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Vascular Dementia and Alzheimer's Disease: Is There a Difference?

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1. Introduction

Dementia is a syndrome that can be caused by a number of progressive disorders that affect memory, thinking, behaviour and the ability to perform everyday activities, with increasing loss of function. Dementia mainly affects older people; after age 65, the likelihood of developing dementia roughly doubles every five years (Alzheimer's Association, 2011; Wimo & Prince, 2010). Patients with dementia usually survive 7-10 years after onset of symptoms, placing a tremendous burden not only on caregivers, but also on society (Alzheimer's Association, 2010; Wimo et al., 2010).

Due to increasing life expectancy the number of people suffering from dementia will increase rapidly in both developed and developing countries. As a result, the management of dementia patients is now becoming one of the most important public health problems (Wimo et al, 2003). It is estimated that 24.3 million people have dementia today, with 4.6 million new cases of dementia every year (one new case every 7 seconds). The number of people affected will double every 20 years to 81.1 million by 2040. Most people with dementia live in developing countries (60% in 2001, rising to 71% by 2040). Rates of increase are not uniform; numbers in developed countries are forecast to increase by 100% between 2001 and 2040, but by more than 300% in India, China, and their south Asian and western Pacific neighbours; i.e. the rate of increase in numbers of people with dementia is predicted to be three to four times higher in developing areas than in developed regions (Ferri et al., 2005). Hence, dementia is one of the most important public health problems.

The syndrome of dementia may be caused by various underlying diseases, each characterised by a specific constellation of signs and symptoms in combination with a presumed underlying substrate of neuropathology. Alzheimer's disease (AD) is the most prevalent cause of dementia. It is a neurodegenerative disorder, generally assumed to be caused by neuritic plaques and neurofibrillary tangles accumulating in the brain. The second most prevalent cause of dementia is vascular dementia (VaD), which may be caused by various types of vascular pathology in the brain, such as ''large vessel''- large territorial or strategical infarctions, and ''small vessel''- lacunes and white matter hyperintensities disease, (Van der Flier & Scheltens, 2005).

Current data from developing countries suggest that age-adjusted dementia prevalence estimates in 65 year olds are high (≥5%) in certain Asian and Latin American countries, but

consistently low (1–3%) in India and sub-Saharan Africa (Kalaria et al., 2008). In 2000, prevalence data from 11 European population based studies were pooled to obtain stable estimates of prevalence of dementia in the elderly (> 65 years); age standardised prevalence was 6.4% for dementia (all causes), 4.4% for AD, and 1.6% for VaD (Berr et al., 2005; Lobo et al., 2000). The ratio between AD and VaD was similar in most studies of US, Europe and Africa. Alzheimer's disease is the most common etiology of dementia and accounts for 50-70% of total dementia cases. The second most common etiology is vascular dementia and account for 20-30% of total dementia (Fratiglioni et al., 1999).

Dementia syndrome develops over a long period of time characterized by progression from normal cognition defined as preclinical stage, through a transition phase of cognitive impairment defined as mild cognitive impairment- MCI, to full-scale dementia. Preventive strategies can be implemented before the onset of the process of dementia by eliminating or treating risk factors, as well as promoting protective factors (primary prevention). Secondary prevention relies on the identification of clinical or biological markers for disorders that lead to dementia in order to detect subjects early who will develop dementia within a few years. Tertiary prevention includes the identification of prognostic factors and the evaluation of the care provided to patients with dementia by comparing different care strategies in terms of specific individual and family outcomes (The Swedish Council SBU, 2008).

In that context, these two common etiology of dementia, i.e. Alzheimer's disease and vascular dementia have different characteristics, and there are diagnostic criteria for each of them. This article will focus on the difference between Alzheimer's disease and vascular dementia in light of recent development of research in each field.

2. Concepts of vascular dementia and Alzheimer's disease – Diagnosis criteria

2.1 Evolution of concepts

Since the 1970s, the concept of vascular dementia (VaD), a type of dementia secondary to stroke and vascular disease, has been distinguished from the purely neurodegenerative form of dementia, (AD). Since then, many clinical, neuropsychological, radiologic, and pathologic criteria have been proposed in an attempt to distinguish these entities in order to identify a homogenous group of patients who supposedly all share a common specific underlying mechanism of dementia; hence, allowing design of mechanism-specific therapies for this homogenous group of patients. The Diagnostic and Statistical Manual (DSM) of the *American Psychiatric Association* is the most influential classification of mental disorders worldwide. The third edition of this manual (DSM-III), published in 1980, was considered to be a major step forward in establishing a reliable diagnostic system based on evidence. The DSM has been revised periodically as new data have emerged, the last major revision having been in 1994 (DSM-IV), and a minor one in 2000 (DSM-IV-TR). The DSM-IV offers guidelines for diagnosis of one type of primary degenerative dementia - dementia of Alzheimer type (DAT) – and one type of VaD - multi infarct dementia (MID), now called VaD (*American Psychiatric Association*, 1994, 2000). ICD-10 offers four main categories of dementia, in which DAT is subclassified with respect to early versus late onset, typical versus atypical clinical features, and pure or combined with VaD; and VaD is described in terms of type of onset and predominant involvement. IDC-10 recognized 6 subtypes of "vascular (formerly arteriosclerotic) dementia", which includes such entities as "VaD of

acute onset", "subcortical VaD", "mixed cortical and subcortical VaD", "other VaD" and "VaD unspecified" in addition to MID. Subcortical VaD with extensive diffuse demyelination and small focal infarctions was also referred to as "Binswanger's encephalopathy" (World Health Organization, 1992). The state of California Alzheimer Disease Diagnostic and Treatment Center (ADDTC) proposed the first set of criteria for the diagnosis of ischemic vascular dementia (IVD) in 1992, describing probable, possible, and definite IVD, as well as mixed dementia. VaD was also defined in terms of brain imaging, thereby extending the concept to include MID, single stroke dementia and Binswanger's disease (Chui et al., 1992). The criteria developed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) (Román et al., 1993), elaborated on the cause-effect relationship between cerebrovascular disease and symptoms of dementia; with the goal of facilitating treatment and epidemiological research, it emphasized the need of clinical and neuroimaging criteria for early and specific diagnosis of probable, possible and definite VaD. The NINCDS-ADRDA work group for standardization of clinical criteria for diagnosis of AD (McKhann et al., 1984) recommended the terms "possible AD" and "probable AD" and "definite AD", along with the pathologic criteria (Mirra et al., 1991). The introduction of MID was followed by the presentation of the Ischemic Score rating scale for differential diagnosis between AD and VaD (Hachinski et al., 1975). Differentiating among dementias presents many difficulties, especially at an early stage, and no single available diagnostic technique can solve all of these problems. The common clinical criteria (ICD-10, DSM-IV, ADDTC, NINDS-AIREN) for VaD are umbrella systems in that they do not consider the specific situation. Comparative studies show a lack of agreement among the systems; despite similarities, they identify different patients and patient groups. Not only do these differences affect prevalence and incidence estimates, but clinical management becomes more capricious. In order to promote the development of more effective pharmacological treatments and other improvements, the criteria systems need to be modified and made more specific. Thus, greater attention should be paid to vascular mechanisms and subtypes.

2.2 The DSM-V neurocognitive disorders cluster

In response to clinical and research developments since the publication of DSM-IV, the process to revise the classification for a DSM-V, to be published in 2012, started in 2006 with the establishment of a DSM-V Task Force, and a Work Group for neurocognitive disorders (Chair: Professor Dilip Jeste) in 2007. The draft proposed criteria from this Work Group was recently put on- line for general comments. The publication of DSM-V will have a major influence on the commonly used classification of neurocognitive disorders (Sachdev, 2010).

Among the major changes in structure and criteria for dementia and related disorders were: the term dementia is replaced with the more descriptive "Major Neurocognitive Disorder" (NCD); the criteria are reworded to reflect a focus on decline from a previous level of performance; also, the requirement for a deficit in memory is removed to better accommodate NCD due to other non-Alzheimer etiologies (Blacker, 2010). The field is moving towards earlier detection of the diseases underlying dementia, such that the disorder can be recognized, and possibly treatment started, before the dementia stage, e.g., the "mild cognitive impairment" stage of Alzheimer disease.

In other disorders, cognitive impairment may be static and not progress beyond the mild stage, but still be a focus for assessment and care. Hence, the category of Minor NCD (similar to Mild Cognitive Impairment**)** has been added given that this syndrome has become a major focus of research and clinical care (Ganguli, 2010).

The definitions of Major and Minor NCD are based on the primary cognitive disturbance, with a requirement for both cognitive symptoms elicited from the subject or an informant or observed by the clinician, and quantifiable deficits on cognitive assessments. At the Minor level, the cognitive symptoms may involve greater difficulty performing cognitive tasks (rather than inability), and the deficits are typically in the range of 1-2 SD below age- and education-adjusted means of neuropsychological tests. At the Major level, the deficits are typically >2 SD below the mean. The distinction between Minor and Major also rests on the preservation or loss of independence. Specific etiologic subtypes will also have specific criteria cutting across Major and Minor NCD (Blacker, 2010).

2.3 The new criteria for Alzheimer's disease

Criteria for the clinical diagnosis of Alzheimer's disease **(**AD) were established in 1984 (McKhann et al., 1984). Owing to clinical and research development, a broad consensus now exists that these criteria should be revised. The National Institute on Aging (NIA) and the Alzheimer's Association sponsored a series of advisory round table meetings in 2009 whose purpose was to establish a process for revising diagnostic and research criteria for AD. Two notable differences from the AD criteria published in 1984 are incorporation of biomarkers of the underlying disease state and formalization of different stages of disease in the diagnostic criteria. The recommendation from these advisory meetings was that three separate work groups should be formed with each assigned the task of formulating diagnostic criteria for one phase of the disease: the dementia phase, the symptomatic pre-dementia phase, and the asymptomatic preclinical phase of AD. A semantic and conceptual distinction is made between AD pathophysiological processes and clinically observable syndromes that result, whereas this distinction was blurred in the 1984 criteria. The new criteria for AD are presented in three documents. The core clinical criteria of the recommendations regarding AD dementia (McKhann et al., 2011) and MCI due to AD (Albert et al., 2011) are intended to guide diagnosis in the clinical setting. However, the recommendations of the preclinical AD workgroup (Sperling et al., 2011) are intended purely for research purposes.

2.4 Vascular dementia nosology

2.4.1 Historical overview

Modern history of dementia began in 1910 with Emil Kraepelin's influential textbook *Psychiatrie*. His work was based on clinical pathology studies by Otto Binswanger and Alois Alzheimer. The brain lesions that were assumed to be responsible for dementia consisted of arteriosclerotic brain atrophy (characterized by multiple lacunar strokes and " état criblé " - dilated perivascular spaces - associated with arteriosclerosis of small and large blood vessels), senile cortical atrophy (granular atrophy and laminar necrosis), periventricular white matter atrophy (Binswanger's disease), perivascular gliosis (wedgeshaped lesions resulting from severe stenosis of a large vessel), arteriosclerotic hemispheric foci

(predisposing for "dementia postapoplexia") and the combined forms of dementia. In practice, arteriosclerotic dementia was synonymous with senile dementia. Successively impaired blood flow was thought to lead to neuron death (Roman, 1999). In the mid 1970s, AD was first regarded as the main cause of brain atrophy and dementia. The notion of chronic brain ischemia as an explanation of dementia was abandoned. Now vascular lesions in patients with dementia are receiving growing attention. Stroke-related dementia is increasingly in the spotlight, as is subcortical VaD with white matter damage and lacunae, regarded by some as the most common form of VaD (Roman et al., 2002).

2.4.2 Heterogeneity of vascular dementia

The increased percentage of elderly in the general population, along with changes in the cerebrovascular disease panorama in terms of reduced stroke mortality, has led to reevaluation and renewal in this field. Instead of using simplified disease categories, the assertion was that vascular mechanisms leading to cognitive impairment should form the basis of disease classification (Gorelick & Mangone, 1991; Hachinski, 1990). Among such vascular mechanisms are thromboembolism, vessel wall damage (Atherosclerosis, hyalinosis, amyloid angiopathy), cerebrovascular insufficiency (Disturbance of systemic circulation, vascular anatomy of the brain, disturbed regulation of cerebral blood flow), hyperviscosity, bleeding. Because several such mechanisms exist (Parnetti et al., 1994; Wallin & Blennow, 1993), there are also several types of VaD (Chui, 1989; Rockwood et al., 1999; Roman et al., 2002).

3. Mixed-type dementia

Mixed dementia is diagnosed when patients have evidence of Alzheimer dementia and cerebrovascular disease, either clinically or based on neuroimaging evidence of ischemic lesions. Growing evidence indicates that vascular dementia and Alzheimer dementia often coexist, especially in older patients with dementia (Langa et al., 2004). The occurrence of vascular risk factors and diseases are regarded as exclusion criteria for the diagnosis of AD. However, longitudinal epidemiological studies have shown that hypertension, diabetes, atrial fibrillation, and smoking are risk factors for AD as well as VaD. Ischemic processes have proven not only to co-exist with AD, but to potentiate its development (Cacabelos et al., 2003; Ravona-Springer et al., 2003; Skoog & Gustafson, 2003). Autopsy studies have shown an association between Alzheimer disease and vascular lesions (Snowdon et al., 1997). Toncosco et al. (2008) report autopsy findings from the Baltimore Longitudinal Aging Study among 122 men and 57 Women; macroscopic and microscopic infarcts contributed equally to dementia risk, and hemispheral infarcts, whether silent or clinically manifest, alone or in conjunction with AD pathology accounted for 35% of dementia cases. The findings support a synergism between AD and vascular pathology and the importance of burden and location of infarcts.

Vascular pathology in the aging brain and AD includes ischemic infarcts, lacunes, cerebral hemorrhages, white matter lesions, blood-brain barrier (BBB) dysfunction, cerebral amyloid angiopathy (CAA), and microvascular degeneration (Jellinger & Attems, 2003). These pathologies are commonly seen in various vascular diseases and can contribute to cognitive impairment by affecting neuronal networks involved in cognition, memory, behavior, and

executive functioning (Jellinger, 2007). The OPTIMA project showed that cerebrovascular disease impaired cognitive performance in early phases of AD but not later in the course of the disease (Esiri et al., 1999). At the same grade of dementia, fewer Alzheimer's lesions were required in patients who had cerebrovascular damage (Zekry et al., 2002a). Another study reported that the combination of Alzheimer's disease and vascular pathology was common in patients with cognitive impairment, however, no threshold effects for the various changes could be found (Neuropathology group - MRC CFAS, 2001).

Recent evidence from epidemiological, clinical, pathological, and Neuroimaging studies implicates neurovascular dysfunction as an integral part of AD. Data from these studies reveal a distinct association between vascular risk factors and AD (Dickstein et al., 2010). These include hypertension (Kivipelto et al., 2001), total cholesterol, type II diabetes mellitus (Ott et al., 1999), hypotension, smoking (Ott et al., 1998) and oxidative stress (Zhu et al., 2007). Furthermore, dysfunction of the endothelial cells that compose the BBB has also been demonstrated and correlates with AD severity (Dede et al., 2007). The degree to which these factors contribute to AD may be influenced by genetic factors such as apolipoprotein E, which has a role in both AD and vascular disease. Ischemia via vasoactive effects of amyloid, impaired blood flow, reduced metabolism, inflammatory mechanisms and changes in the blood-brain barrier are among the factors that have been regarded as the genesis of vascular tissue damage in AD. Some authors have even claimed that AD is primarily microvascular, for which degeneration of the capillaries in the hippocampus and other brain regions, including secondary neuronal hypometabolism, is the central pathophysiological chain of events (De la Torre, 2002).

Identifying patients with AD and concurrent cerebrovascular disease is not easy when the patient lacks markers for AD. That may be one reason for the rate of mixed dementia having been underestimated (Kalaria & Ballard, 1999). According to a relatively current review of clinical neuropathological studies, mixed dementia accounts for 20 to 40% of dementia cases (Korczyn, 2002; Zekry et al., 2002b). Alzheimer's disease pathology occurs frequently in asymptomatic elderly individuals and clinical dementia is more likely to be present when AD is accompanied by strokes and cerebrovascular related brain changes (Riekse et al., 2004). The cognitive consequences of vascular lesions are cumulative. So VaD and perhaps also mixed dementia are potentially preventable if vascular risk factors are controlled and strokes do not recur. To better guide the treatment of patients with mixed dementia, future studies should similarly broaden their criteria to include patients with evidence for mixed causes of dementia, rather than identifying only pure AD and VaD (Langa et al., 2004).

4. Vascular cognitive disorders – Vascular cognitive impairment (VCI)

The term "vascular cognitive disorder" was proposed by Sachdev (1999) to define vascular cognitive deficits of sufficient severity to meet criteria for a diagnosable disorder. It was intended as an umbrella term to include the spectrum of impairment from mild vascular cognitive impairment to vascular dementia (Roman et al., 2002). Vascular cognitive impairment (VCI)) is the modern term related to vascular burden of the brain, reflecting all encompassing effects of cerebrovascular disease on cognition. VCI include all levels of cognitive decline from mild deficits in one or more cognitive domains to a broad dementia-like syndrome. VCI incorporates the complex interactions between vascular risk factors, cerebrovascular disease etiologies and cellular changes within the brain and cognition

(Chui, 2006; Erkinjuntti & Gauthier, 2009). The extent to which cognitive disturbance is progressive or non progressive is important to delineate, because it suggests initiation of a process for development of dementia, or instead a cognitive residual syndrome.

Vascular cognitive impairment (VCI) has continued to evolve over the past year. Much of the data has been confirmatory with further work on risk factors, silent strokes, leukoaraiosis and lesion volume and location. The importance of the interaction between cerebrovascular disease and other causes of cognitive impairment, most importantly Alzheimer disease (AD) remains a prominent theme (Bowler & Gorelick, 2009).

From a neuropathologic perspective, once irreversible parenchymal injury has occurred, there are downstream and retrograde effects in the central nervous system that result from the insult - as a function of Wallerian, trans-synaptic and other types of degeneration which almost certainly affect subsequent neurobehavioral morbidity (O'Brien et al., 2003; Vinters et al., 2000). Subcortical axonal injury and loss might be key elements in VaD pathogenesis and progression (Medana & Esiri, 2003). The identity of the neuropathologic substrates of leukoaraiosis, which also affects subcortical white matter, is still controversial, but might include apoptosis of oligodendroglia (Brown et al., 2000).

VCI represents a paradigm shift from vascular dementia towards a much earlier state, characterized most commonly by a subcortical frontal and executive pattern of cognitive impairment, as opposed to the previous concept of an Alzheimer-based amnestic syndrome. The principal object of VCI as a concept is to facilitate case identification in this early stage, because progression may be preventable through modification of vascular risk factors (Bowler, 2007). Data on VCI are still relatively limited, because much of the research done over the past two decades has been based now on the outdated criteria for vascular dementia. To help resolve this, the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network have recently published comprehensive guidelines for research studies in VCI (Hachinski et al., 2006).

On the other hand, VCI is an evolving concept, and as our understanding grows, new questions arise (Chui, 2006; Merino, 2008). The development of a single, uniform set of criteria that apply to all subtypes of VCI has clearly been challenging, and some experts have recommended that separate criteria be developed for certain subtypes (Roman et al., 2002). (To be discussed in the next section).

5. Mild cognitive impairment (MCI) – Vascular cognitive impairment no dementia (VCIND)

Age-related cognitive change can be placed along a continuum from normal to severely demented, with intermediate stages of cognitive decline. To date, there is no consensus on where boundaries between disease and non-disease lie. Rather than a strict dichotomisation, the determination of impairment may instead be based on the likelihood or probability that ageing is not occurring in accordance with normative expectations (Stephan et al., 2009).

5.1 Mild cognitive impairment

The term mild cognitive impairment (MCI) broadly defines an intermediate state of cognitive decline, predominately linked to impaired memory function, which is thought to

be predictive of dementia, primarily Alzheimer's disease. Various definitions have been proposed in the literature, each with differences in focus- age associated change versus pathological decline, and diagnostic criteria - memory versus non-memory impairment, (Morris, 2006; Winblad et al., 2004).

As a possible tool for identifying individuals at increased risk of dementia, MCI is an important concept. Indeed, in clinical samples, individuals with a case diagnosis of the anmestic subtype of MCI (a-MCI) have been found to progress to dementia at a rate of 10% to 15% per year compared with a progression rate of only 1% to 2% in normal controls (Bruscoli & Lovestone, 2004; Petersen et al., 2001). In contrast, in the general population, the positive predictive validity of a-MCI is poor (Matthews et al., 2008). Many incident dementia cases are found to be excluded from an a-MCI case diagnosis, and of persons with a-MCI, many remain stable or revert to normal cognitive status at follow-up (Matthews et al., 2007). These findings are consistent across all MCI definitions-amnestic versus nonamnestic, and single versus multiple domains MCI- (Matthews et al., 2008).

No MCI criteria can be recommended for population screening of individuals at high dementia risk (Stephan et al., 2008). Poor predictability possibly results from limitations in case findings due to a lack of clinical judgement and inflexibility in operationalisation of criteria when a diagnosis of MCI is made outside the clinical setting. However, it has been suggested that MCI predictability may be improved through consideration of the underlying pathogenesis of cognitive decline (Tervo et al., 2004). Subclassification of MCI with and without co-morbid vascular disease may therefore be important for discriminating individuals at high versus low dementia risk in the general population (Stephan et al., 2009). To better identify the link between vascular disease and cognitive impairment, the term vascular cognitive impairment (VCI) was introduced (Bowler, 2007; Bowler & Hachinski, 1995; Román et al., 2004; Selnes & Vinters, 2006).

5.2 Vascular cognitive impairment no dementia

As already mentioned, vascular cognitive impairment refers to cognitive decline attributable to vascular disease. However, unlike mild cognitive impairment which is a narrow term capturing a pre-clinical form of dementia, vascular cognitive impairment encompasses individuals affected with any degree of cognitive decline caused by or associated with vascular disease and its risk factors. As such, the level of impairment in vascular cognitive impairment ranges in severity from mild cognitive impairment to vascular dementia or mixed vascular dementia, in which cerebrovascular and AD pathologies co-occur. Calls for more specific staging have recently led to further subclassification of vascular cognitive impairment to capture vascular disease-related impairment not fulfilling criteria for dementia. This stage is defined using the term vascular cognitive impairment no dementia (VCIND). Whether within VCIND there is a state predictive of dementia is largely unknown. Where longitudinal outcome across the spectrum of vascular cognitive impairment has been investigated, progression is not always clinical -that is, decline/dementia, with many cases improving or remaining stable at follow-up (Hsiung, 2006; Rockwood et al., 2007; Wentzel et al., 2001). Predictive ability may depend on the nature of the vascular disturbance in addition to methodological factors- case description, sample and nature of cognitive impairment.

As with MCI, terminology and diagnostic criteria for VCIND have not been harmonised, making cross-study comparison of disease outcomes difficult. Generally, the differential diagnosis between MCI and VCIND is clinical and based on the distinction between Alzheimer's disease and Vascular dementia. Alzheimer disease is characterised by a steady and progressive loss of memory and cognitive faculties, including language deterioration, impaired visuospatial skills and poor judgement. In contrast, the disease course of Vascular dementia is highly variable, generally following a stepwise pattern of decline and fluctuating course. For a diagnosis of Vascular dementia , it is recommended that radiographic features of vascular disease, including evidence of an ischaemic lesion, white matter hyperintensities and/or hypometabolism, be confirmed (American Psychiatric Association, 2000). Frequently both pathologies co-occur (Neuropathology group- MRC CFAS, 2001; Snowdon et al., 1997). AD and VaD may share associated risk factors (stroke, arterial hypertension, increasing age and low educational attainment), structural changes, neuropathological profiles (white matter lesions and apoptosis) and neurochemical changes (that is, in the cholinergic system) (Small et al., 2002). In older people, multi-morbidity is common and a strict dichotomisation between degenerative and vascular dementing disorders at both pre-clinical and dementia stages is difficult to undertake, possibly artificial and perhaps not the most useful approach.

5.3 Cognitive, neuroimaging and neuropathological profiles of MCI and VCIND

5.3.1 Cognitive profile

Neuropsychological studies have identified attentional executive deficits and psychomotor slowing, with relatively preserved language and recognition memory in individuals with vascular disease (Hachinski et al., 2006). However, not all studies agree on the importance of each cognitive domain and no single deficit or pattern of deficits as yet accurately signals an underlying vascular cause (Graham at al., 2004). For example, cognitive impairment as a consequence of stroke would likely depend on not only timing and the anatomical location of the stroke, but also the laterality, severity and extent of the lesion.

The focus of MCI is predominantly impaired memory, but deficits in other cognitive domains will also be observed when, by definition, they are also included. Subdivisions between different cognitive subtypes of MCI, amnestic versus nonamnestic, and single versus multi-domain, have implications for inference about aetiology and outcomes. Indeed, while a-MCI (Petersen, 2007) is thought to be a precursor of AD, nonamnestic subtypes of MCI have been found to identify individuals at high risk of both AD and VaD (Rasquin et al., 2005).

Where the cognitive profile of individuals with MCI and comorbid vascular disease has been compared with that of individuals with MCI and no vascular disease, group differences have been reported in some (Hayden et al., 2005; Nordlund et al., 2007), but not all studies (Loewenstein et al., 2006). Where differences have been observed, the MCI vascular group shows more extensive cognitive impairment primarily in speed, attention and executive function, (Nordlund et al., 2007) consistent with the general pattern of cognitive difficulties resulting from vascular disease alone (Román et al., 2004).

The specific type of cognitive impairment associated with vascular disease needs to be defined and measures that are sensitive, specific and appropriate for longitudinal and

observational assessment of cognition in the context of vascular disease (that is, memory versus non-memory domains) need to be identified in order to facilitate the development of diagnostic criteria for cognitive decline in the presence (VCIND) versus the absence (MCI) of vascular disease (Stephan et al., 2009).

5.3.2 Neuroimaging profile

Neuroimaging in VCIND shows a pattern of vascular lesions that are similar to, but less severe than, changes observed in VaD (Meyer et al., 2007). Pathology includes evidence of leukoaraiosis and white matter infarction (Vermeer et al., 2007), with mild hippocampal and entorhinal cortex atrophy relative to the level seen in MCI /AD (Meyer et al., 2007). In contrast, neuroimaging in MCI generally shows a pattern of changes similar to that observed in AD, namely temporal and hippocampal atrophy, reduction in whole-brain glucose metabolism and white matter degeneration, including hyperintensities and white matter lesions identified using diffusion tensor imaging (Assaf et al., 2008; Devanand et al., 2007; Johnson et al., 2006).

The severity and type of lesions required for a diagnosis of MCI and VCIND remain controversial. Vascular disease and its risks are associated with brain changes but the clinical relevance of such changes in the prediction of cognitive decline and dementia progression remains uncertain. Isolating unique disease effects from the effects of ageing and other risk factors (that is, genetic susceptibility) will be important in determining cellular/ molecular /functional vulnerability as a consequence of vascular disease as well as establishing with accuracy those changes that distinguish who will and will not develop cognitive decline and subsequent dementia (Stephan et al., 2009).

5.3.3 Neuropathology profile

MCI cases generally show an increase in neurofibrillary tangle pathology in memory-related cortical regions, including the entorhinal cortex, fusiform gyrus and temporal pole (Bennett et al., 2005). These changes are thought to represent one of the earliest pathological substrates of this condition and have been taken to suggest that many MCI cases are early or prodromal AD (Morris et al., 2001).

Whether there is a consistent neuropathological profile across the spectrum of vascular causes and severity levels of VCI is unknown but seems unlikely. Indeed, VCI is a multifactor disorder related to a wide variety of lesions and causes, and as such the pathological profile, similarly to the psychological and radiological profiles, would be expected to be heterogeneous. In autopsy studies, an increased prevalence of cerebral vascular pathology has been found in individuals with stroke, diabetes mellitus (Arvanitakis et al., 2006), angina with comorbid dementia (Andin et al., 2005) and hypertension (Petrovitch et al., 2000). Pathological features have included large- and small-vessel disease, gliosis, microvascular brain damage (severe cribriform change), white matter damage, microinfarction and haemorrhage (Kalaria et al., 2004). The profile of pathology across the different vascular disease factors is heterogeneous and the significance of such changes in the development of cognitive impairment is not known. Across the spectrum of age-associated brain changes, no neuropathological profile yet exists that reliably

distinguishes impairment of different severity levels and causes. In the general population, currently identifiable pathological features have not been found to correlate well with observed clinical and cognitive profiles: many non-demented healthy controls also show evidence of pathological brain changes associated with both AD and VaD (Jagust et al., 2008). Techniques that better characterise the impact of vascular disease on brain structure and more sensitive measures for accurately staging cognitive status which incorporate known risk factors are needed for diagnostic differentiation between an at-risk and a "not at-risk" brain. However, as with AD, expecting neuropathology to be a gold standard at any given age for the diagnosis of VCI is an oversimplification (Brayne, 1993).

6. Disease manifestations of vascular dementia

6.1 Symptom profile

VaD is an heterogeneous disease group with symptoms that vary according to the type of tissue damage, location, size and number of lesions. The main subtypes of VaD included in current classifications are cortical VaD (or MID) and subcortical vascular dementia (or small vessel disease related dementia) (Brun, 1994; Cummings, 1994; Roman et al., 1993; Wallin et al., 2003). The clinical presentation of cortical and subcortical forms of VaD show remarkable differences. Large vessel occlusions resulting in large cortical infarcts produce cognitive and other deficits that depend on the location of the infarcts, while subcortical vascular dementia may have a relatively characteristic neuropsychological profile that includes early impairment of attention and executive function, with slowing of motor performance and information processing (O'Brien et al., 2003; Roman et al, 2002; Roman & Royall, 1999).

Selected original publications show that executive dysfunction was the key factor underlying functional impairment (Boyle et al., 2002). Disturbances in frontal lobe functions were found to be more pronounced in patients with VaD than AD. Memory disturbances proved to be less pronounced early in the course of the disease than for AD. However, once the disease had progressed to a moderately severe level, the disturbances were just as pronounced as in AD. Executive dysfunction may also appear in AD patients, but it more resembles attention deficit disorder. In VaD, executive dysfunction more involves a fundamental inability to work out strategies and carry out tasks (Cannata et al., 2002). To obtain a greater understanding of the clinical manifestations, many authors have recommended a subtype classification of VaD (Chui, 1989; Erkinjuntti, 1987).

6.2 Small vessel disease and subcortical vascular dementia

Subcortical vascular dementia is the current terminology for severe cognitive impairment associated with small vessel disease (Erkinjuntti et al., 2000). Given its strong vascular component, it is believed to be more preventable than dementia of the Alzheimer's type. Subcortical vascular dementia results from lacunar infarcts or multiple microinfarcts in the basal ganglia, thalamus, brainstem, and focal and diffuse ischaemic white matter lesions (WMLs), and are associated with more than 50% of the VaD cases (Kalaria et al., 2004; Kalaria & Erkinjuntti, 2006). It represents the most homogeneous and probably most common, subtype of VaD (Chui, 2001).

Clinically, subcortical vascular dementia is characterised by pure motor hemiparesis, bulbar signs and dysarthria, gait disorder, variable depressive illness, emotional lability, and deficits in executive functioning; however, these focal neurological signs are often subtle. Upon imaging, patients have multiple lacunes and extensive WMLs and often reveal clinical history of "prolonged transient ischemic attack" (TIA) or "multiple TIAs" which mostly are small strokes without residual symptoms and only mild focal findings (e.g. reflex asymmetry, gait disturbance). This supports the importance of neuroimaging requirements in the criteria (Erkinjuntti et al., 2000).

Most studies on stroke associated with small vessel disease focus on motor impairment and mortality. Few studies have investigated the frequency of differering severity levels of cognitive impairment. Mok et al. (2004) evaluated consecutive patients with or without previous stroke who were admitted to the acute stroke unit. In this hospital based study, half of the patients with stroke associated with small vessel disease had varying severity of cognitive symptoms 3 months after stroke. Pre-stroke cognitive decline and previous stroke predicted severe cognitive impairment. Their findings highlight the importance of cognitive impairment, and in particular, executive dysfunction, in affecting the functional outcome of patients with stroke associated with small vessel disease.

The early cognitive syndrome of subcortical vascular dementia is characterized by a dysexecutive syndrome with slowed information processing, usually mild memory deficit and behavioural symptoms (Kramer et al., 2002; Roman et al., 2002). The dysexecutive syndrome includes impairment in goal formulation, initiation, planning, organising, sequencing, executing, set-shifting and set-maintenance, as well as in abstraction (Desmond et al., 1999). The memory deficit is usually milder than in AD, and is specified by impaired recall, relative intact recognition, less severe forgetting and better benefit from cues. Episodic memory may be relatively spared, compared with AD.There is more learning impairment that can be partially corrected by providing salient cues to encourage learning and promote recognition. Therefore, memory deficits in VaD appear to be caused by problems in retrieval of information (Sachdev et al., 2004); in turn, memory retrieval deficits are due to aberrant frontal and subcortical mechanisms. In contrast, in AD involvement of the hippocampus by neurofibrillary tangles prevents storage of new information causing amnesic mild cognitive impairment.

Eventually, cognitive impairment in small vessel disease may progress from mild to severe cognitive impairment. Behavioural and psychological symptoms in subcortical vascular dementia include depression, personality change, emotional lability, apathy, incontinence, as well as inertia, emotional bluntness and psychomotor retardation. These may include greater tendencies of aggression and agitation. Such symptomatology is attributed to damage to the prefrontal subcortical circuits (Cummings, 1993).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), is an example of familial subcortical vascular dementia that presents with recurrent subcortical strokes and slowly progressing course leading to cognitive impairment and dementia. This disorder is a rare cause of VaD, but is much more common than familial AD (Opherk et al., 2004).

Patients with subcortical VaD had more pronounced impairment than those with AD in their ability to deal with complex information, formulate strategies and exercise self-control.

The executive dysfunction of AD patients was mainly associated with attention deficit disorder and impaired working memory (Cannata et al., 2002). Patients with subcortical VaD have shown less pronounced episodic memory impairment, but more depressive symptomatology and greater variability in progress speed, than those with AD (Bennett et al., 1994). It has been suggested that patients with subcortical microvascular disease are the ones who later develop dementia that shows signs of mild cognitive impairment in the early phases of the disease (Meyer et al., 2002). A disturbance in the executive control function leads to global impairment of the ability to engage in everyday social activities and work, as well as the development of dementia. In addition to being a characteristic disturbance in VaD, there is much to suggest that executive dysfunction is the determining component in the dementia syndrome itself. Changes found by magnetic resonance imaging (MRI) in the subcortical area of patients with VaD showed an association with impairment of executive and psychomotor, but not global cognitive, capacity (Cohen et al., 2002; Libon et al., 2004).

6.3 Stroke

One way to obtain more specific information about VaD is to study cognitive ability in the course of the disease following an established stroke episode. In their recently published review, Leys et al. (2005) and Henon et al. (2006) summarized the previous studies that explored the impact of stroke on the risk of poststroke dementia. According to these studies, stroke increases the risk of dementia, with prevalence rates ranging from 6% to 32% within 3 months to 1 year after stroke, depending on the composition of the patient group and the choice of criteria for the dementia syndrome; and incidence rates of new-onset dementia after stroke ranging from 10% to 24% within 3 years and 15% to 33.3% within 5 years (Censori et al., 1996; Desmond et al., 2000; Kokmen et al., 1996; Tatemichi et al., 1992).

Studies that have examined the role of prestroke cognitive decline in the development of poststroke dementia have reported varying results. Pohjasvaara et al. (1998) found no difference in the proportion of demented and nondemented stroke patients with prestroke cognitive decline. However, Pohjasvaara et al. (1999) later reported that prestroke cognitive was positively correlated with poststroke cognitive decline. Barba et al. (2000) in a series of 251 consecutive unselected stroke patients found that 30% demonstrated dementia at 3-month follow up; and 10% had demonstrated dementia before the stroke. Reitz et al. (2008) in a prospective population-based study, with a mean follow-up time of 6.3 years between first assessment of cognitive function at baseline and time of incident first stroke, in which the slope of cognitive performance before stroke was also taken into account, and which had a nearly complete follow-up with respect to dementia, does not suggest that the prestroke level of cognitive function is a major determinant of the effect of stroke on the risk of poststroke dementia; an incident stroke doubled the risk of subsequent dementia independent of prestroke level of cognitive function and prestroke rate of cognitive decline. This finding contradicts previous studies reporting a higher risk of poststroke dementia in persons with prestroke cognitive impairment compared with persons with normal cognition before stroke (Gamaldo et al., 2006; Mok et al., 2004). In investigating patients during the acute phase, Henon et al. found signs of pre-stroke dementia in 15% of the cases. Gamaldo et al. (2006) study reported an increased risk of

poststroke dementia in persons with prestroke mild cognitive impairment. Barba et al. (2000) commented that the frequency of post stroke dementia depends on various factors such as the exclusion of hemorrhage or recurrent stroke, age range, length of follow-up, and diagnostic criteria. Srikanth et al. (2006) in the first prospective data on long-term cognitive transitions in a population-based first-ever stroke cohort, found that stroke recurrence was associated with an increased rate of long-term global cognitive decline after a first-ever stroke; stroke recurrence, early poststroke cognitive impairment, and increasing age were independently associated with diagnosis of new clinical dementia two years after a first-ever stroke.

The influence of the location of the vascular lesion in the development of dementia remains to be determined. A role of the left hemisphere has been suggested (Lin et al., 2003; Zhou et al., 2004). Poststroke dementia was also found to be more frequent in patients with a hemispheric stroke compared to brainstem/posterior fossa lesions and in patients with a pooled anterior/posterior cerebral artery stroke compared to other locations (Desmond et al., 2000). Many studies did not find any relationship between stroke location and risk of poststroke dementia (Ivan et al., 2004; Madureira et al., 2001; Rasquin et al., 2004).

Strategic infarction dementia is sometimes characterized as a special variety of post-stroke dementia. Isolated bilateral infarctions in the hippocampus can lead to dementia, but milder cognitive disturbances are more common. Bilateral thalamic, unilateral thalamic and basal frontal infarctions, as well as infarctions in the angular gyrus, non-dominant parietotemporal region and dominant hemisphere, are other strategically localized infarctions that reportedly cause dementia (Schmahmann, 2003). In addition to memory impairment, bilateral thalamic lesions yield apathy, attention deficit, and disturbances in wakefulness. Thus, involvement of the thalamus and bordering brain areas is often found. Effects on the extensive reciprocal thalamus-frontal and frontal reticular nerve connections may explain the discrepancy between the relatively limited lesions and the extensive symptomatology. Strategic infarction dementia has been called into question as a disease entity, given that the influence of other lesions is generally ignored (Pantoni et al., 2001). Stroke cause, vascular risk factors, hypoxic-ischemic disorders, radiological data of silent infarcts, cerebral atrophy, white matter changes also play a role in the development of poststroke dementia (Reviewed, Henon et al., 2006). The variation in cognitive status prior to the stroke episode and the development of cognitive dysfunction after stroke, as well as the variation of stroke-related and lesion-related characteristics that contribute to the development of dementia, suggest that post-stroke dementia is a heterogeneous condition for which factors other than the infarction formation itself are of importance.

7. Biomarkers

One of the most important goals of current research in AD is to develop and validate biomarkers, which can detect at an early stage individuals who are likely to develop AD. Important advance in this field have been made recently by the workgroup under the auspice of the National Institute on Aging and the Alzheimer's Association (Sperling et al., 2011). Referring to evidence of the underlying brain disease process as AD-pathophysiological process (AD-P), a biomarker model - solely intended for research

purposes at this time - adapted from the original graph proposed by Jack et al. (2010) has been recently proposed in which the most widely validated biomarkers of AD-P become abnormal and likewise reach a ceiling in an ordered manner. This biomarker model parallels the hypothetical pathophysiological sequence of AD, and is particularly relevant to tracking the preclinical stages of AD (Sperling et al., 2011). Biomarkers of brain Abeta amyloidosis include reductions in CSF Abeta 42 and increased amyloid tracer retention on positron emission tomography (PET) imaging. Elevated CSF tau is not specific to AD and is thought to be a biomarker of neuronal injury. Decreased fluorodeoxyglucose 18F (FDG) uptake on PET with a temporoparietal pattern of hypometabolism is a biomarker of AD-related synaptic dysfunction. Brain atrophy on structural magnetic resonance imaging (MRI) in a characteristic pattern involving the medial temporal lobes, paralimbic and temporoparietal cortices is a biomarker of AD-related neurodegeneration. Although solely intended for research purposes at this time, and pending the translation of research data into clinical practice, this biomarkers model represent an important step forward to advance the study of preclinical AD. Importantly, Lo et al. (2011) reported the result of a longitudinal study; a total of 819 research participants (229 with normal cognition, 397 with MCI, and 193 with AD) were enrolled for the Alzheimer's Disease Neuroimaging Initiative (ADNI) from 59 study sites in the United States and Canada during the period from 2005 to 2007. The authors concluded that trajectories of Abeta 42 level in CSF, FDG uptake, and hippocampal volume vary across different cognitive stages. The longitudinal patterns support a hypothetical sequence of AD pathology in which amyloid deposition is an early event before hypometabolism or hippocampal atrophy, suggesting that biomarker prediction for cognitive change is stage dependent.

For VaD, anatomical brain imaging helps determine the subtypes of VaD (hemorrhage versus ischemia, cortical versus subcortical, strategic infarction versus multi-infarction, large vessel disease versus small vessel disease) and thereby enhances our knowledge of vascular disease processes. Anatomical brain imaging has played a particularly large role in demonstrating small vessel-related white matter changes, evidence of leukoaraiosis and white matter infarction, with mild hippocampal and entorhinal cortex atrophy relative to the level seen in AD (Vermeer et al., 2007). Studies of neurochemical markers for VaD and its subtypes are considerably fewer than those on patients with AD. After acute ischemic stroke the CSF tau protein level is normal for one or two days, after which it increases and peaks after 2–3 weeks. The effect then subsides, and the values normalize after 3–4 months (Hesse et al., 2000). Several studies have shown a significant increase of phosphorylated tau in the fluid of AD patients, while the levels are normal in VaD patients (Blennow & Vanmechelen, 2003). Impaired BBB function occurs in patients with VaD, particularly subcortical VaD (Wallin et al., 2000). The impaired function probably reflects disorders in the arterioles, although the capillary level may also be compromised. Neurofilament, another cytoskeletal component, is concentrated in large myelinized neurons. The greatly increased neurofilament light subunit (NFL) in the CSF that has been found in patients with subcortical VaD has been associated with the presence of white matter changes (Wallin et al., 2001); while CSF-NFL has been shown to be normal in patients with pure AD. Knowledge of neurochemical markers may also be important to understanding mixed dementia (Rockwood et al., 2000).

8. Conclusions

The dominant view in the literature is that the symptom profile for vascular dementia differs from that of Alzheimer's disease. Vascular dementia is characterized by mental slowness; impaired initiative, planning, and executive function impairment; personality changes; and gait disorders. Thus, methodological advances aimed at identifying and measuring the severity of the cardinal symptoms of mental slowness and executive dysfunction and better clinical criteria, are needed for vascular dementia to help us reliably distinguish it from Alzheimer's disease.

Greater attention should be paid to vascular mechanisms and subtypes. The few studies that have attempted to consider the full range of cerebrovascular lesions have found them to be common, particularly the subcortical, small vessel disease and white matter damage that increasingly appears to be among the key factors underlying the origin of vascular dementia. Further studies are needed to identify the pathological changes that are most important in the disease and as a result, neuropathological criteria and examination methods need to be specified and standardized. Anatomic brain imaging is a good deal more reliable in helping to identify vascular lesions than Alzheimer's lesions, which is still under ongoing screening. The clinical criteria systems need to be modified and made more specific in the vascular dementia field.

Although much remains to be done, the ongoing process of revision of clinical criteria, the refinement of neuropathologic studies, the progress in biomarkers development with disease stage specificity including the preclinical one; along with identification, validation and refinement of predictors of cognitive decline and dementia, will pave the way for a very promising and hopeful future, in the prevention, treatment and management of Alzheimer's disease and vascular dementia. Earliest stage interventions may be the most efficacious.

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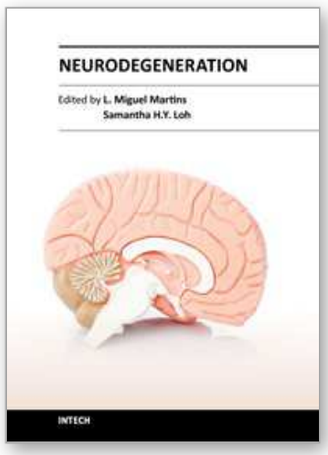

Neurodegeneration

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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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