persons is oftentimes something more than a mere decay of memory…'

2.2.2. Popular beliefs about cognitive decline: Tithonus' myth

2.2.2.1. Hesiod

The myth of Tithonus reflects the concern ancient Greeks had about aging and cognitive deterioration. It provides an early recollection on how maturing was mostly perceived under a gloomy light in Western civilization. The Homeric 'Hymm to Aphrodite', reflects how Zeus granted Eos with eternal life for her lover Tithonus, yet not eternal adolescence (Hesiod, circa 700 BC). During this period, the perspective of a prolonged life without a preserved cognition was already of serious concern.

2.2.2.2. Ovid

Roman lyricist Publius Ovidius Naso (Ovid) (43 BC – AD 18), depicted the topic of aging in his poem Metamorphoses (Translation by Kline):

'The priestess gazed at him…I was offered eternal life without end, if I would surrender my virginity to Phoebus my lover…he said:

"Virgin of Cumae, choose what you wish, and what you wish you shall have." Pointing to a pile of dust, that had collected, I foolishly begged to have as many anniversaries of my birth, as were represented by the dust. But I forgot to ask that

the years should be accompanied by youth. He gave me the years, and lasting youth, as well, if I would surrender: I rejected Phoebus's gift, and never married'.

'But now my more fruitful time has turned its back on me, and old age comes, with tottering step, that must be long endured…The time will come when the passage of days will render such body as I have tiny, and my limbs, consumed with age, will reduce to the slightest of burdens…I will go as far as having to suffer transformation, and I will be viewed as non-existent, but still known as a voice: the fates will bequeath me a voice.'

2.2.2.3. Tennyson

Tennyson's interpretation of the "Tithonus" myth reflects the perception of aging and dementia in the XIX century. It examines the concept of the "Tithonus error" that Ovid's Sybil of Cumae had avoided in the Homeric Hymn to Aphrodite version. In Tennyson's poem, Eo does accept Zeus' offer. Thus, Tithonus is granted immortality. Once Tithonus starts maturing, Tennyson describes:

'The woods decay, the woods decay and fall,

The vapours weep their burthen to the ground,

Man comes and tills the field and lies beneath,

And after many a summer dies the swan…

Me only cruel immortality consumes…

Alas! for this gray shadow, once a man.."

2.2.3. John Cooke's contributions

John Cooke provided clinical descriptions of post-stroke cognitive impairment:

'I have in several instances seen palsy terminating in childishness, or complete imbecility' ('A treatise on Nervous Diseases', 1820). He also elaborated on further descriptions of pseudobulbar palsy, and cognitive decline. Cooke (1820) interpreted his wonderful clinical descriptions in the context of modifications of the humor's theory. In fact, apoplexy was still thought to be a consequence of 'brain hyperemia' (Roman, 2003). Actually, brain plethora is an ancient Greek concept already developed by Herophilus (circa 300 BC) (Roman, 2003).

2.2.4. Concept of lacune & état lacunaire

Dechambre (1838) coined the term lacune to describe small cavities caused by reabsorption of small deep cerebral softening (1838). "Lacunes result from liquefaction and partial reabsorption in the center of the cerebral softening". Roman (2002a) depicts Maxime Durand-Fardel's work and how described in his "Traité du Ramillissement du Cerveau" (1843) an "interstitial atrophy of the brain" consisting of: "an alteration of the cerebral pulp...[that] seems quite different from the infarct proper. ... It does not seem to be due to a change in the consistency of the brain but to a rarefaction of the pulp ... a mere interstitial atrophy. ... If a section is performed at the center of the changes, it can be seen that the white matter is rarefied. ... We do not know any symptom characteristic of this change." He also defined 'état criblé', the dilatation of perivascular spaces around cerebral arterioles. He differentiated it from lacunes.

Pseudobulbar palsy was then associated with lacunar lesions in a pathological series by Compte (1900). Pierre Marie (1901) described 'état lacunaire' (lacunar state), emphasizing the presence of multiple lacunes in subcortical territories: "small and irregular (the size of a bird seed, pea or haricot bean)." Since there seemed to be atherosclerosis in the vessels, the immediate assumption was that ischemia could be involved in lacunar pathogenesis: "One could therefore picture the anatomo-pathological process of formation of lacunes in the following manner: the influence of the general causes of atherosclerosis, the vessels which irrigate the brain change, the nutrition of the brain diminishes, its parts become atrophied, which contributes to the dilatation of the ventricles of the perivascular spaces. As the vascular lesions progress, one or more small vessels break or are obliterated, hence the production of one or more lacunes. In effect, it is known that in the central areas of the brain the blood vessels are terminal, that is, there are no anastomoses, so that the whole territory is irrigated by the blood vessel which is obliterated is inevitably infarcted". He noted some surrounding necrosis and hypothesized that there could be destruction on nearby areas that eventually would trigger a lacunae formation ("vaginalité destructive"). Foix and Chavany (1926) reflected on the topic and reported sclerotic foci in lacunes. Along with lacunae, Marie (1901) and Ferrand (1902) described ventricular dilatation, moth-eaten rag looking like white matter ('étoffe mitée'), and islands of fibrillary glia. Ferrand (1902) confirmed a transition of lacunae from rarefaction to sclerotic lesion. Given this description, it has been suggested that 'état lacunaire' could be the same condition as 'arteriosclerotic brain atrophy' described by Alzheimer and Binswanger (Roman, 2002). Thereby, two theories for lacunae formation were current. The question remained unresolved until Hughes (1954) established the

relationship between hypertension and lacunae. Finally, Fisher's magnificent work in eighteen brains definitively demonstrated that lipohyalinosis (secondary to hypertension) (Fisher and Curry, 1965; Fisher, 1991) triggered local ischemia at single penetrating vessels territory level. Other etiologies he described were micro-atheroma within the small vessel wall, edging atheroma at the junction between penetrating and larger vessel, or embolism in healthy vessels (Fisher, 1965a, b, 1969, 1979; Fisher and Caplan, 1971). Marie had already described motor deficits and dysarthria due to lacunes (1901). However, it was through Fisher's descriptions that the main lacunar syndromes were identified (Fisher 1965a, 1965b, 1978a, 1978b, 1979, 1982a, 1982 b, 1989) and (Fisher & Caplan, 1971). Eventually, Lammie and colleagues (1997) added to the field by examining lacunae in patients who were normotensive, and proposing that conditions that increased vessel permeability could also contribute to the pathophysiology of 'état lacunaire'.

2.2.5. Otto Binswanger

Otto Binswanger was a Swiss physician educated in the field of pathology by von Recklinhausen and Meynert, as well as in psychiatry (Schneider, 1991; Roman, 1992). During his career, he worked with Wernicke and Pick at the Charité Hospital in Berlin in 1880. Once in Jena, his interest for syphilitic general paralysis led to the publication of a book on the topic (1893). Binswanger was interested in other forms of paresis and dementia, since he felt those entities needed be defined and thus differentiated from the most frequent syphilitic etiology. A year later, Binswanger identified a patient who had received a diagnosis of neurosyphilis (Binswanger, 1894; Schorer & Rodin, 1990). While trying to capture other forms

of dementia besides progressive syphilitic paralysis, Binswanger added a brief clinico-pathological description of seven additional cases. He discussed these data at the Dresden meeting of the German Psychiatric Society, and published it as "The Demarcation of General Paresis of the Insane" (Binswanger, 1894; Schorer & Rodin, 1990; Blass et al, 1991). Binswanger believed that syphilis "poisoned the nerves" through "chemical effects", and acted as an "indirect disease" by overexerting the central nervous system. He portrayed cases of "encephalitis subcorticalis chronica progressive", "diffuse brain sclerosis", and "arteriosclerotic brain degeneration". Binswanger summarized the current opinion of those times that "all diseases of the central nervous system, and specifically of the brain, that directly follow the syphilitic infection are to be assigned to the specific processes, while all late forms, i.e. all diseases of the central nervous system that lag behind the specific syphilitic manifestations, so to speak, belong to the group of illnesses that are brought about indirectly by syphilis (tabes and paresis)" (Binswanger, 1894; Blass et al, 1991). Moreover, Binswanger elaborates "…in the area of neurologic diseases, the localization and extent of a disease process will be determined primarily by the degree of anatomic and physiologic development of some segment of the nervous system in the determination of the level of resistance that precisely this segment possesses against pathologic influences".

Clinically he distinguishes patients with "early stages of paresis" vs. those with "atypical paresis". In the first group, "Arteriosclerotic brain degeneration" is described as different from "general paresis" in that it had an abrupt onset, localized to certain areas that undergo injury (Binswanger, 1984; Schorer & Rodin, 1990; Blass et al, 1991). Within the "so-called atypical paresis",

Binswanger defends that “Arteriosclerotic brain degeneration” is different from “simple presenile dementia” because it has an intermittent course and progresses faster. He continues describing the differences between “encephalitis subcorticalis chronica progressive” and “progressive paralysis”. Herein, Binswanger provides an example of what would be acknowledged later as Binswanger’s disease (Binswanger, 1894; Schorer & Rodin, 1990). Indeed, this patient had been treated for central nervous system syphilis in his 40s. Hence, the contributions of this infection to the findings in the autopsy remain open to discussion. However, the clinical description is rich in detail and endowed through years of follow up. Binswanger already brought up the possibility of damage to association fibers driving many clinical deficits in this patient. He expands in the differential diagnosis of “encephalitis subcorticalis chronica progressive” from general paresis (syphilis) and notes that “These cases distinguish themselves from paresis, first by the stable deficits; second, through the peculiar development of intellectual deficit (disappearance of partial memory, impeded and interrupted connection between the various cortico-motor and cortico-sensory centers); third, through the unique course (average illness duration much longer than the usual paresis); and fourth, by the postmortem findings”. Binswanger adds the differential facts between “encephalitis subcorticalis chronica progressive” and “arteriosclerotic brain degeneration” are “apparent…in that…the focal features are transient and the deficits point from the beginning to diffuse brain disease, while here the disease process possesses initially a circumscribed character limited to specific hemispheric regions, and therefore isolated deficits of the type described dominate the clinical picture from the start” (Binswanger, 1894; Schorer & Rodin, 1990). In addition, when

reckoning the similarities with other forms of paresis, he suggests that there might be a spectrum '…there are doubtless transitional forms occurring where the stable pathological symptoms limited to specific sensory or motor functions are less pronounced and overshadowed by the overall dementia resulting from the widespread loss of fibers or associative connections" (Binswanger, 1894; Schorer & Rodin, 1990).

2.2.6. Alois Alzheimer and the concept of Binswanger's disease

Alois Alzheimer reviewed those cases and added the description of a new patient (Schorer, 1992). Alzheimer concluded they represented a distinct clinico-pathological entity that triggered dementia and named it "Binswanger's disease" (Alzheimer, 1902). He mentioned (1902): "In 1894, Binswanger and this reviewer first described arteriosclerotic brain atrophy and emphasized the need to differentiate it from paralysis." Alzheimer also coined the name "Binswanger's disease" for the "subcortical arteriosclerotic encephalopathy" described in 1894 by his colleague.

2.2.7. Emil Kraepelin's contributions

Emil Kraepelin was a most prominent pathologist and father of modern psychiatry. Among other achievements, Kraepelin provided the first description of Alzheimer's disease (1910 (a)). In addition, his psychiatric encyclopedia included an extensive chapter about the pathological findings in arteriosclerotic brain degeneration (Kraepelin 1910 (b)). Kraepelin notes cortical atrophy, laminar necrosis, and describes lacunar strokes, état criblé, and diffuse

arteriosclerosis of small and large vessels. He indeed mentions severe periventricular white matter atrophy.

In regards to vascular dementia, Kraepelin introduced the concept of "Das arteriosklerotische Irresein" (arteriosclerotic insanity/psychosis)" (a.k.a. vascular dementia) in his Lehrbuch der Psychiatrie (1910 (a, b)). His ideas developed from previous work from Binswanger (1893, 1894) and Alois Alzheimer (1894, 1895, 1898, 1899, 1902). Kraepelin described Binswanger's disease in his Textbook of Psychiatry, chapter on 'Senile and presenile dementia' (1910 (a, b)). Given Kraepelin's prominence, vascular dementia became a synonym with senile dementia.

2.2.8. Paradigm shift in the second half of the XX century

Finally, the dementia field started to change and the vascular etiology yielded its prominence to Alzheimer's disease. Olszewski proposed the name of "subcortical arteriosclerotic encephalopathy" for Binswanger's disease (1962). Hachinski's landmark contribution, the concept of multi-infarct dementia, substituted the term 'cerebral atherosclerosis (Hachinski et al, 1974). Subsequent vascular dementia criteria were suggested in 1993 (Roman G, et al). Meanwhile, Bowler & Hachinski (1995) proposed the vascular cognitive impairment criteria in 1995 and Petersen popularized the concept of mild cognitive impairment in 1999.

3

Justification & Objectives

3.1. JUSTIFICATION

3.1.1. Epidemiological & Economic perspective

The study of dementia secondary to small vessel ischemic disease is relevant from the epidemiological perspective for dementia has become a major healthcare burden in developed countries. A panel of experts involved in the Delphi Study (Ferri et al. Lancet, 2005) estimated that 24.3 million people suffer from dementia today, with 4.6 million new cases of dementia being diagnosed every year (one new case every 7 seconds). The numbers of people afflicted will double every 20 years reaching 81.1 million by 2040. Late in the XX century in the USA alone, dementia costs were estimated to be around $52,600 per dementia patient each year, which summed up to a total of $86.9 billion in 1994 (Ernst, 1994). More importantly, the Delphi report also warned that most people with dementia live in developing countries (60% in 2001, rising to 71% by 2040) (Ferri, et al. Lancet, 2005).

Regarding cognitive deficits driven by cerebrovascular disease, Vascular Cognitive Impairment (VCI) secondary to small vessel disease is a frequent condition (Bogousslavsky, 1992; Rockwood et al, Neurology 2000; Ramos-Estébanez et al, 2008 & 2011) that ultimately evolves to vascular dementia. Notably, small-vessel ischemic events and penetrating artery strokes account for 25 % of symptomatic ischemia (Petty et al, 1999). This type of vascular affection is also most frequent in elderly populations when presenting as silent ischemia (Vermeer et al, 2003). Indeed, both manifestations of microvascular disease have been related to short-term milder cognitive affection (Mock et al, 2005; Prins et al, 2005). Importantly, when these patients are followed in the long term, outcomes

turn out to be less benign than expected in terms of mortality, morbidity and quality of life (Vermeer et al, 2003; Prins et al, 2005). Thereby, early identification and intervention in this group might render a most valuable impact on these patients' quality of life and survival.

Once developed, vascular dementia (VaD) is the second-most frequent type of dementia (Rockwood et al, Neurology 2000; Ramos-Estébanez and colleagues, 2008 & 2011). Certainly, there are studies addressing the cost of dementia, Alzheimer's disease, and stroke. However**,** financial accounts relating to the cognitive effects of small vessel chronic ischemic disease and vascular dementia are required.

3.1.2. Clinical perspective

Clinical observations revealed that a large subset of the elderly presents with vague subtle cognitive symptoms that do not reach the severity of dementia. While research on the field of vascular dementia had rapidly developed, those patients with mild vascular cognitive impairment had not been thoroughly studied before this project had started.

3.1.2.1. Dementia diagnostic criteria

The diagnosis of cognitive impairment without dementia has been a field subject to rapid development during the past three decades. Indeed, small vessel disease may present with cognitive deficits that do not meet the severity required to fulfill dementia criteria. Nevertheless, diagnostic criteria to address this condition had not been defined when this Ph.D. project was initiated, and have been lacking till fairly recently (Erkinjuntti, et al; 2000). The American Psychiatric Association

released the DSM-III classification (1980), which defined an early dementia stage (American Psychiatric Association, 1980). Later, Hughes & colleagues published the Clinical Dementia Rating (CDR) scale (1982), and Reisberg the Global Deterioration Scale (GDS) (1982); both focusing on Alzheimer's disease. These classifications identified dementia precursors. A CDR 0.5 score was described as "questionable dementia". Notably, it included both mild dementia and earlier deficits. Concerning the GDS, grade 2 reflected "subjective cognitive impairment". A GDS grade 3 portrayed a pre-dementia condition termed "mild cognitive decline". Significantly, a GDS stage 3 recognized the occurrence of executive level functional deficits at work and did not command memory complaints. Nevertheless, GDS and CDR were designed for Alzheimer's evaluation and therefore GDS stage 3 and later mild cognitive impairment criteria (Petersen et al, 2001) exhibit similar duration and outcomes. Those stage 3 subjects fulfilled all of the inclusion and exclusion criteria listed by McKhann & colleagues (1984) for a diagnosis of Alzheimer's, yet the former do not match the required severity for dementia.

3.1.2.2. Mild Cognitive Impairment

Certainly, the Alzheimer's disease literature has dominated the dementia field during the past decades. Petersen's group attempted to characterize the prodromal stages prior to the development of dementia and labeled this condition as mild cognitive impairment (1999). Subsequently, a relevant position paper proposed a definition for "mild cognitive impairment" (Petersen, et al; 2001). It describes the heterogeneity of the literature on the mild cognitive impairment that precedes the development of Alzheimer's disease. Petersen mentions three

subtypes of mild cognitive impairment (with an amnestic component, multiple cognitive domain involvement, and single domain involvement). The proposed definition for mild cognitive impairment required: memory complaint, preferably corroborated by an informant; objective memory impairment; normal general cognitive function; intact activities of daily living; not demented. Certainly, there is a bias toward screening for an amnestic mild cognitive impairment component. Thereby, Alzheimer's disease or a fronto-temporal dementia syndrome might be readily identified. Notably, conditions without an early amnestic component (i.e. prodromal stages of dementia of a vascular origin) might remain undetected.

3.1.2.3. Cognitive decline of vascular origin

Cognitive decline secondary to cerebrovascular etiology had clearly not been defined prior to this project started. Notably, Bowler and Hachinski pointed out that the earlier cases of vascular dementia were not diagnosed, while vascular cognitive impairment is a treatable condition. Thus, these leading researchers advanced a proposal to embrace the concept of VCI (Bowler & Hachinski, 1995). This proposition did not receive the deserved attention since the dementia criteria were still a matter of heated debate.

3.1.2.4. Diagnostic criteria for vascular dementia

Diverse classifications such as the DSM IV (APA, 1994), ICD-10 (WHO, 1993) had been used in the past to diagnose vascular dementia. Indeed the ADDTC (Chui et al, 1992) and NINDS-AIREN (Roman et al, 1993) criteria provided notable efforts in this direction. However, the comparability of different diagnostic criteria was a matter of discussion for different sets produced distinct incidence and prevalence

rates when applied (Gold et al, 1997; Chui et al, 2000). Thus, no criterion was deemed superior (Rockwood et al, 1994). After all, it seemed that Hachinski's Ischemic Score (Hachinski et al, 1975) had a greater inter-rater reliability than any other set of criteria (Chui et al, 2000). Indeed, the vascular dementia field was certainly undefined.

Added to the absence of clinic-radiological consensus, pathological criteria for vascular dementia are still lacking (Roman et al, 1993, 2002b; Vinters et al, 2000; Kalaria et al, 2004; Pantoni et al, 2006; Jellinger, 2008; Grinberg & Heinsen 2012). Thus, clinico-radiological definitions have remained the mainstay in a very heterogeneous field.

3.1.2.5. The role of small vessel cognitive disease

An expert committee defined subcortical vascular dementia research criteria for deep vascular territory involvement might provide a more homogeneous model to study cerebrovascular cognitive decline (Erkinjuntii et al, 2000). This approach would have critical consequences in terms of the reliability of results extracted from therapeutic trials (Inzitari et al, 2000). Cortical (multi-infarct dementia), strategic infarctions, subcortical dementia groups were defined. Subcortical cases incorporate lacunar state cases and Binswanger's disease. These new research criteria for subcortical vascular dementia (Erkinjuntti, et al; 2000) portrayed a cognitive syndrome (dysexecutive syndrome, a mild memory deficit, indication deterioration from a previous higher cognitive level of functioning and are interfering with complex (executive) occupational or social activities) and behavioral and psychological symptoms (such as depression, personality change, emotional incontinence, psychomotor retardation).

3.1.2.6. Mixed dementias

Adding complexity to the field, the Nun Study evidenced a relationship between the incidence of Alzheimer's disease and the presence of cerebrovascular events (Snowdon & colleagues, 1997). Thus, the field established an additional confounder; those patients that seemed to have strokes and cognitive decline were in many cases developing Alzheimer's disease or mixed Alzheimer's and vascular dementia.

In an effort to at least separate Alzheimer's disease from vascular cognitive deficits, the 'International Working group on Mild Cognitive Impairment' abounded on the concept that mild cognitive impairment should not be defined necessarily by memory deficits (Winblad et al., 2004). In addition, it highlighted the informant role while addressing cognitive decline in the setting of mild cognitive impairment. Moreover, it agrees that mild cognitive impairment is accompanied by "minimal impairment in complex instrumental functions." Finally, this consensus also added "evidence of decline over time on objective cognitive tasks may qualify as mild cognitive impairment".

3.1.2.7. Vascular cognitive impairment

Given the pervasive lack of homogeneity in definitions and methodologies across studies, another consensus of experts provided with some initiatives to harmonize the research tools in VCI (Hachinski, et al; 2006). However, from the clinical perspective, diagnosing this patient population still remains certainly challenging. Cognitive decline may be preceded by symptomatic ischemic insults (lacunar strokes) (Petty et al, 1999; Rockwood et al, 2000; Ramos-Estébanez et al,

2008 & 2011). This type of clinical onset was defined as post-stroke cognitive impairment or dementia (Tatemichi et al 1994; Pohjasvaara et al, 1999; Henon et al, 2001). However, many patients develop cognitive impairment not yet Dementia (CIND) without clinically overt strokes. Some of these patients may be identified when they develop a stroke, but have nonetheless had prior unrecognized cognitive deficits (Henon et al, 1997). Among those subjects with CIND and no clinical strokes, clinically silent (asymptomatic) lacunes (Vermeer et al, 2003; Liebetrau et al, 2004) may be detected in the white and the gray matter in neuro-radiological studies (Boiten et al, 1999; Ramos-Estébanez et al, 2008 & 2011).

3.1.2.8. Mild cognitive decline diagnosis in primary care

As a medical student and primary care medicine resident, this clinician realized that identifying these patients with cognitive deficits in the absence of strokes might prove demanding in the primary care setting (Ramos-Estébanez et al, 2008 & 2011), where neuroimaging is not readily available. Symptoms are typically vague and might be confused with depression (Roman et al, 1993; Rockwood et al, 2000; Roman 2002b; Pantoni et al, 2010). More importantly, a popular cognitive tool like the Minimental test typically fails to identify these patients (O'Sullivan et al, 2005). Moreover, there was sparse evidence in the literature about the natural history of this condition till the late 1990s. Most studies conducted at the beginning of the 1990s have focused on prodromal stages of Alzheimer's disease (Fratiglioni et al, 1992; Tatemichi et al, 1994; Levy, 1994; Bowen et al, 1997; Rockwood et al, 2000; Wentzel et al, 2001; Unverzagt et al, 2001; Bozoki et al, 2001; Engels et al, 2002; Sacuiu et al, 2005). Therefore,

vascular cognitive impairment's natural history needed to be described.

3.1.2.9. Anatomical basis for neuropsychological testing

The density of white matter lesions and the clinical findings observed in the outpatient clinic led us to consider that damage to networks involving frontal cortico-subcortical loops was critical in the development of subtle cognitive changes in our sample. Indeed, Alexander had already thoroughly described the basal ganglia circuitry and its cortical connections (Alexander et al, 1986; Alexander, 1990; Alexander & Crutcher 1990). Parent provided further data about extrinsic connections of the basal ganglia (1990). Besides, excellent work has established the role of the thalamus in behavior (Cummings, 1993; Mega & Cummings 1994; Goldman-Rakic 1985; Jones 1998; Sherman & Guillery, 2005). Moreover, there is evidence about changes at a molecular level at subcortical level adding to cognitive decline (Feifel, 1999; Messulam 1986, 1990; Mesulam et al 2003).

3. 2. OBJECTIVES

3.2.1. Ramos-Estébanez et al, 2008:

1. We ought to describe the natural history of ischemic mild cognitive decline during the vascular cognitive impairment period (prior to the development of dementia). For this purpose, we will provide a description of:

- Epidemiological characteristics such as vascular risk factors, and demographics.
- Notable physical examination findings.
- Clinical description of the disease based on the onset of the cognitive decline (with or without over ischemic events).

2. We wonder whether there are any epidemiological or clinical factors associated with an unrecognized diagnosis of vascular cognitive impairment in the primary care setting. We hypothesize that an onset with no overt ischemic events will difficult an early identification of cognitive decline. It is intriguing to discern if subtle white matter deficits would contribute to a delay diagnosis.

3. We aim to characterize what is the role of informants in the early diagnostic suspicion of vascular cognitive impairment in our sample. Our hypothesis rests upon the belief that a proper questionnaire directed to co-dwellers would help elucidate the presence not only of dementia but also of early cognitive deficits (Roth et al, 1986).

4. We seek to define if there are any variables correlating with an onset with cognitive impairment without ischemic events in our sample:

- Uncontrolled hypertension is an attractive a priori candidate for it may affect the small vessel disease territory in a distinctive manner when compared to large vessel disease, given the different physiology of both vascular beds.
- The presence of silent ischemia in neuroimaging putatively involves a burden in vascular reserve and therefore in cognition.

3.2.2. Ramos-Estébanez et al, 2011:

1. Prior basic science work suggests that the small vessel territory may be a source of cognitive impairment (Goldman-Rakic & Porrino, 1985; Alexander et al, 1986; Alexander, 1990; Alexander & Crutcher, 1990); Parent, 1990; Cummings, 1993; Mega & Cummings 1994; Jones 1998; Sherman & Guillery, 2005). We will test the hypothesis that small vessel ischemic disease has a distinct neuropsychological profile compared to large vessel cerebrovascular disease.

2. Moreover, we support the idea that executive dysfunction is central to small vessel ischemic cognitive decline. Our contention is founded on excellent basic science work about the anatomy and physiology or cortico-subcortical connections (Nauta, 1964; Mesulam, 1982 (a, b), 1986, 1990, 2000; Mesulam et al, 2003; Alexander et al, 1986; Alexander, 1990; Alexander & Crutcher, 1990).

3. We will explore the question of whether patients with small vessel gray and white matter lesions present with a different neuropsychological profile. We postulate that based upon the anatomical and physiological basis of cortico-subcortical loops, both types of small vessel disease will clinically express similar neuropsychological deficits.

3.2.3. Ramos-Estébanez et al, 2012:

1. We shall provide an account of the tertiary care expenses during the vascular cognitive impairment stage in our cohort for each diagnostic group. This would be the first account on small vessel disease vascular cognitive impairment expenditures.

2. Tertiary care costs in the vascular dementia period will be also addressed. We hypothesize that in the dementia stage the expenditures might be similar to those of Alzheimer's disease patients in Spain. Our clinical observations suggest that once patients reach a level of cognitive impairment that makes them dependent for activities of daily living, the reasons for their admission are largely similar irrespective of their dementing etiology.

3. We postulate that the care of large vessel disease patients is more onerous than small vessel disease inpatient services at a tertiary care level during the initial vascular cognitive impairment stage. Our contention is based on our clinical observations suggesting that these patients may be prone to symptomatic ischemic events that would involve more complex diagnostic related group coding. This line of reasoning is supported by literature on stroke expenses and Alzheimer's disease.

4. Likewise, we hypothesize that a vascular cognitive impairment onset with stroke will levy a heavier financial burden than an initial stage without overt ischemic events.

5. Does the isolated presence of clinical surrogates of white matter disease influence costs? We believe that executive dysfunction, and frontal gait disorders

will be harder to detect and will likely not reach the degree of acuity required for a tertiary care level admission.

6. Are there any expenditure disparities between the group with pervasive white matter disease and the rest of the cohort? We reckon it is likely that this type of a patient will bear a lesser financial burden for the health care system when compared with patients with large vessel disease in the early stages of vascular cognitive impairment. This result might be explained once again by the impact of overt stroke in expenditures.

7. How do expenses in our region (located in Southwestern Europe) behave when compared to other areas of Europe or the USA? There was no data on tertiary costs of vascular dementia in Southern Europe at the time this project started. We believe that tertiary care expenses should be on the realm of those reported in advanced dementia cases (Fratiglioni et al, 1992).

4

Subjects & methods

4.1. Study Population and Design

A sample of 1,257 inpatients from the community (not previously institutionalized) with an initial diagnosis of stroke, transient ischemic attack (TIA), neuroradiological vascular disease, cognitive impairment or dementia fulfilling the International Classification of Diseases, Tenth Revision (ICD- 10) criteria was investigated. The study was carried out in a 1,100-bed teaching tertiary institution in Northern Spain, from January 1990 through April 2003. Our hospital serves as a reference center for a region with a population that fluctuated from 527.437 in January 1996 to 549.690 in January 2003 (Spanish National Institute of Statistics, 2011). Clinician researchers received information from the medical records department and followed those cases in-house for diagnostic purposes, and as outpatients for cognitive assessments. Per the study design, the primary teams were blind to our assessments. All patients underwent a standardized dementia protocol that in all cases included vitamin B12, folic acid, thyroid-stimulating hormone and free thyroxin serum levels, VDRL and TPHA tests. Patients were also screened for HIV infection if risk factors were present.

A subgroup of 332 patients (26.4% of the whole sample) developed VaD, and 314 were included in the study (fig. 1). A group of 226 patients with VCI (72% of the sample) was assessed prospectively, whereas 88 subjects had been diagnosed of VaD previously.

4.1.1. Prospective Sample:

Amongst those VCI patients followed prospectively, 159 patients developed large or small vessel disease (not mixed pictures), and were tested from a neuropsychological perspective. Patients with a mixed (cortico-subcortical) component, and 18 additional subjects with strategic strokes were excluded. Therefore, 141 patients received prospective neuropsychological testing: Binswanger's disease n = 69, lacunar state= 28 or large vessel disease n = 44.

4.1.2. Subset of the sample involved in the financial analysis:

We selected the prospective cases in the cohort (n=141), and removed seven patients who had been institutionalized. Thereby, we assessed community-dweller expenses. However, the expenditure data were not available for our analysis prior to 1996 because the Spanish National Health Institute established a diagnosis-related group (DRG) coding system that year (Spanish Ministry of Health and Consumption, 1999). Hence, another twelve subjects were removed. We report tertiary level of care annual expenditures data from January 1996 to December 2002 in 122 patients: Binswanger's disease, n = 60; lacunar state, n = 26; large-vessel disease, n = 36.

4. 1. 3. Clinical data from charts:

Data obtained from clinical charts selected from the computerized hospital database were studied independently by two of the authors. A neuroradiologist and two other authors assessed CT scans independently. All patients were followed up and underwent at least a total of three neuroimaging studies. Disagreements (<5%) were resolved by consensus.

4. 1. 4. Clinical examination and caregiver interview:

A neurologist and a trained primary care provider assessed gait features. The patient and co-dwellers or caregivers (205 cases) were interviewed personally in 60% of the cases lacking information (n = 123), or by telephone in the remaining instances. This type of evaluation has already been successfully used to study clinical determinants of prestroke dementia (Pohjasvaara et al, 1999) and stroke cases (Tatemichi et al, 1994; Henon et al, 1997 & 2001).

4.1.5. Exclusion Criteria

Subjects who had previously met criteria for Alzheimer's disease or any other type of dementia (e.g. Pick, Parkinson) were not included in the present study. We emphasized the need to rule out an Alzheimer's component by removing from the sample those patients with early memory impairment, early naming deficits and neuroimaging data suggestive of Alzheimer's disease. Figure 1 shows the study flowchart. Those patients without dementia or cognitive impairment data, or lacking clinical or radiological cerebrovascular disease, were rejected. Other causes of VaD such as hemorrhagic diseases, hereditary etiologies (such as CADASIL) or any kind of mixed presentations of dementia (that is the combination of any subtype of VaD with any other entity that could by itself trigger dementia) were excluded. Other conditions excluded are shown in figure 1 (first manuscript: Ramos-Estébanez et al, 2008).

4.2. Working Definitions

4.2.1. Cognitive impairment was determined by involvement of a single cognitive area. Cognition was assessed in seven domains (orientation, memory,

attention, executive function and reasoning, praxis, language and visuospatial). Folstein's Mini Mental State Examination (MMSE) cutoff point was set at 21 points for dementia (Folstein et al, 1975) and at 27 for cognitive impairment (Fan et al, 2003).

4.2.2. Neuropsychological testing

All prospective patients underwent Hachinski's Ischemic Scale (Hachinski et al, 1974), Revised Wechsler Adult Intelligence Scale (WAIS-R) (Satz & Mogel, 1962; Wechsler, 1981): (judgment with the comprehension subtest; similarities subtest, digit symbol and substitution subtest; block design subtest, and digit span); Exit-25 (Royall et al, 1992) and Trail Making test (Reitan, 1958). The Blessed Dementia Scale (Blessed et al, 1968) and Camdex H schedule questionnaire (Roth et al, 1986) were assessed. Retrospective patients were examined by the MMSE (Folstein et al, 1975), and informants underwent the Camdex H questionnaire (Roth et al, 1986).

We were particularly restrictive about the value required for a patient to be diagnosed with cognitive impairment because our operational criteria for cognitive impairment observed failure in a single field. We selected only patients with persistent cognitive impairment in the area evaluated to avoid, as much as possible, disagreement between the authors assessing the patients or informant reports. When comparison with published normative data was possible, cognitive test results within the lower 5% range defined impairment (Serrano et al, 2007). In addition, more than 50% of the tests addressing each cognitive domain needed to meet our criteria for impairment for the patients to qualify as such (Serrano et al, 2007).

All patients received at least two cognitive assessments (one month after their first admission, three months after their first admission, and if required an additional time at the moment of dementia diagnosis). We report the results at the three-month mark.

4.2.3. Executive dysfunction was defined as failure in the ability to conceptualize all aspects of an activity and translate this conceptualization into appropriate and effective behavior (Lezak, 1995). The Exit-25 evaluates the executive function in an overall manner (Royall et al, 1992), whereas WAIS-R subtests account for different areas within this domain: the similarities subtest for the volitional stage, the digit span test for the monitoring phase of execution, while the trail B focuses on the adjust/stop aspect. MMSE items on orientation to time, orientation to place and delayed memory also assessed execution (Albert et al, 2001; Chen et al, 2001; Jones et al, 2004). Two out of the former three items needed to be impaired in the MMSE. The authors hypothesized that the nature of each test that assesses this area of cognition would eventually yield discordant results across tests within each patient. To resolve this problem, we pursued a restrictive approach defining as impaired those patients who fell in the lower 5% of the WAIS-R (Satz & Mogel, 1962; Wechsler, 1981) normative scores for the digit span and similarities sub- tests, plus the Trail Making test lower 10% normative data (Tombaugh 2004), and those who had an Exit-25 score 115/50 (Royall et al, 1992). More than 50% of these tests were needed for the executive function to be considered as being impaired (Serrano et al 2007).

4.2.4. Depression was diagnosed by Geriatric Depression Scale scores 110 (Yesavage et al, 1982), or in those patients already depressed shown by a Hamilton's Depression Rating Scale 110 (Hamilton, 1960).

4.2.5. Clinical Onset

The nomenclature identifying the period prior to the development of vascular dementia varied in two manuscripts per expert reviewers' preferences. Therefore, prodromal vascular dementia stage (pVaD) or vascular cognitive impairment stage (VCI) are synonymous.

We divided **VCI** into two groups depending on the clinical onset:

1. **Onset with Cognitive Impairment No Dementia (CIND):** Patients with cognitive impairment in one or more cognitive areas (that did not reach the degree of dementia), and no symptomatic cerebrovascular events, started with CIND. These patients may or may not have experienced symptomatic ischemic events after onset with CIND. Eventually these individuals developed vascular dementia.
2. **Onset with ischemic events:** It was present in those subjects without cognitive impairment and a first symptomatic ischemic insult (LI or cortical stroke or TIA). These patients developed cognitive impairment after their initial ischemic insult, and then progressed to dementia. These individuals could have experienced (or not) symptomatic ischemic events after the initial ischemic event at onset. Eventually these subjects developed vascular dementia.

4.2.6. Age of onset with VCI

The age of the patients at the moment of VaD diagnosis was dichotomized (<85 and ≥85 years). This cut-off point was selected because VaD is the most frequent type of dementia in subjects ≥85 years (Kase, 1991; Mahler and Cummings, 1991).

4.2.7. Unrecognized VCI onset refers to the ability of physicians not participating in the study (and hence not necessarily focused on cognitive impairment but more acute issues) to detect the condition in real clinical practice. It depends on the time between the onset of the VCI and its diagnosis by the physicians (not researchers).

1. If less than one month had elapsed between the onset and recognition of VCI, the patient was considered to be **identified on time**.

2. If this period was longer than a month, the onset was characterized as **unrecognized**. Unrecognized onset with CIND was defined by the findings in clinical charts as compared to the information gathered by the authors through physical examination, history and cognitive testing plus Camdex questionnaires.

4.2.8. Vascular Cognitive Impairment (VCI) was defined as four different blocks of time from the onset of clinical data of CIND or overt ischemia to the moment the diagnosis of a fully developed VaD was made: less than one month, 1–12 months, 13 to ≤24 months, and also >24 months.

4.2.9. Stroke and TIA were determined by acute focal deficits confirmed by medical examination, in the presence or absence of related lesions on early CT scans (<48 h after the event had happened). Additionally, TIA patients had a

normal physical evaluation, with a history concordant with recent acute ischemic deficit confirmed by CT scan findings.

1. **Stroke or TIA at admission previous to diagnosis of VaD** happened during the admission prior to the moment at which the diagnosis of dementia was initially suspected.

2. **Stroke or TIA at diagnosis of VaD** happened during the admission at which the diagnosis of dementia was suspected (and then confirmed in a two- to three-month period).

4.2.10. Clinical diagnosis of VaD was achieved when a patient who had previously presented an onset with CIND or ischemic insults met the criteria for any of the following subtypes of vascular dementia:

4.2.10.1. Lacunar infarctions had one of the classical presentations (dysarthria-clumsy hand, motor pure stroke, sensory pure stroke, mixed motor-sensory stroke and hemiparetic ataxia), as well as radiological features matching Bogousslavsky's definition in all cases (Bogousslavsky, 1992). **Lacunar state** was diagnosed in those patients who showed isolated multiple lacunes in CT scan assessment in the absence of cortical infarctions or white matter disease.

4.2.10.2. Binswanger's disease was diagnosed when Caplan's criteria (1995) and those of Bennett and colleagues (1990) were met. Additionally, patients with lacunar infarctions and those with Binswanger's disease were grouped as **demented subjects of subcortical nature**.

Bennett's Criteria for Binswanger's disease

1. Dementia diagnosed through neuropsychological testing.

2. An item is required from each of the next three groups:

   - Presence of vascular risk factors or evidence of systemic vascular disease, for example: hypertension, diabetes mellitus, history of myocardial infarction, cardiac arrhythmia, or congestive heart failure.
   - Evidence of cerebrovascular disease, for example: history of stroke, focal pyramidal deficits or sensory signs.
   - Evidence of "subcortical" cerebral dysfunction, for example: senile gait, parkinsonian or gegenhalten rigidity, or history of urinary incontinence due to spastic bladder disorder.

3. Radiological criteria: bilateral leukoaraiosis in computed tomography (CT) or magnetic resonance imaging (MRI) showing bilateral, multiple or diffuse, subcortical hyperintense lesions in T2 with a diameter > 2 x 2 mm. These criteria lose their validity in the presence of: Multiple or bilateral cortical lesions on CT or MR or; Severe dementia (for example, MMS < 10).

4.2.10.3. Cortical dementia was addressed when patients met the ADDTC criteria (Chui et al, 1992) for probable VaD and had a cortical distribution of the ischemic lesions found in CT scan.

a) Dementia defined as a decline from a known or estimated previous level of cognitive ability that is sufficient to widely interfere with the patient's conduct. This decline is not restricted to a single cognitive area and is independent from the level of consciousness. This decline will be

documented in the medical history and will be documented through a brief mental status exam or ideally by a detailed neuropsychological evaluation with measurable normalized tests.

b) Evidence of two or more ischemic strokes by history, examination and/ or neuroimaging: computerized tomography (CT) or magnetic resonance imaging (MRI) in T1 sequences or history of a well-documented isolated stroke with a temporal relation with the onset of dementia.

c) Evidence of at least an infarct outside of the cerebellum by CT or MR in the T1 sequence.

4.2.10.4. Cortical-subcortical dementia was diagnosed when the subject met the ADDTC criteria (Chui et al, 1992) and presented cortical plus subcortical affection in neuroimaging.

4.2.10.5. Strategic infarct dementia was defined as a clinical picture characterized by the abrupt onset of cognitive impairment and behavioral changes in relation to the occurrence of a single infarct in specific regions of the brain. Clinical stroke may or may not be present, but new ischemic imaging data at locations such as the thalamus, the caudate nucleus, the angular gyrus, the frontal white matter and the genu of the internal capsule will be present (Mahler & Cummings, 1991; Roman et al, 1993; Konno et al, 1997). In addition, any additional ischemic insults, when present, were separated by at least 12 months from the first event and the subsequent cognitive decline derived from this insult.

4.2.11. Radiological definitions:

1. Silent ischemia*:*

It was defined by the evidence in the CT scan of one or more infarcts without a history of a corresponding symptomatic stroke or TIA at any point of the follow-up. Patients with silent ischemia were included in the CIND or the onset with ischemic events group depending on the presence or absence of symptomatic ischemic events prior to the development of cognitive impairment.

2. Ischemic white matter disease:

CT scan hypodense lesions in the frontal or occipital horns, and/ or in periventricular areas.

4.2.12. Vascular risk factors definitions:

1. Hypertension met the current Joint National Committee definitions, and subjects with diastolic values ≥90 mm Hg, or systolic pressure ≥140 mm Hg, were defined as hypertensive (JNC, 1997).

2. Diabetes mellitus patients met the ADA criteria (Expert Committee, 1997).

3. Dyslipemia was present if fasting total serum cholesterol was greater than 200 mg/dl (5.2 mmol/l), or fasting triglycerides were greater than 200 mg/dl (2.2 mmol/l).

4. Embolic cardiopathy at diagnosis included hyperthrophic or dilated cardiomyopathy of any etiology, valvulopathy or hypo/akinetic myocardial

areas secondary to previous infarction proved by echocardiogram (six months before or after diagnosis). Left ventricle hypertrophy cardiomyopathy was also assessed by electrocardiography and Sokoloff's criteria. Atrial fibrillation or any anomalous cardiac rhythm assessed by a good-quality electrocardiogram was also addressed. Clinically proven cardiac failure and any combination of the prior set of embologenous affection were also evaluated.

4.2.13. Prophylactic treatment against cerebral ischemia (acenocumarol or antiplatelet therapy) was assessed at admission.

4.2.14. Financial Analysis Definitions

Only those admissions for which a primary or secondary diagnosis was related to cerebrovascular disease, cognitive impairment or dementia, or VaD were considered.

1. Diagnosis has been coded using **ICD-10 codes**: Presenile dementia (290.1), cerebral atherosclerosis (437.0), and acute confusional states (293, 289.9, 293.0, 780.09) were coded when appropriate. When VaD was suspected or confirmed, coding reflected dementia (290.0 or 290.2–4 or 290.8–9).

2. Diagnosis-related groups (**DRGs)**

DRGs classify patients admitted to the hospital into groups based on their expected use of resources (New Jersey Medical Association, 1981; Hasio et al, 1986). DRGs address secondary diagnoses for specific complications. In addition, DRGs account for variables such as age, sex, and complications

developed during admission or related to procedures. Local Spanish DRG weights were fully implemented in 2003, (Statistics Portal of the National Health System in Spain), which required an initial period from 1996 to 2003 (Spanish Ministry of Health and Consumption, 1999), during which US DRG values were used (Healthcare Cost and Utilization Project (HCUP) website).

Recoding the DRGs using the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification codes allowed conversion of those to DRG codes (Statistics Portal of the National Health System in Spain). Thus we recoded the DRGs for patients with both VCI and VaD, including degenerative central nervous system disorder (12); stroke (14); transient ischemic attack (15, 524); nonspecific cerebrovascular disease (16, 17); hypertensive encephalopathy (22); seizure with and without complications (24, 25); "other disorders of the nervous system" (34, 35); "organic disorders and mental retardation" (429); "other mental disorders" (432); pulmonary codes, such as 79, 80, 88, 89, 90; cardiovascular conditions (121–125, 127–134, 138–145, 478, 479); orthopedic diagnoses (210, 211, 218–220, 223, 224, 235, 236); and diabetic decompensations (300, 301). We included urinary tract infections (320, 326) and skin ulcers (264, 271) in only the VaD period.

3. Comorbidities

The Charlson comorbidity index score (Charlson et al, 1987) and the index's validated version for stroke populations (Goldstein et al, 2004)

allowed comorbidities stratification. AIDS infection was removed from the index because it was an exclusion criterion in our study.

4. Economic Analysis

This is a cost description of direct inpatient expenditures from the Spanish National Health Institute and regional government perspectives. We report the average cost for each DRG for those seven years adjusted by purchasing power parity (Organization for Economic Cooperation and Development website).

4.3. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, or mean ± standard error of the mean, or N (%). Univariate analysis with λ^2 test and Student's t-test, Kruskall– Wallis H, Mann–Whitney's U test and ANOVA (with post hoc Bonferroni's confirmation) tests were performed when required. Subsequent logistic regressions were performed when needed. All associations were estimated by the odds ratio with a 95% confidence interval. Bootstrapping methods are used to ensure the internal validity of the results (Efron & Gong, 1983).

Z-scores are provided for each significant executive function test. We created an executive function composite z-score for each participant by adding up the value for the z-score for each test included in the score. Discriminant analysis allowed determining which tests fit our sample better.

Expenditures do not follow a Gaussian distribution. Therefore, the Kruskal-Wallis one-way analysis of variance and Mann-Whitney U test were performed. In addition, data were log-transformed and, once normalized, analyzed when the size of the sample ($n > 30$ in all groups) permitted analysis with parametric methods (analysis of variance, t test, and chi-square test), which confirmed the validity of the results (Diehr et al, 1999). Calculations were performed with SPSS software, version 15.0.

5

Results (manuscripts)

Vascular Cognitive Impairment:
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Vascular Cognitive Impairment: Prodromal Stages of Ischemic Vascular Dementia

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Key Words
Lacune · Binswanger's disease · Silent ischemia · Stroke · Cognitive impairment · Vascular dementia

Abstract
Background/Aims: To describe the natural history of the prodromal stages of ischemic vascular dementia (pVaD). ***Methods:*** A sample of 314 inpatients with pVaD or a clinical diagnosis of vascular dementia (VaD; lacunar state, Binswanger's disease, pure cortical VaD, corticosubcortical and strategic infarctions) admitted to a teaching tertiary center during a 13-year period was assessed (retrospectively n = 88, prospectively n = 226). Prospective neuropsychological assessment consisted of Mini Mental State Examination, Revised Wechsler Adult Intelligence Scale, Exit-25, Trail Making tests, Blessed Dementia Scale and Camdex H, Global Depression Scale and Hamilton Depression Rating Scale tests. Univariate analysis and logistic regressions are displayed. ***Results:*** An unrecognized pVaD was related with a clinical onset with cognitive impairment no dementia (CIND) versus symptomatic cerebrovascular events ($p < 0.0001$), and with being under therapy with anticoagulant or antiplatelet agents ($p < 0.01$). Age <85 years at diagnosis of VaD ($p < 0.01$) correlated with a delayed pVaD diagnosis. CIND onset was associated with a longer prodromal stage ($p < 0.01$), no clinical strokes during pVaD ($p < 0.001$), silent ischemia ($p < 0.01$) and Binswanger's disease ($p < 0.01$). ***Conclusions:*** Vascular cognitive impairment remains an underdiagnosed, yet treatable entity. A brief neuropsychological examination and informant interviews should become standard practice in elderly populations with vascular risk factors. Small-vessel disease is a prevalent condition with a distinct natural history.

Introduction

Several classifications for vascular dementia (VaD) have been proposed and proven to be valuable in diverse situations [1]. Likewise, the concept of mild cognitive impairment has recently been described, and for this reason its use is neither widespread nor employed in the design of the major studies. Some groups attempted to describe the prodromal phases of VaD (pVaD) focusing on the clinical and radiological determinants of VaD in pre-

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stroke and poststroke populations [2–5]. Nevertheless, current criteria for the diagnosis of VaD do not identify another group of patients that presents with subtle loss of cognitive functions and abnormal behavior not related to overt stroke. As a matter of fact, clinical criteria for mild 'cognitive impairment not reaching the degree of dementia' (CIND) of vascular origin are still lacking, and there is major discussion ongoing on this topic. Despite contributions by the Canadian Health Study [6–8] and the Indianapolis Study for Health and Aging [9] as well as indirect evidence extracted from VaD research [10, 11], additional information is needed regarding those patients with CIND. Moreover, the role of small- and large-artery disease on pVaD needs to be highlighted. Most relevant studies [2–4] do not address small-vessel disease, but cerebrovascular disease overall. However, small-vessel and penetrating artery strokes account for one third of symptomatic ischemia. This type of vascular affection is most frequent in elderly populations when presenting as silent ischemia. Both manifestations of microvascular disease have been related to short-term milder cognitive affection [12]. Conversely, when these patients are followed in the long term, outcomes turn out to be less benign regarding mortality, morbidity and quality of life. Thereby, early identification and intervention in this group might render a most valuable impact on these patients' quality of life and survival.

Our study intends to provide further information about the natural history of pVaD focusing on the information that is available on daily medical practice: informant reports and general medical information (medical history, current vascular risk factor control, general neurological examination findings, cognitive data and neuroradiological information). We will describe the overall epidemiological features of our sample, and compare the physician's findings with the co-dwellers' input. Once a general background on the sample features is given, our focus will turn to describing the clinical features that identified those patients with pVaD that were not recognized by the physician and informant. Hence, we have divided the onset of pVaD into the two typical forms of presentation in the clinical arena, the patients who present with overt ischemic features – transient ischemic attack (TIA) or stroke – and those with CIND in the absence of prior symptomatic ischemia. Besides, we will seek differences in the way pVaD evolves into the diverse types of VaD – lacunar state, Binswanger's disease (BD), cortical dementia, mixed dementia and strategic strokes – from the clinician's perspective.

Patients and Methods

Study Population and Design

A sample of 1,257 inpatients from the community (not previously institutionalized) with an initial diagnosis of stroke, TIA, neuroradiological vascular disease, cognitive impairment or dementia fulfilling the ICD-10 criteria was investigated. The study was carried out in a 1,100-bed teaching tertiary institution in Northern Spain from January 1990 to April 2003. A subgroup of 332 patients (26.4% of the whole sample) developed VaD, and 314 were included in the study (fig. 1). A group of 226 patients with pVaD (72% of the sample) was assessed prospectively, whereas 88 subjects had been diagnosed of VaD previously.

Data obtained from clinical charts selected from the computerized hospital database were studied independently by two of the authors. CT scans were assessed independently by a neuroradiologist and two other authors. All patients were followed up and underwent at least a total of 3 neuroimaging studies. Disagreements (<5%) were resolved by consensus. The patient or co-dwellers (205 cases) were interviewed personally in 60% of the cases lacking information (n = 123), or by telephone in the remaining instances. This type of evaluation has already been successfully used to study clinical determinants of prestroke dementia [2] and stroke cases [3–5].

All patients underwent a standardized dementia protocol that in all cases included vitamin B_{12}, folic acid, thyroid-stimulating hormone and free thyroxine serum levels, VDRL and TPHA tests. HIV infection was also screened if risk factors were present.

Exclusion Criteria

Subjects who had previously met criteria for Alzheimer's disease or any other types of dementia (e.g. Pick, Parkinson) were not included in the present study. We emphasized the need to rule out an Alzheimer's component by removing from the sample those patients with early memory impairment, early nomination abnormalities and neuroimaging data suggestive of Alzheimer's disease. Figure 1 shows the study flow chart. Those patients without dementia or cognitive impairment data, or lacking clinical or radiological cerebrovascular disease, were rejected. Other causes of VaD such as hemorrhagic diseases, hereditary etiologies (such as CADASIL) or any kind of mixed presentations of dementia (that is the combination of any subtype of VaD with any other entity that could by itself trigger dementia) were excluded. Other conditions excluded are shown in figure 1.

Working Definitions

Cognitive impairment was determined by affection in a single cognitive area. Cognition was assessed in 7 domains (orientation, memory, attention, executive function and reasoning, praxis, language and visuospatial). Folstein's Mini Mental State Examination (MMSE) cutoff point was set at 21 points for dementia [13] and 27 for cognitive impairment [14].

All prospective patients underwent Hachinski's Ischemic Scale [15], Revised Wechsler Adult Intelligence Scale (WAIS-R) [16, 17] (judgment with the comprehension subtest; similarities subtest, digit symbol and substitution subtest; block design subtest, and digit span), Exit-25 [18] and Trail Making test [19]. Mood was assessed with the Geriatric Depression Score [20]; Hamilton's Depression Scale [21] ruled out cognitive affection due to concomitant depression. The Blessed Dementia Scale [22] and Cam-

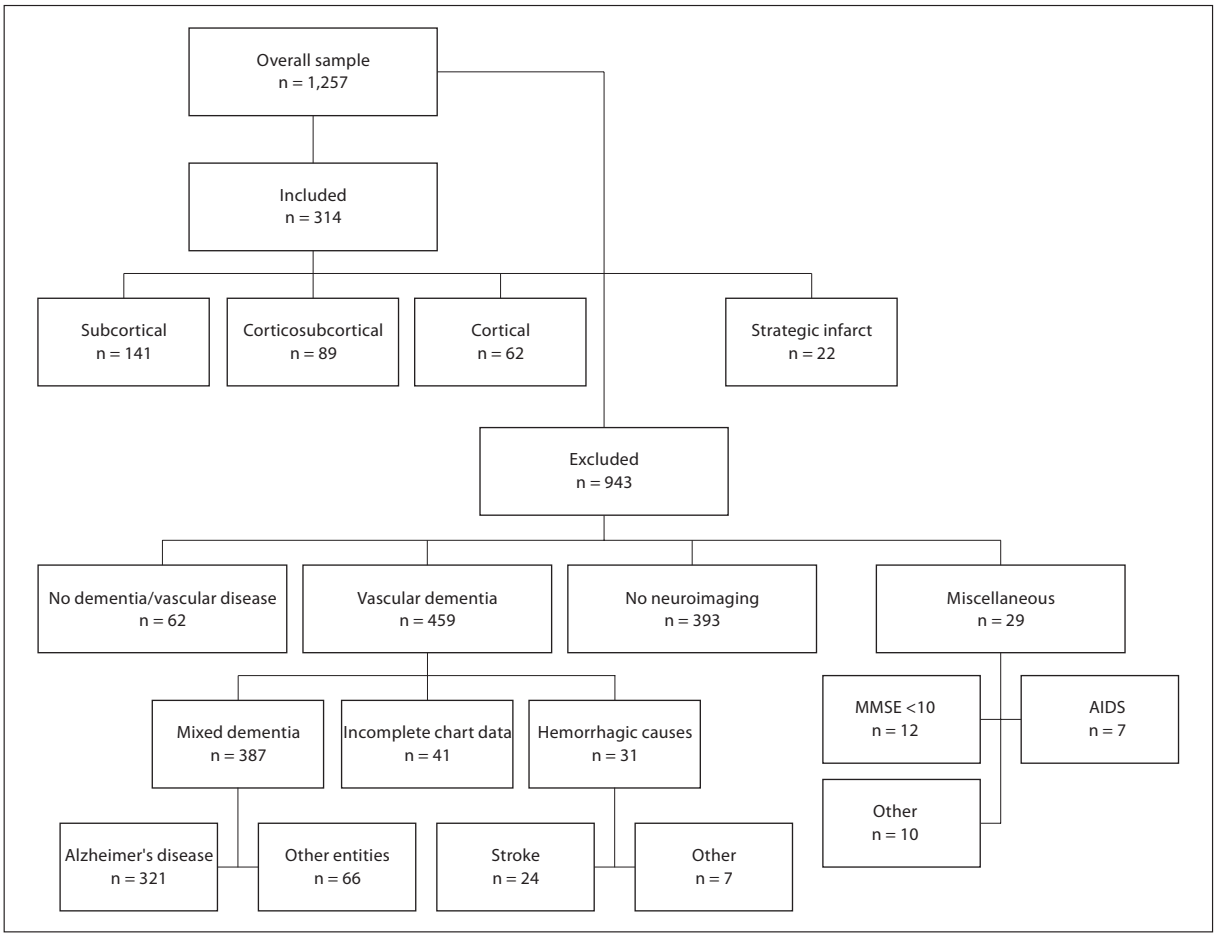

Fig. 1. Flow chart with the distribution of the study sample. MMSE = Mini Mental State Examination.

dex H schedule questionnaire [23] were assessed. Retrospective patients were examined by the MMSE, and informants underwent the Camdex H test.

We were particularly restrictive about the value required for a patient to have cognitive impairment because our operational criteria for cognitive impairment observed failure in a single field. We selected only patients with persistent cognitive impairment in the area evaluated to avoid as much as possible disagreement between the authors assessing the patients or informant reports. When comparison with published normative data was possible, cognitive test results within the lower 5% range defined impairment [24]. In addition, more than 50% of the tests addressing each cognitive domain needed to meet our criteria for impairment for the patients to qualify as such [24].

All patients received at least two cognitive assessments (1 month after their first admission, 3 months after their first admission, and if required an additional time at the moment of dementia diagnosis).

Executive dysfunction was defined as failure in the ability to conceptualize all facets of an activity and translate this conceptualization into appropriate and effective behavior [25]. The Exit-25 evaluates the executive function in an overall manner [18], whereas WAIS-R subtests account for different areas within this domain: the similarities subtest for the volitional stage, the digit span test for the monitoring phase of execution while the trail B focuses on the adjust/stop aspect. MMSE items on orientation to time, orientation to place and delayed memory also assessed execution [26–28]. Two out of the former 3 items needed to be impaired in the MMSE. The authors hypothesized that the nature of each test that assesses this area of cognition would eventually yield discordant results across tests within each patient. To resolve this problem, we pursued a restrictive approach defining as impaired those patients who fell in the lower 5% of the WAIS-R [16, 17] normative scores for the digit span and similarities subtests, plus the Trail Making test lower 10% normative data [29] and those who had an Exit-25 score >15/50 [18]. More than 50%

of these tests were needed for the executive function to be impaired [24].

Depression was diagnosed by Geriatric Depression Scale scores >10 [20] or in those patients already depressed shown by a Hamilton's Depression Rating Scale >10 [21].

Stroke and TIA were determined by acute focal deficits confirmed by medical examination, in the presence or absence of related lesions on early CT scans (<48 h after the event had happened). Additionally, TIA patients had a normal physical evaluation, with a history concordant with recent acute ischemic deficit confirmed by CT scan findings.

Stroke or TIA at diagnosis of VaD happened during the admission at which the diagnosis of dementia was suspected (and then confirmed in a 2- to 3-month period).

Stroke or TIA at admission previous to diagnosis of VaD happened during the admission prior to the moment at which the diagnosis of dementia was initially suspected.

pVaD had an initial phase of cerebrovascular disease that was to develop into dementia according to the authors' assessment based on history, physical examination and Camdex (informant) data. Two groups were defined:

In *onset with CIND,* patients with impairment in one or more cognitive areas (that did not reach the degree of dementia), happening prior to any symptomatic cerebrovascular events, started with CIND. These patients could have (or not) symptomatic ischemic events after cognitive impairment onset.

In *onset with ischemic events*, subjects without cognitive impairment data and a first symptomatic ischemic insult (lacunar or cortical stroke or TIA) were included. These patients developed cognitive impairment after their initial ischemic insult and then progressed to VaD. These patients could have (or not) symptomatic ischemic events after the initial ischemic event at onset.

Silent ischemia was defined by the evidence in the CT scan of one or more infarcts without a history of a corresponding symptomatic stroke or TIA at any point of the follow-up. Patients with silent ischemia were included in the CIND or the onset with ischemic events group depending on the presence or absence of symptomatic ischemic events prior to the development of cognitive impairment.

Recognized or unrecognized pVaD refers to the ability of physicians not participating in the study (and hence not necessarily focused on cognitive impairment but more acute issues) to detect the condition in real clinical practice as compared to the information gathered by the authors through physical examination, history and cognitive testing plus Camdex questionnaires.

Unrecognized pVaD onset is defined by the time between the onset of the pVaD and its diagnosis by the physicians taking care of the patient. If less than 1 month had passed between the onset and recognition of pVaD, the patient was considered to be identified on time. If this period was longer than a month, the onset was characterized as unrecognized. Unrecognized onset with CIND was defined by the findings in clinical charts and Camdex questionnaires of co-dwellers' perceptions (29.1% of the sample), plus by directly interviewing the patient, and co-dwellers through the Camdex (69.9% of the cases).

pVaD period was defined as 4 different blocks of time from the onset of clinical data of CIND or overt ischemia to the moment the diagnosis of a fully developed VaD was made: less than 1 month, 1–12 months, 13 to ≤24 months, and also >24 months.

Clinical diagnosis of VaD was achieved when a patient who had previously presented an onset with CIND or ischemic insults met the criteria for any of the following subtypes of vascular dementia:

Lacunar infarctions had one of the classical presentations (dysarthria-clumsy hand, motor pure stroke, sensory pure stroke, mixed motor-sensory stroke and hemiparetic ataxia), as well as radiological features matching Bogousslavsky's definition in all cases [30]. *Lacunar state* was diagnosed in those patients who showed isolated multiple lacunes in CT scan assessment in the absence of cortical infarctions or leukoaraiosis.

BD was diagnosed when Caplan's criteria [31] and those of Bennett et al. [32] were met. Additionally, patients with lacunar infarctions and those with BD were grouped as *demented subjects of subcortical nature*.

Cortical dementia was addressed when patients met the ADDTC criteria [33] for probable VaD and had a cortical distribution of the ischemic lesions found in CT scan.

Cortical-subcortical dementia was diagnosed when the subject met the ADDTC criteria [33] and presented cortical plus subcortical affection in neuroimaging.

Strategic infarct dementia was defined as a clinical picture characterized by the abrupt onset of cognitive impairment and behavioral changes in relation to the occurrence of a single infarct in specific regions of the brain. Clinical stroke may or may not be present, but new ischemic imaging data at locations such as the thalamus, the caudate nucleus, the angular gyrus, the frontal white matter and the genu of the internal capsule will be present [34–36]. In addition, any additional ischemic insults, when present, were separated by at least 12 months from the first event and the subsequent cognitive decline derived from this insult.

Hypertension met the current Joint National Committee definitions, and subjects with diastolic values ≥ 90 mm Hg, or systolic pressure ≥140 mm Hg, were defined as hypertensive [37]. Patients with *diabetes mellitus* met the ADA criteria [38]. *Dyslipemia* was present if fasting total serum cholesterol was greater than 200 mg/dl (5.2 mmol/l), or fasting triglycerides were greater than 200 mg/dl (2.2 mmol/l).

Embolic cardiopathy at diagnosis included hyperthrophic or dilated cardiomyopathy of any etiology, valvulopathy or hypo/akinetic myocardial areas secondary to previous infarction proved by echocardiogram (6 months before or after diagnosis). Left ventricle hypertrophy cardiomyopathy was also assessed by electrocardiography and Sokoloff's criteria. Atrial fibrillation or any anomalous cardiac rhythm assessed by a good-quality electrocardiogram was also addressed. Clinically proven cardiac failure and any combination of the prior set of embologenous affection were also evaluated.

Prophylactic treatment against cerebral ischemia (acenocumarol or antiplatelet therapy) was assessed at admission.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation. Univariate analysis with χ^2 test and subsequent multivariate approach via a logistic regression were performed defining unrecognized pVaD onset as dependent variable. The associations were estimated by the odds ratio with a 95% confidence interval. Bootstrapping methods are used to ensure the internal validity of the results [39]. Subsequent secondary logistic regression models featuring the type of pVaD (CIND vs. stroke) and

Table 1. Baseline features of the sample

Characteristic	Overall sample (n = 314)	Unrecognized VaD prodromal onset (n = 254)	Diagnosed VaD prodromal onset (n = 60)
Males	152 (48.4)	127 (83.6)	25 (16.4)
Females	162 (51.6)	127 (78.4)	35 (21.6)
Age, years	77.6 (7.5)	77.3 (7.3)	78.9 (8.2)
Cortical dementia	62 (19.8)	48 (77.4)	14 (22.6)
BD	94 (29.9)	77 (81.9)	17 (18.1)
Lacunar state	47 (15)	39 (83)	8 (17)
Corticosubcortical infarct	89 (28.3)	74 (83.1)	15 (16.9)
Strategic infarct	22 (7)	16 (72.7)	6 (27.3)
Current smoker	23 (7.3)	18 (78.3)	5 (21.7)
Ex-smoker	78 (24.8)	70 (89.7)	8 (10.3)
Current drinker	43 (13.7)	38 (88.4)	5 (11.6)
Ex-drinker	42 (13.4)	38 (90.5)	4 (9.5)
Diabetes mellitus	70 (22.3)	56 (80)	14 (20)
Hypertension	185 (58.9)	151 (81.6)	34 (18.4)
Dislipemia	49 (15.6)	44 (89.8)	5 (10.2)
Cardiopathy	155 (49.4)	124 (80)	31 (20)
Atrial fibrillation	57 (18.2)	46 (80.7)	11 (19.3)
Left ventricle hypertrophy	21 (6.7)	18 (85.7)	3 (14.3)
Dilated cardiomyopathy	24 (7.6)	20 (83.3)	4 (16.7)
Congestive cardiac failure	12 (3.8)	10 (83.3)	2 (16.7)
Cardiac ischemic disease	37 (11.8)	30 (81.1)	7 (18.9)

For characteristics, see definitions in the text. Data are expressed as number, with percentage in parentheses; age is expressed as mean, with standard deviation in parentheses. No significant differences were found between groups.

possibility of being on prophylaxis for cerebrovascular ischemia as dependent variables are described. The age of the patients at the moment of VaD diagnosis was dichotomized (<85 and ≥85 years). This cut point was selected because VaD is the most frequent type of dementia in subjects ≥85 years [40].

Results

We analyzed 314 patients with a diagnosis of VaD (fig. 1). Baseline features of the sample regarding recognition of pVaD on vascular risk factors and co-dweller versus physician detection of symptoms are shown in tables 1 and 2, respectively. Additional information relayed by informants about the patient's performance revealed difficulty with house chores (n = 74; 23.6%), nocturnal disorientation (n = 17; 5.4%), early personality changes (n = 75; 23.9%) and conduct disturbances (n = 15; 4.8%).

Onset with data of CIND, being on current prophylaxis versus ischemic events at the moment of VaD diagnosis, and age <85 years favored not recognizing pVaD (table 3).

Table 2. Prodromal phase clinical features comparing the information provided by informants and that obtained by history and physical examination

Finding	As per relatives or co-dwellers	Per physical examination and history	p
Early executive dysfunction[1]	32 (10.2)	214 (68.2)	<0.01
Early gait disturbance	79 (25.2)	150 (47.8)	<0.02
Early urinary incontinence	62 (19.7)	88 (28)	n.s.
Dizziness[2]	213 (67.8)	70 (22.3)	<0.01
Difficulty to dress up	24 (7.6)	37 (11.5)	n.s.
Calculus[3]	13 (4.1)	22 (7)	n.s.
Depression	58 (18.5)	25 (8)	<0.02
Seizure events	53 (16.9)	79 (25.2)	n.s.

Data are expressed as numbers, with percentages in parentheses.

[1] Defined as the ability to conceptualize all facets of an activity and translate this conceptualization into appropriate and effective behavior.

[2] Dizziness of cerebrovascular origin.

[3] Problems handling money.

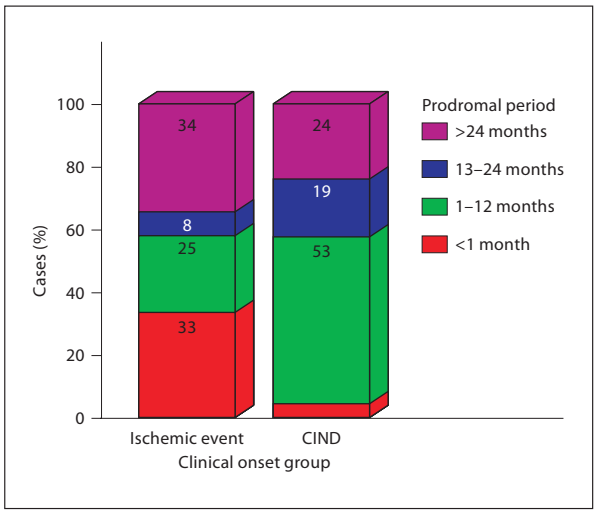

Fig. 2. Cumulative frequencies chart for clinical onset (ischemia vs. CIND) relative to the prodromal period length.

Table 3. Multivariate analysis regarding the variables involved in the nonrecognition of the onset of pVaD

Characteristic	OR	95% CI	p
Features of VaD onset (CIND vs. ischemia)	16.6	6.9–39.9	<0.0001
Prophylaxis for ischemic events (yes vs. no)	2.5	1.3–4.9	<0.01
Age (<85 vs. ≥85 years)	2.8	1.3–6.1	<0.01

OR = Odds ratio; CI = confidence interval.

Within the subset of individuals with BD, those ≥85 years did not show a trend towards either delay (46.7%, n = 7) or early recognition (56.3%, n = 8), whereas in those <85 years the tendency to not recognize the early onset was again evident (11.8%, n = 10, vs. 88.2%, n = 75; $p < 0.01$).

A univariate cluster analysis of the most relevant variables related to the natural history of pVaD onset is shown in table 4. Figure 2 shows that ischemic onset follows a U-shaped distribution (more prominent in <1 month and >24 months). Those patients with >24 months prodromal period and ischemic onset presented with lacunar strokes (n = 42, 80.8%; $p < 0.01$).

A multivariate approach to variables related to pVaD onset type confirmed that BD patients had a twofold probability to present with CIND (table 5). Those who started with CIND tended towards not presenting with overt ischemia at VaD diagnosis, as compared to subjects with stroke onset, who developed further insults at diagnosis. The presence of silent ischemia was a predictor for CIND onset. Out of 38 subjects with a delayed pVaD diagnosis and presenting silent ischemia with a prodromal phase longer than 2 years, 34.2% (13) had BD, 18.4% (7) lacunar infarction, 13.2% (5) cortical stroke and 34.2 % (13) had mixed dementia. There was a significant association between a prodromal onset >2 years with silent ischemia and the presence of an isolated subcortical affection (86.8%, 33/ 38; $p < 0.01$). In addition, the presence of silent ischemia in CIND patients (n = 54; 45.4%) was not significantly different as compared to those with ischemic onset (n = 65; 54.6%).

A third logistic regression addressed the variables characterizing the patients that are on prophylaxis for cerebrovascular event. A majority of the subjects with documented ischemic events (n = 63; 75%) occurring at the admission before the diagnosis of VaD was suspected are more frequently under treatment with antiplatelet or anticoagulant drugs (odds ratio = 2.3, 95% confidence interval = 1.1–4.5; $p < 0.001$). Patients with embologenous cardiac disorders (49.4%, n = 155) were also predisposed to be treated (odds ratio = 2.2, 95% confidence interval = 1.4–3.5; $p < 0.001$). Moreover, both antiplatelet agents and the absence of therapy are significantly more frequent than anticoagulation in subjects with cardiopathy. Half of the patients with previous ischemic events (56%, 47/84) had a stroke at diagnosis. Most of the subjects with previous ischemic events and no prophylaxis for ischemia (15/21, 71.4%, $p < 0.01$) had a new stroke at diagnosis independently of the effect of other vascular risk factors.

Bootstrap methods (randomly selecting 80% of the sample) were applied for each of the different logistic regressions previously described. The results were identical regarding the coefficients and p values for each variable studied.

Discussion

pVaD remains undefined despite several initiatives to develop a different set of criteria for its diagnosis and the growing body of literature regarding vascular risk factors. The concept of mild cognitive impairment has been introduced recently, focusing on Alzheimer's disease [41, 42]. It highlights the role that minor disturbances in memory affection display in the future development of

Table 4. Univariate analysis describing the natural history of VaD according to its prodromal onset subtype (cognitive impairment vs. stroke)

	Feature	Ischemia (n = 153)		CIND (n = 161)		p
		n	%	n	%	
Prodromal period	<1 month (no delay, n = 57)	51	87.9	7	12.1	<0.001
	1–12 months (n = 124)	38	30.6	86	69.4	
	13–24 months (n = 42)	12	28.6	30	71.4	
	>24 months (n = 90)	52	57.8	38	42.2	
Stroke at admission before VaD diagnosis[a]	No (n = 236)	89	37.7	147	62.3	<0.001
	TIA (n = 3)	1	33.3	2	66.7	
	Cortical (n = 46)	40	87	6	13	
	Lacunar/perforating artery (n = 29)	23	79.3	6	20.7	
Silent ischemia (n = 119)	Present	54	45.4	65	54.6	n.s.
	Absent	99	50.8	96	49.2	
Suspicion of stroke at VaD diagnosis[b]	No (n = 165)	56	33.9	109	66.1	<0.001
	TIA (n = 7)	3	42.9	4	57.1	
	Cortical (n = 71)	48	67.6	23	32.4	
	Lacunar/perforating artery (n = 71)	46	64.8	25	35.2	
VaD diagnosis	Cortical (n = 62)	39	62.9	23	37.1	<0.01
	BD (n = 93)	36	38.3	58	61.7	
	Mixed (n = 89)	39	56.2	50	48.3	
	Strategic stroke (n = 22)	15	68.2	7	31.8	
	Lacunar state (n = 48)	24	51.1	23	48.9	

χ^2-related p values represent the result of cluster analysis of each variable on the initial column on the far left with regard to the onset subtype.

[a] VaD diagnosis was suspected at an admission posterior to the one referring to this stroke.

[b] VaD diagnosis was suspected during this admission and confirmed 3 months later.

clinically demonstrated dementia of the Alzheimer type. Regarding cerebrovascular disease, the literature refers to cognitive impairment in one or several domains that does not meet the current criteria of dementia (CIND) and thus does not interfere with the patient's occupational or social life [6–8]. However, cognitive impairment of vascular origin is not well characterized. In our sample, early executive dysfunction, initial gait disturbances, early urinary incontinence or personality changes featured a classical vascular profile of cognitive impairment onset. Memory loss was frequent as a late finding, as we excluded those cases with early memory affection to exclude Alzheimer's cases.

In our sample, the co-dwellers disclosed data regarding nocturnal disorientation, person-

Table 5. Multivariate analysis of onset with CIND versus cerebrovascular events

Feature	OR	95% CI	p
Stroke at admission before VaD diagnosis[1]	0.4	0.2–0.5	<0.001
Prodromal period			
1–12 months (n = 124)	30.9	11.9–80.8	<0.0001
13–24 months (n = 42)	31.1	9.9–96.6	<0.0001
>24 months (n = 90)	0.2	0.1–0.6	<0.0001
Silent ischemia	2.2	1.2–4	<0.01
BD	2.4	1.3–4.5	<0.01

OR = Odds ratio; CI = confidence interval. Number of patients in parentheses.

[1] VaD diagnosis was suspected in an admission posterior to the one referring to this stroke.

ality changes and conduct disturbances through the Camdex H questionnaire. The physical examination was more accurate at identifying executive affection or gait disturbances as well as seizure events or dizziness. Even though informants overreported depression, they provided an indirect clue to search for CIND for physicians. Previous reports highlight that informants are more likely to predict dementia development in the context of memory impairment either isolated [44] or associated with deficits in an additional cognitive area [43–45]. However, given the heterogeneity of vascular cognitive impairment, we believe that co-dweller information is both critical and complementary to the facts retrieved by the physician.

In an effort to clinically describe the pVaD, we sought variables that could eventually relate to an unrecognized onset of the condition and were at hand at the bedside. The onset symptoms, presence or absence of prophylaxis for ischemic events and the age were relevant in our sample. Regarding the clinical presentation, we compared an onset with ischemic events (lacunar or cortical strokes, or TIA) with an outbreak defined by CIND because these are the two clinical presentations both informants and physicians encounter. Not surprisingly, an onset with CIND was markedly associated with a missed diagnosis of pVaD. It was particularly relevant in BD patients, who may initially present with a clinically overt lacunar stroke, but most frequently develop an onset with CIND due to subtle white-matter affection. The latter group is harder to detect as cognitive subcortical affection may progress slowly and in the absence of overt stroke in a proportion of cases. If patients have white-matter ischemic insults that do not affect the major motor and sensory pathways (as often happens in BD, and also in our cases with mixed dementia when affection is initially circumscribed to deep subcortical domains), their cognitive deficits may not be recognized.

One limitation of the current criteria for CIND progressing to vascular dementia is the requirement of an ischemic event to be related in time with the presenting deficits which prevents a number of diagnoses. It should be highlighted that cognitive impairment can precede stroke or lead to a fully developed VaD. This is a key issue as isolated subcortical affection could progress in the absence of overt strokes to a CIND state defined by a dysexecutive syndrome, loss of motivation and decay in attention or ability to concentrate when it progresses towards a fully developed VaD [46]. In this regard, the information the clinicians gather from co-dwellers is limited, as informants are more predisposed to be alerted by alarming overt ischemic events than by subtle changes in cognition. Hence, the physician may search for the presence of silent ischemia in neuroimaging. This seems critical in pVaD as silent ischemia correlates in our series with CIND onset and thus with delay in the early diagnosis of pVaD. Specifically, the longest period from onset to diagnosis (>2 years) in our sample was linked to the presence of silent ischemia in the context of small-vessel affection in mixed dementia, lacunar state or BD. Silent ischemia has previously been associated with memory impairment in patients with thalamic strokes and psychomotor speed deficits in nonthalamic ischemic areas [47]. We believe that it is vital for general practitioners to acknowledge these findings in neuroimaging as alert markers for further decline and worse prognosis [48].

Interestingly, a group of pVaD patients, those with large-vessel disease, were diagnosed at very early stages. This may reflect that both physicians and relatives mostly focus on cognitive deficits in the context of evident cortical dysfunction and thus greater acute impairment. However, a group of large-vessel disease patients was identified after 2 years of progression. These individuals seemed to be hard to treat due to social factors, lack of therapeutic adherence and the absence of follow-up, which could explain the difficulty to identify these cases.

We believe these differences between large- and small-vessel disease are clinically critical. Microvascular disease seems to present with milder cognitive affection at early stages of the disease [12], when detection and intervention would be highly valuable. At this stage tight control of vascular risk factors and, in the future, therapies in current development may play a key role in stopping or eventually reversing disease.

Younger patients are prone to remain undetected in our series, particularly those with ages <85 years. However, there were no remarkable differences concerning risk factors matched by age groups. Nevertheless, BD patients behaved differently as compared to other groups of patients. pVaD in BD cases <85 years remained mostly not diagnosed, whereas those ≥85 years did not show a defined trend regarding recognition of pVaD. Conversely, the overall sample of patients ≥85 was identified more timely. Hence, it seems that white-matter affection is a benign form of ischemic disease as compared to the other subgroups of vascular cognitive disease.

While describing the natural history of pVaD from the cognitive point of view, we are probably referring to a continuum from physiological aging, subtle CIND and the final development of VaD. Therefore, as younger pa-

tients could be expected to possess a greater vascular reserve, the development of VaD in this group might occur after a longer prodromal stage. In this situation small strokes would be better tolerated, and thus would have a lesser effect on cognition, while a large ischemic injury would uncover the subtle basal CIND. Accordingly, in our series pVaD was significantly better identified in those younger patients after a previous inpatient evaluation due to stroke. Conversely, patients older than 85 years are more easily diagnosed as probably a lesser vascular reserve is present, so these subjects are more vulnerable to ischemic insults. Supporting this idea, we see that although Alzheimer's disease is the most prevalent type of dementia, VaD is the first cause of dementia in patients older than 85 years [34].

Prevention with antiplatelet or anticoagulant therapy was associated with an unrecognized onset of pVaD in our series. Subjects with embologenous cardiopathy presented a clinically relevant trend to be under treatment, particularly antiplatelet therapy, although only left-ventricle hypertrophy and the subsequent dilated cardiomyopathy were related with higher treatment rates.

As previously discussed, a prodromal onset with ischemia correlated with further cerebrovascular events. In fact, half of the patients with previous ischemic events had a stroke at VaD diagnosis. Moreover, most of the subjects with previous ischemic events and on no prophylaxis for ischemia had a new stroke at VaD diagnosis independently of the effect of any vascular risk factors. However, anticoagulant or antiplatelet therapy seemed protective as far as those treated had a lower rate of recurrence as compared to those not treated.

Our study presents some limitations. First, our results are based upon our local population, thus some variables might behave in a different way in other settings. Nonetheless, external validity is assured by the analysis of the whole sample of patients with a diagnosis of VaD in our area during 13 years. Second, there is a loss of follow-up of 13% of the VaD population. However, external validity should not be affected by these circumstances [49], and internal validity is guaranteed by the bootstrap method [39].Third, no neuropsychological assessment has been performed besides MMSE and Camdex H in the retrospective part of the sample as happened in most clinical settings by that time. However, this group of the patients behaves as the prospective group regarding all aspects of the study. Besides, a neuropsychological battery fitted to detect a vascular cognitive impairment profile is yet to be established, while the limits for normal cognition remain undefined. Fourth, CIND progression to VaD or Alzheimer's disease is very similar [7]. We cannot totally exclude that some of our cases could be mixed dementias (Alzheimer plus VaD) as our study, as happens with other trials in the field, lacks pathological confirmation [7–9]. However, we excluded those cases that met the current clinical-radiological criterion for Alzheimer's disease plus those with a pVaD profile with early memory affection, and thus believe that our methods guarantee an accurate clinical diagnosis of VaD according to the current guidelines.

Strong points of the study pertain to a description of the unique role of small-vessel disease as a highly prevalent entity with a distinct natural history in Southwestern Europe. This fact may account for the high rate of subtle impairment of frontal subcortical function as compared to prior series [7–9]. We also described CIND and the relevant but limited role of informants in its detection. Hence, neuropsychological testing remains the mainstay for diagnosis and should be considered in aged subjects with cerebrovascular risk factors that visit the medicine clinic for other reasons. The diagnosis of CIND is critical as these patients are known to show worse outcomes compared to cognitively normal individuals, which could be modified as treatment may slow or even stop the development of VaD [5].

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We include the PubMed reference and link for the following manuscripts for the journal's Editor did not authorize the direct access to the published version through this thesis.

Vascular cognitive impairment in small vessel disease: clinical and neuropsychological features of lacunar state and Binswanger's diseas
Ciro Ramos-Estebanez, Ignacio Moral-Arce, Andres Gonzalez-Mandly, Vinoop Dhagubatti, Jesus Gonzalez-Macías, Roberto Muñoz, Jose Luis Hernández-Hernández

Age and Ageing 2011; 40: 175–180.

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Vascular Cognitive Impairment and Dementia Expenditures: 7-year Inpatient Cost Description in Community Dwellers
Ciro Ramos-Estebanez, Ignacio Moral-Arce, Fernando Rojo, Jesus Gonzalez-Macías, Jose Luis Hernandez

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6

Discussion

Dementia is a frequent condition in the elderly and major public health concern in the present and future (Ferri et al, 2005). VaD and its prodromal stage of VCI are prevalent disorders (Fratiglioni et al, 1992; Rockwood et al, 2002; Ferri et al, 2005; Ramos-Estébanez et al, 2008 & 2011; Gorelick et al, 2011; Wimo et al, 2011). However, the VCI stage remains undefined, despite several initiatives to develop a different set of criteria for its diagnosis and the growing body of literature regarding vascular risk factors (Bowler & Hachinski, 1995; Hachinski et al, 2006).

The concept of mild cognitive impairment has been introduced focusing on the amnestic component that typically heralds Alzheimer's disease (Levy, 1994; Petersen et al, 2001). With regards to cerebrovascular disease, the literature refers to cognitive impairment in one or several domains that does not meet the current criteria of dementia and thus does not interfere with the patient's occupational or social life (Rockwood et al, 2000; Wentzel et al, 2001; Engels et al, 2002). However, cognitive impairment of vascular origin is not well characterized. We feel this is important not only in large vessel disease cases, but also when addressing the small vessel vasculopathy. We believe that cognitive disease secondary to small vessel territory involvement exhibits relevant prevalence rates, and is likely to exert a high economic impact. Moreover, although the prognosis of lacunae is benign in the first year after stroke (Jackson & Sudlow, 2005), these patients have a mortality rate of 25% after 5 years of follow-up (Eriksson & Olsson, 2001) that increases to 60–75% after 10–15 years since the first lacune happened (Staaf et al, 2001; Wentzel et al, 2001).

6.1. Clinical features of VCI in our sample: informant and physician roles

Our study depicts early executive dysfunction; initial gait disturbances, early urinary incontinence or personality changes as the most notable features of patients with VCI onset. Although memory deficits could be present in early VCI, memory loss was frequent as a late finding in our cohort. This is a consequence of our methodology, which emphasized excluding those cases with early memory decline in an effort to remove Alzheimer's cases.

As expected, the informant's role is indeed quintessential in providing diagnostic cues to the primary care clinician. Co-dwellers described nocturnal disorientation, personality changes, and conduct disturbances through the Camdex H questionnaire. However, physical examination was more accurate at detecting executive affection or gait disturbances. The physician's history of personal illness was superior to relative's reports in identifying seizure events or dizziness of vascular origin. It seems that subtle cognitive deficits may be not perceived or might be considered 'normal' by patient's relatives. This is not surprising for previous reports highlight that informants are more likely to predict dementia development in the context of memory impairment either isolated (Bowen et al, 1997) or associated with deficits in an additional cognitive area (Bowen et al, 1997; Bozoki et al, 2001; Sacuiu et al, 2005). Even though informants over-reported depression, they provided an indirect diagnostic clue to physicians since it should raise the possibility of VCI. Overall and given the heterogeneity of vascular cognitive impairment, we believe that co-dweller information is both critical and complementary to the physician's findings.

6.2. Clinical diagnosis of VCI

In an effort to clinically describe VCI, we sought variables that could eventually relate to the diagnosis of VCI and were at hand at the bedside. The onset symptoms, presence or absence of prophylaxis for ischemic events and age were relevant in our sample.

6.2.1. VCI clinical onset

Regarding the clinical presentation, we compared an onset with ischemic events (lacunar or cortical strokes, or TIA) with an outbreak defined by CIND because these are the two clinical presentations both informants and physicians encounter. Not surprisingly, an onset with CIND was markedly associated with a missed diagnosis of VCI. It was particularly relevant in Binswanger's disease patients, who may initially present with a clinically overt lacunar stroke, but most frequently develop an onset with CIND due to subtle white-matter affection. The latter group is harder to detect as cognitive subcortical affection may progress slowly and in the absence of overt stroke in a proportion of cases. If patients have white-matter ischemic insults that do not affect the major motor and sensory pathways (as often happens in Binswanger's disease, and also in cases with mixed dementia when affection is initially circumscribed to deep subcortical domains), their cognitive deficits may not be recognized.

One limitation of the VaD criteria when this study started is that for VCI progressing to VaD, an ischemic event needs to be related in time with the presenting deficits. This approach prevents a number of diagnoses for cognitive impairment can precede stroke or lead to a fully developed VaD. This is a key

issue because a patient presenting with isolated subcortical involvement could progress in the absence of overt strokes to a CIND state defined by a constellation of behavioral symptoms (Royall, 2000). In this particular situations, the information the clinicians gather from co-dwellers is limited, as informants are more predisposed to be alerted by alarming overt ischemic events than by subtle changes in cognition. Hence, the physician may search for the presence of silent ischemia in neuroimaging. This seems critical in VCI as silent ischemia correlates in our series with CIND onset and thus with delay in the early diagnosis of VCI. Specifically, the longest period from VCI onset to VaD diagnosis (>2 years) in our sample was linked to the presence of silent ischemia in the context of small-vessel affection in mixed dementia, lacunar state or Binswanger's disease. Silent ischemia has previously been associated with memory impairment in patients with thalamic strokes and psychomotor speed deficits in non-thalamic ischemic areas (Vermeer et al, 2003). We believe that it is vital for general practitioners to acknowledge these findings in neuroimaging as alert markers for further decline and worse prognosis (Liebetrau et al, 2004).

Conversely, those patients with VCI due to large-vessel disease were diagnosed earlier. This may reflect that both physicians and relatives mostly focus on cognitive deficits in the context of evident cortical dysfunction. However, a group of large-vessel disease patients was identified after two years of progression. These individuals seemed to be hard to treat due to social factors, lack of therapeutic adherence and the absence of regular follow- up, which could explain the difficulty to identify these cases.

We believe these differences between large- and small- vessel disease are clinically critical. Microvascular disease seems to present with milder cognitive affection at early stages of the disease (Mock et al, 2005), when detection and intervention would be highly valuable. At this stage tight control of vascular risk factors and other therapies such as acetylcholinesterase inhibitors may play a key role in stopping or eventually reversing disease.

6.2.2. The role of age in diagnosis of VCI in our sample

Younger patients with VCI tend to remain undetected in our series, particularly those with ages <85 years. While describing the natural history of VCI from the cognitive point of view, we are probably referring to a continuum from physiological aging, subtle CIND and the final development of VaD. Therefore, as younger patients could be expected to own a greater vascular reserve, the development of VaD in this group might occur after a longer prodromal stage. In this situation small strokes would be better tolerated, and thus would have a lesser effect on cognition, while a large ischemic injury would uncover the subtle basal CIND. Accordingly, in our series VCI was significantly better identified in those younger patients after a previous inpatient evaluation due to stroke. Conversely, the overall sample of individuals ≥ 85 years was identified more timely. In the latter case, a lesser vascular reserve is probably present. Thus, these subjects are more vulnerable to ischemic insults. Supporting this idea, we see that although Alzheimer's disease is the most prevalent type of dementia, VaD is the first cause of dementia in patients older than 85 years (Mahler & Cummings, 1991; Kase, 1991). Binswanger's disease behaved differently in terms of the impact of age in the presentation. Those patients younger than 85 years

undergoing VCI remained mostly not diagnosed, whereas those ≥85 years did not show a defined trend regarding recognition of VCI. Thereby, it seems that white-matter affection is a subtler and sometimes more benign form of ischemic disease as compared to the other subgroups of vascular cognitive disease.

6.2.3. Relevance of the prophylaxis for stroke status in VCI diagnosis

A third factor that related to the ability to diagnose VCI was antiplatelet or anticoagulant therapy status. If the patient was on therapy, VCI seemed harder to identify. Subjects with embologenous cardiopathy presented a clinically relevant trend to be under treatment, particularly antiplatelet therapy, although only left-ventricle hypertrophy and the subsequent dilated cardiomyopathy were related with higher treatment rates.

As previously discussed, a VCI onset with ischemia correlated with further cerebrovascular events. In fact, half of the patients with previous ischemic events had a stroke at VaD diagnosis. Moreover, most of the subjects with previous ischemic events and not on prophylaxis for ischemia had a new stroke at VaD diagnosis independently of the effect of any other vascular risk factors. However, anticoagulant or antiplatelet therapy seemed protective as far as those treated had a lower rate of recurrence as compared to those not treated.

6.3. White matter ischemic disease in VCI diagnosis

We have established that VCI secondary to small vessel disease is a very common condition (Rockwood et al, 2000; Ramos-Estébanez et al, 2008) that may present as symptomatic ischemic insults (lacunes) (Bogousslavsky et al, 1988; Rockwood et al, 2000; Ramos-Estébanez et al, 2008) or as CIND in the context of silent

(asymptomatic) lacunes (Vermeer et al, 2003; Ramos-Estébanez et al 2008) or white matter disease in radiological studies (Boiten et al, 1993; Ramos-Estébanez et al, 2008). VCI diagnosis is difficult and usually delayed (Ramos-Estébanez et al, 2008). Therefore, further insights on the disruption of white matter cortico-subcortical loops are critical to identify CIND in small vessel disease (Cummings, 1993; Mesulam et al, 2003; Prins et al, 2005 Charlton, et al, 2006). Bearing this concept in mind, the prospective arm of our cohort underwent a careful account of vascular risk factors, physical examination and neuropsychological testing.

6.3.1. Vascular risk factors

1. Hypertension

We have confirmed prior observations establishing hypertension as the most relevant vascular risk factor for white matter disease (Fisher, 1969; Caplan & Schoene, 1978). In Binswanger's disease, the chronic effect of hypertension on the vessel wall adds to the loss in the ability of small vessels to autoregulate blood flow and manifests as silent ischemia and chronic white matter disease (Kario et al, 2003). Thus, hypertension was more frequent in our Binswanger's group. This is relevant because we have compared three groups of patients that have a higher incidence of hypertension than the general population.

2. Cardiopathy

We know that embologenous cardiopathy is a relevant risk factor for stroke and VCI. However, this effect was more prominent in the large vessel disease group (typically medium cerebral artery territory cortical strokes secondary to atrial fibrillation). Interestingly, Binswanger's disease and large vessel disease patients

shared a higher cardiopathy incidence than lacunar state cases, probably due to the higher hypertension incidence in the Binswanger's group.

6.3.2. Physical Examination findings: Gait disturbances

With respect to physical examination findings, gait abnormalities were more frequent in patients with small vessel disease in our population. Large vessel disease patients had cortical lesions and most frequently presented with a hemiparetic gait after medium or anterior cerebral artery stroke. Conversely, we observed a typical frontal gait ('marché á petit pas') in Binswanger's disease (Caplan & Schoene, 1978) when there was white matter disease in CT scan in the tracts connecting subcortical areas to the frontal lobes (Thompson & Marsden, 1987). These patients had a wide-based, stooped, shuffling gait, with trunk rigidity, preserved arm swing and turns broken down in many steps or turning on one leg (Caplan & Schoene, 1978). Recognizing these patterns is essential because these patients have a higher risk of developing CIND and eventually dementia (Verghese et al, 2008).

6.3.3. Neuropsychological testing: Executive dysfunction

Early executive dysfunction, though not specific to vascular disease, is a prominent feature of small vessel disease in our sample and in prior studies (Cummings, 1993; Graham, et al, 2004; Grau-Olivares et al, 2007). White matter disease and lacunes may disrupt the networks connecting the basal ganglia and dorsolateral prefrontal cortex. These lesions hinder the patient's ability to conceptualize all aspects of a task and translate it into appropriate and effective behavior. Generally, patients with Binswanger's disease and those with lacunar

state presented with executive dysfunction. These results are on the same line of previous work on lacunar state, white matter disease and Binswanger's disease. With regards to Binswanger's disease, these deficits underline the importance of extensive white matter disease on the neural networks (Gunning-Dixon & Raz, 2000; de Groot et al, 2001; Graham et al, 2004; O'Sullivan et al, 2005; Prins et al, 2005; Charlton et al, 2006; Sachdev et al 2006; Grau-Olivares et al, 2007).

It is difficult to define a specific cognitive profile given the heterogeneity of the anatomical lesions and sample populations reported in diverse small vessel disease studies (Gunning-Dixon & Raz, 2000; de Groot et al, 2001; Graham et al, 2004; O'Sullivan et al, 2005; Prins et al, 2005; Charlton et al, 2006; Sachdev et al 2006; Grau-Olivares et al, 2007). Nevertheless, it seems that executive function testing may be distinctly impaired in small vessel disease patients. We detected significantly worse scores in digit span and digit symbol, TRAIL B, TRAIL B-A and EXIT 25. These tests take a limited amount of time to perform with exception to the EXIT 25 (10, 3, 10 and 45 min, respectively) and may be useful as a screening tool in the office (O'Sullivan et al, 2005; Ramos-Estébanez et al; 2008).

6.4. Economic impact of VCI & VaD on tertiary care expenditures

Once our VCI cohort was characterized from the epidemiological, clinical and neuropsychological perspectives, we pursued an economic analysis of tertiary care inpatient costs. Studying these data is important since most studies about dementia-associated costs have focused on either a generic diagnosis of dementia or Alzheimer's disease (Hay & Ernst, 1987; Ostbye & Crosse, 1994; Menzin et al, 1999; Bynum et al, 2004; Gustavsson, et al, 2010). Indeed, those reports have shown a notable impact of dementia on expenses. Although VCI and VaD are

prevalent disorders (Fratiglioni et al, 1992; Rockwood et al, 2002; Ferri et al, 2005; Ramos-Estébanez et al, 2008 & 2011; Gorelick et al, 2011; Wimo et al, 2011), economic studies devoted to these entities are rare. Only Canadian (Rockwood et al, 2002) and Swedish cohorts (Fratiglioni et al, 1992; Wimo et al, 2003) have thoroughly examined VCI and VaD expenses. The paucity of literature about the topic may be due to diagnostic difficulties and a focus on other aspects of cerebrovascular disease (Ramos-Estébanez et al, 2008 & 2011).

In the more easily identifiable cases of cerebrovascular disease presenting with stroke, patient care (mainly inpatient) during the first year after the event and prior to VaD development is similar to or more onerous than care for patients with Alzheimer's disease (Fratiglioni et al, 1992; Rockwood et al, 2002; Lopez-Bastida et al, 2003; Wimo et al, 2011). However, cognition is rarely assessed in the clinic once a patient has been discharged from the hospital (Ramos-Estébanez et al, 2008 & 2011). Therefore, there are many studies addressing stroke expenses, but scarce data on VCI expenses, even when it presents with stroke. Economic studies in populations with dementia in Spain are scarce and usually devoted to Alzheimer's disease populations (Martínez Lage et al, 2000; Lopez-Bastida et al, 2003; Atance Martinez et al, 2004).

6.4.1. Did the Severity of Cognitive Impairment Correlate with Costs?

The dementia and Alzheimer's disease literature support the idea that the severity of cognitive impairment correlates with higher expenses (Kronborg et al, 1999; Fillenbaum et al, 2001; Atance Martinez et al, 2004) and the likelihood of hospitalization (Fillenbaum et al, 2001). It was unclear whether this is the case in patients with cognitive cerebrovascular disease. Our sample showed a correlation

between the degree of cognitive impairment and expenditures. Indeed, during the VaD stage expenses per patient (~$22 631) doubled the cost of VCI care. Demented patients showed a trend toward admissions prompted by both neurological and non-neurological conditions. This finding contrasts with the VCI period, when neurological diagnoses were predominant. Overall, a higher level of cognitive decline correlated with more admissions.

6.4.2. Did the Presence of Clinical Surrogates of Binswanger's Disease Influence Costs?

1. Gait disturbances:

It seems that patients with white matter involvement presented with fractures more frequently. This trend was more noticeable in individuals with a frontal gait pattern. Although not all patients underwent surgical management, this condition certainly involves a larger expense in terms of diagnostic coding and reimbursement.

2. Executive dysfunction:

Cognitive deficits within the executive function realm were common in our series. Interestingly, there was a distinct trend of hospital admissions in the context of chronic obstructive pulmonary disease and diabetes-related decompensations in individuals with executive dysfunction. We hypothesize that difficulty with therapeutic compliance explains these results (Allen et al, 2003).

6.4.3. Did the Type of Clinical Onset Influence Costs?

The literature on cognitive impairment and dementia expenditures has focused on Alzheimer's disease. On the other hand, stroke motivated the financial analysis work with regards to cerebrovascular disease. Certainly, the societal cost of stroke accounts for a sizeable percentage of health care expenditures. There is an emphasis on inpatient costs during the first year and a subsequent shift to outpatient care in the following years (Evers et al, 2004). Once the studies focus on the direct cost, stroke accounts for approximately 45% of the expenditures in health care systems as divergent as Sweden (Terént, 1983) and the United States (Taylor et al, 1996).

Approximately half of the patients in this study progressed with stroke during the VCI stage (Ramos-Estébanez et al, 2008 & 2011). Initially, the large-vessel disease group typically presented with ischemic events, which involved slightly higher VCI costs per patient, as reported in the literature (Terént, 1983; Taylor et al, 1996; Carod-Artal et al, 1999; Everts et al, 2004; Hervás-Angulo et al, 2006). Conversely, VCI onset without stroke was a distinct feature of patients in the small-vessel disease (lacunar state and Binswanger's disease) group (Ramos-Estébanez et al, 2008 & 2011) and was initially associated with lower expenditures. However, once VaD criteria were met, the costs per patient in the small-vessel disease group increased significantly because these patients were admitted more often due to both stroke and other diagnoses. Moreover, the small vessel group diagnostic codes, particularly those in the Binswanger cases, were more expensive. These findings are also in agreement with Canadian and Swedish reports, which noted higher VaD costs and steeper increases in expenditures

associated with mild- to-moderate dementia in patients with VaD compared with those associated with Alzheimer's disease (Fratiglioni et al, 1992; Rockwood et al, 2002; Wimo et al, 2003 & 2011). The authors in these reports attributed the results to stroke comorbidities and the presence of residual deficits.

6.4.4. How Do These Results Compare with the Literature?

The average per-capita cost during the course of cognitive cerebrovascular disease in this cohort was approximately $33 740. These expenditures are not comparable with previous similar reports (Fratiglioni et al, 1992; Rockwood et al, 2002; Wimo et al, 2003) due to differences in methodology (e.g., perspective, definitions, and outcome measures). Those cohorts (Fratiglioni et al, 1992; Rockwood et al, 2002; Wimo et al, 2003) estimated the total societal cost, while this study focused on inpatient services. In addition, we did not account for the cost of institutionalized patients. Thus, our figures are smaller. Nevertheless, our sample follows similar trends.

Another relevant factor in the interpretation of the data is that there are regional health care expenditure differences within Europe. The ICTUS trial (Gustavsson et al, 2010) and the Eurocode project (Wimo et al, 2011), although devoted to Alzheimer's disease, support the idea that direct costs are higher in Northern Europe (compared with southern and western countries, such as Spain, Italy, and Greece). Our results are similar to those seen in other studies with regard to the effect that the degree of cognitive impairment (Fratiglioni et al, 1992; Rockwood et al, 2002; Wimo et al, 2003) or stroke has on costs (Fratiglioni et al, 1992; Rockwood et al, 2002; Wimo et al, 2003).

6.5. Study limitations

The data presented presents some limitations that need to be acknowledged:

1. These results are based upon our local population, thus some variables might behave in a different way in other settings. Nonetheless, external validity is assured by the analysis of the whole sample of patients with a diagnosis of VaD in our area during 13 years.
2. There is a loss of follow-up of 13% of the VaD population. However, external validity should not be affected by these circumstances (Laupacis et al, 1994). Internal validity is guaranteed by the bootstrap method (Efron & Gong, 1983).
3. No neuropsychological assessment has been performed besides MMSE and Camdex H in the retrospective part of the sample as happened in most clinical settings by that time. However, this group of the patients behaves as the prospective group regarding all aspects of the study.
4. CIND progression to VaD or Alzheimer's disease is clinically very similar (Wentzel et al, 2001). We cannot totally exclude that some of our cases could be mixed dementias (Alzheimer plus VaD) as our study, as happens with other trials in the field, lacks pathological confirmation (Wentzel et al, 2001; de Groot et al, 2001; Unverzagt et al, 2001; Engels et al, 2002; Graham et al, 2004; O'Sullivan et al, 2005; Sachdev et al, 2006; Grau-Olivares et al, 2007; Verghese et al, 2008). However, we excluded those cases that met the current clinical-radiological criterion for Alzheimer's disease plus those with a VCI profile with early memory involvement. Thus, we believe that our methods guarantee an accurate clinical diagnosis

of VaD according to the current guidelines. Yet, there is increasing evidence that many cases will eventually develop a pathological profile consistent with a mixed dementia. This situation should not deter clinicians from seeking an early diagnosis of VCI. In this context, our goal remains to provide practitioners with clinical hints that may lead to a further work up.

5. The same diagnostic problem applies to small vessel disease cases with respect to CADASIL. We carefully excluded those patients with a family history of dementia and those with early temporal lobe involvement. However, there was no genetic testing available when the study started.
6. We reported white matter disease in CT scans according to the ADDTC criteria (Chui et al, 1992). While CT is less sensitive than MRI at detecting small vessel disease, it has a higher specificity and positive predictive value. Hence, we only detected severe white matter disease cases. Besides, we do not provide with a quantitative measure of white matter disease. Yet, our approach pertains to daily primary care practice, where MRIs and quantitative measures of white matter disease are not available. We focused on clinical aspects (i.e. gait disturbance/subtle cognitive deficits) that might hint the need for further testing.
7. The economic analysis reflects the costs and organization of a tertiary-care center in a single region within the Spanish National Health Institute. However, the demographic characteristics in our region and the expenses in our center are similar to those of other areas in Spain (Spanish National Institute of Statistics website).

8. Besides our design provides a retrospective description and does not allow for predictions or policy recommendations about expenditures.
9. Notably, we focused on inpatient costs in community dwellers and excluded those who were institutionalized. However, deceased patients and those who became institutionalized had similar follow- up periods irrespective of DRG or VCI type.
10. Our estimations are limited for these are based on DRG values. This methodology averages pharmaceutical costs. Besides, DRGs do not include rehabilitation costs.
11. We did not study caregiver burden and derived expenditures, which are very important, but may also be subject to a strong cultural bias.

7

Conclusions

Ramos-Estébanez et al, 2008

1. Our study portrays the unique role of small-vessel disease as a relevant and prevalent contributor to dementia with a distinct natural history during the VCI period.

Nuestro estudio demuestra un papel relevante y prevalente de la enfermedad cerebrovascular de pequeño vaso en el desarrollo de demencia, con una diferente historia natural durante el período de deterioro cognitivo leve de perfil vascular.

2. An age < 85 years, prophylaxis for stroke status, and VCI clinical onset with CIND were the factors that correlated with an unrecognized diagnosis of vascular cognitive impairment in the primary care setting in our sample.

Una edad <85 años, la profilaxis de accidente cerebrovascular y el inicio del deterioro cognitivo vascular sin demencia, se correlacionaron con una ausencia de diagnóstico en el inicio de la fase de deterioro cognitivo leve de origen vascular

3. The role of informants in the early identification of VCI is very important. Their report is particularly valuable in terms of nocturnal disorientation, and conduct disturbances. Clinicians taking cues from the history elucidated the presence of executive dysfunction more accurately.

La contribución de los familiares y cuidadores es muy importante para establecer el diagnóstico precoz de deterioro cognitivo leve de tipo vascular. En nuestra muestra, la alerta sobre episodios con

desorientación nocturna, o cambios en la conducta del paciente fueron significativos para alcanzar el diagnostico. Los clínicos detectaron la presencia de disfunción ejecutiva de manera más acertada.

4. A special emphasis on characterizing VCI starting with CIND and no strokes proved clinically relevant for its clinical diagnosis is difficult. They tended to have fewer ischemic events before dementia diagnosis, undergo longer VCI periods, were diagnosed with silent ischemia through imaging, and were more prone to fulfill Binswanger's disease criteria.

La caracterización de la etapa de deterioro cognitivo vascular leve que comienza sin eventos isquémicos es relevante desde el punto de vista clínico, puesto que su detección es difícil. Estos pacientes tienden a presentar menos accidentes cerebrovasculares antes del diagnostico de demencia, presentan un periodo prodrómico más prolongado, suelen padecer isquemia silente en las pruebas de neuroimagen, y frecuentemente cumplen los criterios de la enfermedad de Binswanger.

Ramos-Estébanez et al, 2011

1. Our data evidence a pervasive executive dysfunction in patients with small vessel disease.

   Nuestros resultados evidencian una frecuente disfunción ejecutiva en los pacientes con enfermedad cerebral de pequeño vaso.

2. Executive dysfunction is central to small vessel cerebrovascular disease, though it may be present in large vessel cases and other types of dementia.

   La disfunción ejecutiva es un déficit característico de la enfermedad cerebrovascular de pequeño vaso. Este déficit no es exclusivo de esta tipo de patología, puesto que puede ocurrir en pacientes con deterioro cognitivo secundario a lesiones de gran vaso o en otro tipo de demencias.

3. We could not find significant differences in the neuropsychological profile for lacunar state and Binswanger's disease cases. These findings underline the relevance of white matter lesions in cognition.

   No se objetivaron diferencias desde el punto de vista del perfil neuropsicológico entre los pacientes diagnosticados de estado lacunar y aquellos con enfermedad de Binswanger. Estos resultados subrayan la relevancia de las lesiones de la sustancia blanca desde el punto de vista cognitivo.

4. We showed that a brief and simple executive function battery performed by general physicians (or trained nurses) in the outpatient clinic for 30 minutes may help detect early VCI.

   Hemos mostrado que unas pruebas cognitivas simples y breves aplicadas e interpretadas por médicos generales (o enfermeras entrenadas en su utilización) en la consulta externa durante 30 minutos pueden contribuir a la detección precoz del deterioro cognitivo leve de perfil vascular.

5. Ultimately, the diagnosis of VCI is critical for these patients are known to show worse outcomes compared to cognitively normal individuals. Notably, cerebrovascular cognitive ischemic disease may be treated during its early VCI stage.

   Finalmente, el diagnostico del deterioro cognitivo leve de tipo vascular es crítico, puesto que estos paciente presentan un mal pronóstico comparado con el de los individuos sanos. Además, el deterioro cognitivo leve podría ser tratado en sus fases iniciales.

Ramos-Estébanez et al, 2012

1. Our results illustrate the inpatient tertiary care expenditures during the VCI and VaD phases for each diagnostic group.

   Nuestros resultados ilustran el coste económico del cuidado intrahospitalario de tercer nivel durante las fases de deterioro cognitivo leve de perfil vascular y de demencia vascular.

2. As expected, patient care was more economical at the VCI stage than at advanced VaD stages.

   Tal y como se esperaba, el gasto sanitario fue menor en el período de deterioro cognitivo leve que en la fase de demencia vascular.

3. Medical attention for VCI presenting with stroke or TIA (either a large or small vessel episode) was more expensive than VCI cases presenting without ischemic events.

   El consumo de recursos sanitarios en la fase de deterioro cognitivo leve que se inicia con un episodio isquémico (de gran o de pequeño vaso) fue mayor que en aquellos casos que debutan sin eventos isquémicos.

4. Large vessel patient care per-patient was more onerous in the VCI stage compared to other diagnostic groups. This was due to the higher cost stroke care conveys.

   El gasto por paciente fue más elevado en los pacientes con

enfermedad cerebrovascular de gran vaso durante la etapa de deterioro cognitivo leve comparado con el resto de grupos diagnósticos. Esto fue debido al alto coste de los cuidados hospitalarios en el caso de los eventos isquémicos.

5. The existence of white matter disease correlated with the presence of a frontal gait disorder and bone fractures. In addition, executive dysfunction was abundant in individuals admitted with diabetic and chronic obstructive pulmonary disease decompensations, though the size of this subset of the sample was modest.

La existencia de enfermedad crónica isquémica de la sustancia blanca se correlacionó con la presencia de un trastorno de la marcha de tipo frontal y con la presencia de fracturas óseas. Asimismo, la disfunción ejecutiva era frecuente en pacientes ingresados por descompensaciones diabéticas o de su EPOC, aunque el tamaño de estos subgrupos fue menor.

6. Overall, the tertiary care expenditures per capita for the Binswanger group were lighter during the VCI stage for there was a lesser incidence of stroke compared to the other diagnostic groups. However, during the VaD period the small vessel (Binswanger and lacunar state) cases became more onerous for they were admitted more often than the large vessel disease patients and their diagnostic codes were more expensive.

En general, los gastos por paciente en el grupo con enfermedad de Binswanger fueron menores durante la fase de deterioro cognitivo

leve de perfil vascular. Este hecho se debe a que estos pacientes experimentaron una menor incidencia de ictus. Sin embargo, durante el período de demencia vascular, el cuidado de los pacientes con enfermedad de pequeño vaso (estado lacunar y enfermedad de Binswanger) resultó más elevado debido a un mayor volumen de ingresos hospitalarios y a un mayor coste por ingreso.

8

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