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Vascular Cognitive Impairment

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LESSON SUMMARY: Cognitive impairment of vascular cause, henceforth referred to as Vascular Cognitive Impairment (VCI), refers to any type of cognitive or behavioral impairment that results from cerebrovascular disease, regardless of its severity and impact on the person's functionality. Vascular Cognitive Impairment, as a broad concept, encompasses associations of other etiologies, including mixed etiologies. In its most severe form - Vascular Dementia (VaD), it implies a significant loss of function and behaves as a degenerative pathology which is therefore progressive. Vascular dementia is the second most common cause of dementia (after Alzheimer's disease), but its prevalence is uncertain. Although cognitive impairment caused exclusively by vascular pathology is uncommon, vascular pathology is often associated with other degenerative pathologies, especially with advancing age. Cognitive impairment resulting from the vascular component is often underdiagnosed, especially in its mild stage, as it is typically characterized by alterations in executive functioning, attention, processing speed, and less memory alterations. As it is a potentially preventable clinical entity, there is an urgent need to promote better knowledge of the disease and its identification. Cognitive assessment should be targeted at the defects mentioned, as the screening measures and global cognitive assessment commonly used (designed mainly with Alzheimer's disease in mind) may not be enough to detect them. Structural imaging tests are essential for diagnosis. There are no other biomarkers (apart from imaging) that can identify VCI in any of its stages, whether mild or more advanced. There are no approved therapies for the condition, and intervention should be aimed at vascular prevention and promoting better vascular health of the brain and better protection against injury.

KEY WORDS: Vascular Cognitive Impairment, Vascular Dementia, Cerebrovascular Disease, Cognitive Impairment, Executive Functioning, Vascular Pathology

Previous considerations

This lesson has not been designed for any particular audience. It is intended to be clear and simple to understand, but also thoughtful and cover the most recent and innovative aspects of the subject, including current research projects, so that it can inspire future lines of research.

This lesson could be adapted to integrate postgraduate training programs, for example in one of the PhD courses at the Faculty of Medicine of the University of Lisbon - the Neurosciences Doctoral Program or the Doctoral Program of the Academic Center of Medicine of Lisbon (CAML).

A comprehensive overview is given of the concept of Vascular Cognitive Impairment. Its evolution, the personal contributions and those of our working group to better understand the clinical condition and the diagnostic approach and intervention are highlighted. These contributions include participation in groups and in national and international studies, as well as the publications on the topic. In the field of research, Vascular Cognitive Impairment due to small cerebral vessel disease is covered in more detail, as it has been a major focus of our research.

CHAPTER 1
CONTEXTUALIZING THE CONCEPTS AND KNOWLEDGE OF PATHOLOGY

Conceptual evolution: from Dementia to Vascular Cognitive Impairment

Vascular dementia (VaD) has been known for several centuries, with historical accounts varying according to the sources[1]. It is possible that the first explicit reference was made by Jason Pratensis in the 16th century, in what is considered to be the first book dedicated to general neurology, *De Cerebri Morbis*[2], followed by Tomas Willis' descriptions in the 17th century, with the name *Dementia postapoplexya*. However, it truly became known just over a hundred years ago, when Otto Biswanger, Alois Alzheimer and Pierre Marie described, at the end of the 19th century and the beginning of the 20th century, patients with the clinical picture and neuropathological alterations characteristic of cerebral vascular pathology. Following these descriptions, Emil Kraepelin introduced the term *Arteriosclerotic dementia*. In 1894, during a conference in Dresden, Otto Biswanger described the macroscopic findings associated with a progressive clinical picture that he considered rare, distinct from that caused by syphilis, and called it *Encephalitis Subcorticalis Chronica Progressiva*[3,4]. It should be noted that, at this time, Biswanger described with particular emphasis the severe atrophy of the cerebral white matter, which in this form of the disease was mainly located in the occipital and temporal regions. The atrophy was associated with enlargement of the ventricular cavities, especially in the inferior and posterior horns. At the time, the frontal lobes seemed to be relatively spared, and the cortex had minimal involvement, so he justified his findings with a "diffuse nutritional" problem. The clinical picture consisted of progressive cognitive loss, with focal signs such as aphasia, visual alterations, unilateral motor or sensory defects. These focal signs fluctuated over time and co- existed with seizures. The condition began at the age of 50 and lasted at least 10 years, with periods of clinical stability[4,5]. At the same time, Otto Biswanger also described conditions resulting from atherosclerosis of large cerebral arteries - *Atherosclerotic Brain Degeneration*, and from embolic or thrombotic lesions of the arteries, which caused cerebral infarcts, calling them *Dementia Post Apoplexiam*, associated with acute lesions. In 1902, Alois Alzheimer used the term *Biswanger Disease* and histologically described the existence of neuronal loss, demyelination and sclerosis of the small perforating arteries of the cerebral white matter, with concomitant lesions in the white matter, internal capsule, lenticular nucleus, thalamus and protuberance, without alterations in the cerebral cortex[4]. Curiously, Alois Alzheimer already postulated the existence of an entity (in addition to those proposed by Biswanger) that he called *Senile Cortical Atrophy*, characterized by cortical small vessel disease, characterized by small wedge-shaped cortical infarcts, associated with gliosis and softening of some circumvolutions, which became severely atrophic and with indentations in the cortex[4]. At the time, he admitted the existence of mixed cases in its etiopathogenesis, as well as describing cases with very typical characteristics[4,6]. It should be noted that Pierre Marie had described *État criblé* in 1901, corresponding to the disease of small perforating vessels[5]. It should be noted that it was only much later, in 1974, that Hachinski introduced the term *multi-infarct dementia*[7], despite the concept already being subliminally understood beforehand.

As can be understood from the brief description above, which is not without controversy, cognitive impairment caused by cerebral vascular disease has been accepted as a clinical entity distinct from Alzheimer's disease for over a hundred years, and its histopathological characteristics were already well known[8].

In recent decades, evidence has emerged to support the broader concept of cognitive impairment of vascular cause (henceforth referred to as Vascular Cognitive Impairment - VCI), which encompasses any type of cognitive impairment, regardless of the severity of the cognitive condition, resulting from cerebral vascular disease, ranging from cognitive impairment without criteria of dementia (Mild Cognitive Impairment of Vascular etiology - MCIVasc) to impairment with functional and autonomy impairment (Vascular Dementia - VaD, or major neurocognitive disorder of vascular etiology, depending on the criteria used)[9-14]. On the other hand, the concept of cognitive impairment of vascular etiology encompasses the whole spectrum of vascular pathology (in the diversity of cerebral vascular pathologies) to vascular contributions in other cognitive pathologies, often referred to as "mixed etiologies", i.e. in concomitance with other degenerative pathologies. This entity is considerably more useful clinically than the "traditional" VaD and allows for the identification of patients at a time of mild pathology, and where, from a theoretical point of view, a preventative intervention effort is possible. On the other hand, the identification of cerebral vascular pathology in other pathologies (particularly common in Alzheimer's disease, but let's not forget other etiologies such as Lewy body disease) [15,16] allows for better prevention even in the case of other degenerative diseases[17].

Therefore, the investigation of a patient with cognitive impairment should always be an opportunity to detect concomitant vascular pathology and an opportunity for better prevention. For this reason, in a joint European initiative, and under the auspices of the *European Stroke Organization* (ESO), I was able to lead a recent publication with suggestions for a very practical approach, dedicated to identifying and guiding the diagnosis of cerebral vascular pathology in patients being investigated for cognitive complaints[18].

Diagnosis and diagnostic criteria

Vascular Cognitive Impairment is a very heterogeneous entity, both in its clinical manifestations and in the diversity of cerebral vascular lesions that can cause it, which includes the location of the lesion/lesions and their severity, and the form of onset (from the acute to the more chronic form).

Turning now to vascular dementia, it is important to remember that dementia syndrome implies a loss of cognitive abilities (reflecting a clear decline from a previous level), and this loss has repercussions on professional, family or social life, with a corresponding loss of autonomy[9,10].

To make a diagnosis of VD or major neurocognitive disorder due to cerebrovascular disease, it is necessary to have dementia syndrome (with a characteristic cognitive profile), imaging evidence of cerebrovascular disease, and a possible association between the observed cerebrovascular pathology and the clinical picture, in addition to excluding other causes of dementia[9, 10].

For more than 30 years, there have been various criteria, which I will refer to as "classic" VaD, which have tried to encompass the three aspects mentioned[9,10,19,20]. The classic clinical criteria for VaD have several limitations. One of the biggest limitations of these more traditional criteria was the neuropsychological model used, often influenced by the Alzheimer's disease model in which memory deficits predominate[9,10]. Another limitation came from the definition of vascular pathology and its relationship with cognitive impairment, which was often limited to a temporal relationship, which did not include more chronic forms of damage, such as small cerebral disease. An effort was made to make the criteria more adapted to the pathology. However, there were still limitations, particularly in terms of their ability to identify cases, i.e. their specificity and their sensitivity. The criteria of the *Alzheimer's Disease Diagnostic and Treatment Centers* (ADDTC)[20] take up the historic Haschinski scale (*Hachinski Ischemia Score*)[1] [21] and adapt the neuropsychological profile, no longer making memory impairment mandatory. In the criteria of the *National Institute of Neurological Disorders and Stroke* (NINDS) and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (AIREN) - NINDS-AIREN, although the profile should include alterations more typical of vascular disease, the memory impairment remained mandatory[19]. Both the ADDTC and NINDS-AIREN criteria include the possibility of a possible or probable diagnosis and the definition of

1 The Hachinski scale was originally developed to help differentiate between multi-infarct dementia and Alzheimer's disease and has become a useful clinical and research tool.

the necessary neuroimaging. Some of the studies that evaluated the clinicopathological correlation and compared the diagnostic identification capacity between these different criteria found a low probability of a patient being simultaneously identified by the various criteria, i.e. low reproducibility[22-24]. In addition, half of the patients who met the neuropathological criteria for Vascular Dementia did not have a clinical diagnosis of Vascular Dementia because they did not meet the diagnostic criteria, particularly regarding the temporal relationship between the clinical picture and the vascular lesion[25,26]. The evolution of the concept of Vascular Cognitive Impairment went hand in hand with the evolution of the diagnostic criteria proposed for cognitive impairment due to cerebrovascular disease, which, although not overlapping and still not consensual, very broadly designate the same entity. Various criteria have been proposed[12,13,27,28]. Recently, an international group of experts, in which we participated, drew up a consensus on this definition[12,28]. This consensus, like others based on the opinions of experts in the field, has made a clear effort to define the cognitive condition and the underlying vascular pathology, but it still lacks clinical validation in prospective studies and lacks neuropathological validation[12,13,27,28].

Trying to address the prevalence

In general, Vascular Dementia is the second most frequent cause of dementia and is generally attributed to around 20% of dementia cases[13]. The prevalence is highly dependent on studies, varying between 8 and 15% in the community, and between 0.03 and 58% in anatomopathological studies[29] with an incidence rate varying between 0.42 and 2.86%, increasing with age, and doubling in prevalence every 5.3 years after the age of 65[30,31]. The epidemiological data on cognitive impairment caused by vascular pathology is particularly difficult to interpret, due to all the aspects mentioned above, in addition to the difficulty in capturing the prevalence of cerebrovascular disease as a contributor to cognitive impairment with a mixed etiology[32]. Although it is very common with ageing, especially when co-existing with other pathologies[30], cerebrovascular pathology in isolation (or so-called "pure", without any other mark of degeneration) is not very common as an etiology of cognitive impairment, especially in the brains of older people. For this reason, there is enormous variability in the data available, depending on the methodologies used[33,34]. It is therefore possible that estimates of cognitive impairment caused exclusively by vascular pathology do not reflect the magnitude of the impact of vascular pathology on cognitive impairment in general, and dementia in particular. In our country, the prevalence study using the methodology of the "10/66 Dementia Research Group"[35] estimated the prevalence of dementia in the community at 9.23% (95% CI 7.8-10.9)[36], a much higher figure than would be obtained using the *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM) classification[9]. The estimated proportion of cases of vascular dementia was 16.3% (including 10.9% of "pure" cases and 5.4% of "mixed" cases with associated Alzheimer's disease). However, it should be noted that in 30.2% of the cases identified as "dementia" by the 10/66 DRG algorithm, we were unable to assign a specific subtype diagnosis. Despite the few studies in our country[35,37,38], the predominant impact of vascular risk factors on patients with cognitive impairment has recently been emphasized[37]. Internationally, depending on the type of studies and the criteria, prevalences of between 4.5% and 48.5% are found for isolated vascular disease in clinical studies, the highest in Japan for small vessel disease over the age of 65[39]. In anatomopathologically confirmed studies, the variability is also marked, with an average of 11% (ranging from 8 to 35%) of pure vascular disease in neuropathological studies[29], and concomitant disease with other degenerative pathology between 10 and 12%[40], making up to 25% of the vascular contribution from a neuropathological point of view[41]. In the *Rush Memory and Aging Project*, a longitudinal study with neuropathological assessment, Schneider and colleagues found a vascular contribution in 54% of the patients who developed dementia, with only 12% having isolated vascular pathology[33]. Also in neuropathological studies, in a 30-year retrospective study, Brunnström and colleagues found that vascular dementia existed in 23.7% of patients, while the combined etiology of vascular disease and Alzheimer's disease was reported in 21.6% of patients[40].

CHAPTER 2
CLINICAL ASPECTS OF VASCULAR COGNITIVE IMPAIRMENT

Vascular Cognitive Impairment can present phenotypically in different ways, which is due, on the one hand, to the diversity of vascular etiologies and the heterogeneity of the lesions, and on the other hand, to the

way in which these vascular pathologies can manifest themselves (abrupt or progressive).

Annex 1 summarizes the possible etiologies of Vascular Cognitive Impairment. When cognitive impairment occurs after a stroke, the impairment may be immediate (in the case of lesions in strategic areas)[42] or it may appear progressively after the stroke and is referred to as post-stroke cognitive impairment. Vascular lesions can be of different types, ischemic or hemorrhagic, single or recurrent. They can correspond to situations such as venous thrombosis or subarachnoid hemorrhage, arise because of vascular events in a post-traumatic context, be the consequence of small perforating vessel disease, or even compromise cerebral circulation and oxygenation secondary to systemic pathology or genetically determined diseases.

The difficulty created by these various clinical conditions, and the multiplicity of aspects linked to them, led to a European initiative with the production of a document with a practical clinical approach, in which the cognitive profile in patients with cerebral vascular disease was emphasized, as well as suggestions for guiding these patients[43].

In this lesson, we will look in more detail at the clinical aspects of Vascular Cognitive Impairment due to small vessel disease, as it is the most common form of the disease and the one to which our research group has been most dedicated. Post-stroke cognitive impairment is also addressed, as it is the next most common form of VCI and represents a good example for understanding the underlying mechanism.

The clinical presentation

When there are no focal signs resulting from vascular lesions, or a clear previous cerebrovascular episode (as is the case with VCI due to small vessel disease), the vascular cognitive impairment can be particularly difficult to identify. In the early stages of the disease, symptoms are dependent on the involvement of cognitive domains such as mental processing speed, attentional capacities and executive functioning, with difficulty in tasks mediated by programming and planning, as well as a reduction in initiative, affecting memory-related processes to a lesser extent, as is the case in Alzheimer's disease[44-46]. It should be noted that the involvement of memory does not exclude the possibility of diagnosis[44]. Since it can develop very slowly, the condition may not be noticed until the advanced stages of disability, and in the early stages it can be mistaken for the ageing process itself. It should be noted that these patients typically have no subjective complaints[46], which can make it even more difficult to suspect the diagnosis. In the LADIS (*Leukoaraiosis and Disability*) study[2], we found that the participants included in the first assessment who had subjective memory complaints (and who were completely autonomous in activities of daily living) performed worse in the neuropsychological assessment, especially in memory measures (even if they were within normal parameters)[47]. In these same participants, there was no correlation between these complaints (and their neuropsychological assessment) with the severity of cerebrovascular lesions[47]. Over time, we found that these same participants with memory complaints had, after three years, an increased risk of progressing to Alzheimer's disease and not to Vascular Dementia[48]. The vascular cognitive condition can often be attributed to other co-morbidities, such as depression. This aspect seemed particularly important to us, and we have shown that depressive symptoms can themselves be a hallmark of vascular pathology[49] and are associated with an increased risk of cognitive impairment. In the LADIS study, we confirmed that, in patients with evidence of cerebral small vessel disease, depressive symptoms were associated with an increased risk of cognitive decline and progression to dementia after three years of follow-up[50]. For this reason, the study of a patient with suspected VCI must necessarily include an assessment of neuropsychiatric symptoms[43].

It's not surprising, given all the aspects mentioned, that the global measures of cognition usually used may not be sensitive to identifying these cognitive conditions[43]. The *Mini Mental State Examination* (MMSE)[51], although a very useful and well-known instrument, may represent a particular limitation, as it focuses mainly on memory and language. The *Montreal Cognitive Assessment* (MoCA)[52], which includes items designed to assess functions other than memory and language, would be additionally useful. However, the fact that it is highly dependent on the level of education and literacy requires that the results be carefully integrated into the clinical context. For these various reasons, patients suspected of having VCI should un-

2 The LADIS (Leukoaraiosis and Disability) study, European multicenter study in which we participated, with European funding, sought to investigate the impact of age-related vascular changes in the white matter (one of the manifestations of cerebral small vessel disease) on disability over time. Our group was responsible for standardizing and coordinating the cognitive component throughout the study.

dergo formal neuropsychological assessment, whenever it is accessible and feasible. The neuropsychological assessment must include an evaluation of the cognitive domains most affected[43]. In the LADIS study, we developed a neuropsychological battery specifically designed for this type of patient[53], which was developed with the particularity that it could be implemented in several European countries, and whose validity we confirmed through a confirmatory factor analysis[54], and which was used on the participants in the LADIS study throughout the three years of follow-up. Over the last two decades, various batteries for assessing Vascular Cognitive Impairment have emerged, and in the work already mentioned, in the context of the *European Stroke Organization*[43], we made a very practical application suggestion based on the experience of various European groups in this field. However, it is important to point out that, in the absence of access to formal neuropsychological assessment, global cognition assessment measures continue to be used. As we showed in the LADIS study, the global measures of cognition used in that study were important predictors of dementia after three years of follow-up in people with evidence of changes in small vessel disease[55]. Additionally, and in the group of Portuguese participants included in our center, we showed that the MMSE was the most useful instrument for predicting dementia after 10 years of follow-up[56].

The identification of the clinical picture is therefore highly dependent on the existing suspicion and knowledge of the disease, on the one hand, and on the other, the sensitivity of the clinician approaching the patient. The interview should be detailed, gathering additional information on non-cognitive alterations. There is currently some evidence that the neuroimaging findings of small vessel disease are associated with a range of clinical manifestations, suggesting a phenotype of multi-system involvement, a field that is certainly yet to be explored[57]. Among the symptoms most classically associated with Vascular Cognitive Impairment caused by cerebral small vessel disease, non-cognitive motor symptoms are frequent[58], with gait changes[59] (usually short strides), frequent falls and increased lower limb tone, hypophonia, dysphagia and altered fine movements[58]. Another frequent symptom is urinary control dysfunction. In the LADIS study, we showed how participants with severe cerebral small vessel pathology, at a time when they were still autonomous, without significant cognitive decline, had complaints about urinary control, particularly urinary urgency[60]. Recently, in a systematic review, our group showed that moderate to severe alterations of cerebral white matter are associated with complaints of overactive bladder and incontinence with urinary urgency[61, 62], and a detailed evaluation of these complaints is currently under investigation.[3]

Imaging assessment

Neuroimaging is fundamental to the diagnosis of VCI. Structural imaging lesions consist of sub-cortical or cortical ischemic lesions of different sizes, hemorrhagic lesions, changes due to small vessel disease - such as cerebral white matter changes, lacunae or microhemorrhages. Some aspects are more specific to certain etiologies, such as cortical microhemorrhages and superficial cortical siderosis, for example, which are particularly associated with cerebral amyloid angiopathy. In the LADIS study, we showed how moderate to severe cerebral white matter changes (considering the Fazekas visual scale, which defines three severities - mild, moderate and severe)[63] and lacunes[64], considering their location particularly in the subcortical gray matter, were associated with worse cognitive performance[65], both in global cognitive measures[66] and in measures of mental processing speed, attention and executive functioning in autonomous people with evidence of cerebral small vessel disease[65]. In these patients, atrophy co-exists, even cortical atrophy, with subcortical atrophy being more characteristic. We also found that corpus callosum atrophy was associated with cognitive decline and a decline in motor skills over time[67]. It is possible that corpus callosum atrophy is a mechanism involved in the decrease in psychomotor speed, as it is associated with altered communication of inter-hemispheric information between homologous cortical areas[68]. In view of our findings, we also believe that there is a synergistic effect between cortical atrophy and the severity of white matter alterations, which determines cognitive deterioration in these patients[69]. Atrophy can be diffuse or focal after localized vascular lesions[43]. However, brain atrophy profiles with more focal characteristics should lead to the suspicion of other neurodegenerative diseases, such as atrophy of the internal temporal lobes in Alzheimer's disease or fron-

3 PhD project underway at CAML entitled Age-Related White Matter Changes and Lower Urinary Tract Dysfunction - One Step Towards OverActive Bladder Phenotyping (OSTOAP Study), doctoral student: Dr. Ricardo Pereira da Silva.

totemporal atrophy in frontotemporal lobar degeneration[43].

The most sensitive structural test for identifying cerebral vascular pathology is brain magnetic resonance imaging (MRI). If this is not possible, computerized axial tomography (TC) is clinically useful. When magnetic resonance imaging is performed, the appropriate sequences for identifying vascular pathology must be included. Annex

2 provides a schematic presentation of the information that can be provided by each sequence, which is commented on below. In addition to the 3D T1 and T2 sequences, the FLAIR (*Fluid Attenuated Inversion Recovery*) sequence should be performed to detect small cortical infarcts and accurately assess changes in the cerebral white matter, and also the SWI (*Susceptibility-Weighted Imaging*) sequence or Gradient Echo or T2* to detect microhemorrhages, superficial cortical siderosis (both of which are again usually missed on CT) and even old macrohemorrhages. Finally, the diffusion sequence (DWI - Diffusion-Weighted Imaging) is essential for detecting acute lesions, especially if they are small[43]. In the LADIS study, the alterations found in the diffusion sequences, in apparently normal brain tissue in the other sequences, were associated with a faster decline in cognitive processing speed, executive functions and working memory, as well as greater functional incapacity and increased mortality[70]. More recently, and with a view to research in the context of clinical trials, we took part in drawing up a guiding document for the use of cognitive instruments in clinical trials, particularly designed for small vessel disease and based on the literature published in this area, called Structure for Clinical Trials in Small Vessel Brain Diseases (FINESSE)[4][71]. Following on from this initiative, and in line with previous work, the use of additional sequences is suggested, namely the Diffusion Tensor sequence (DTI, encompassing fractional anisotropy - FA and mean diffusivity - MD), which allows subtle losses of tissue microstructural integrity to be assessed in regions where conventional MRI sequences are normal[57]. These losses of microstructural integrity correlate with cognitive ability, which could make it possible to identify patients with very early disease and, as such, those who can be better and more effectively intervened in clinical trials[73, 72].

MRI is also better at distinguishing other pathologies such as inflammatory demyelinating lesions, vasculitis, infectious, metabolic (ionic), toxic processes, and changes more typical of some genetic vascular pathologies (such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy - CADASIL, and adult leukodystrophies).[43]

The lesion pattern of the vascular disease can also guide the diagnosis. A high lesion load of white matter changes, lacunes and microhemorrhages in the basal ganglia suggests the effect of vascular risk factors, particularly hypertension. Severe cerebral white matter disease with extension to the temporal lobe, associated with lacunes, in younger patients suggests a monogenic disease (such as the afore mentioned CADASIL). Multiple cortical infarcts, especially in multiple cortical territories, suggest a cardioembolic source. Subcortical and basal ganglia microhemorrhages are typical of arterial hypertension, while their lobar location at the cortico-subcortical junction is more indicative of cerebral amyloid angiopathy, especially if associated with superficial cortical siderosis[43].

Implications for the identification of cerebral small vessel disease

The prognosis of cerebral small vessel disease, which is manifested by the clinical picture described above, which is indolent and slow, can be very unfavorable[74]. The LADIS study has shed more light on the impact of small vessel disease on cognition and the transition from a state of health to a state of dependence.[5] In this same study, we found that severe white matter alterations were associated with worse cognitive performance in global cognitive functions, executive functions, attention and motor speed[65]. In a 3-year follow-up of this same population, we confirmed that severe white matter changes were a poor prognostic factor for cognitive decline over time, tripling the risk of progressing to dementia after three years[73]. In this population, *de novo* lacunes[76] and worsening global atrophy[77] were also associated with progression to cognitive impairment. Erkinjuntti proposed specific research criteria for subcortical ischemic vascular disease[78]. Using Erkinjuntti's criteria[78,79], we found that small vessel disease was associated with poorer performance in cognitive processing speed, attentional abili-

4 The Framework for Clinical Trials in Small Vessel Brain Diseases (FINESSE) was created under the aegis of the International Society of Vascular Behavioral and Cognitive Disorders.

5 The participants in the LADIS study cohort, aged over 65, were autonomous and had no significant cognitive defects when they were included in the study.

ties and executive functioning, as well as poorer verbal fluency[80]. Over the three years of follow-up, an acceleration of decline was observed, especially in mental processing speed and cognitive functioning, as well as in global measures of cognition[81].

Cognitive impairment after acute vascular injury

The study of cognitive impairment secondary to acute cerebral vascular injury, which is the second most frequent cause of cognitive impairment due to vascular pathology, is a good model for highlighting the vascular mechanism as a cause of cognitive impairment and is not only limited to strategic infarcts.

The recognition of cognitive impairment after acute vascular lesions has been complemented in recent years by the identification of an increased risk of cognitive impairment even after transient lesions (Transient Ischemic Attack - TIA), underlining the role of vascular disease as a phenomenon that goes beyond the scope of focal lesions[82].

In the case of cognitive impairment following acute vascular injury, it should be borne in mind that isolated sequelae (such as aphasia) can imply functional impairment even without being sufficient criteria for dementia and can remain relatively static over time.

On the other hand, the sequelae defects (e.g. motor, sensory, visual) of a vascular injury can make it difficult to perceive the existence of a functional defect secondary to cognitive decline and can make it more difficult to identify. In addition, depressive symptoms are common after a stroke[83]. In a prospective study of stroke survivors, we showed how the presence of these same symptoms can already indicate an evolution towards cognitive impairment[83].

Acute vascular injury produces damage to a specific area of the brain, with focal signs and symptoms associated with that damaged area. Additionally, in the hyperacute phase (a concept closely associated with reperfusion therapies, and which covers the first few hours after the stroke)[84], there is a process that some authors call *transient cognitive impairment*, for which a possible inflammatory or cholinergic etiology is postulated, reactive to the acute vascular injury[85,86]. This transient condition seems to be distinct from confusional syndrome or *delirium*, a well-known condition in the acute context of stroke, which our work group described more than two decades ago[87]. Although it still lacks a definition of its own, *transient cognitive impairment* is broader in its symptomatic expression, not only reflecting the manifestation of the focal lesion area, and its prognostic value is still unclear[85,86]. After the acute phase, the focal vascular lesion can be associated with cognitive deterioration with two different evolutions. These developments may reflect two different mechanisms, which is why they will be briefly discussed below. On the one hand, a progressive deterioration over time after the acute vascular event, which may represent a form of anticipation of degenerative dementia due to the stroke. This mechanism has been epidemiologically supported by the fact that the risk of a dementia diagnosis doubles in stroke survivors compared to people who have not had a stroke[82]. These diagnoses of dementia shortly after a stroke (even if they don't involve a strategic area for cognition) share characteristics with Alzheimer's disease, and the presence of the APOE ε4 genotype has been identified as a factor that increases the risk of post-stroke cognitive impairment, as well as the presence of brain and temporal lobe atrophy[82,88-90]. On the other hand, there is a distinct evolution, characterized by an initial phase of recovery from the vascular lesion, with stabilization for some time, followed by a later decline, which is more frequent in patients with recurrence or multiple stroke locations. Levine and colleagues found in a sample of 23,572 participants (515 of whom had had a stroke) how stroke was associated with cognitive loss associated with the acute event, but above all with deterioration over the years after the stroke, both in global measures and in executive functioning, and how this evolution was different from people who had not had a stroke[81]. The same type of trajectory was described in a sample based on nine longitudinal hospital cohorts from seven different countries, published by Jessica Lo and colleagues[92] in 2022, finding that in 1,488 stroke survivors (from an initial sample of 2,295) followed over time there was an initial period of improvement in the first year after the stroke, followed by a decline in global cognition, with the most marked progression being associated with stroke recurrence and advanced age. Several studies have investigated whether amyloid pathology could be the determining factor in post- stroke cognitive decline, having carried out positron emission tomography (PET) with radiopharmaceuticals labeling the amyloid peptide in stroke survivors. In these studies, they found that most of these stroke survivors who developed dementia in the years after the stroke did not have amyloid uptake suggestive of concomitant Alzheimer's

disease[93-95]. Using advanced magnetic resonance imaging methods, Duering and colleagues found aspects compatible with remote neurodegeneration after subcortical vascular lesions, causing a focal reduction in cortical thickness and loss of white matter[96], with a poorly understood mechanism, possibly due to an inflammatory reaction[97] or synaptic damage[98]. This phenomenon has been understood as a process of distant disconnection and has been investigated[99]. Some studies carried out on experimental animals (which are clearly outside the scope of this lesson) have sought to replicate this same mechanism[100]. Finally, there is no evidence to support that vascular pathology is a trigger for the formation of amyloid plaques, despite the frequent co-existence of the two pathologies, especially with advancing age[101].

While the degenerative phenomenon that occurs in many stroke survivors remains unexplained, the existence of partial or temporary reversibility that is observed in patients with cognitive impairment of vascular cause is well accepted, and an additional motivation for identifying this entity with the aim of intervening. Unlike the typical fluctuations of Lewy body disease, which oscillate around a progressive deterioration plan, and contrary to the usually progressive and continuous evolution of Alzheimer's disease, patients with vascular pathology do have a possibility of reversibility when the lesion is in the context of an acute stroke[102], or even in a systemic vascular context[103].

CHAPTER 3
PREVENTION AND TREATMENT

Risk and protective factors

In recent decades, observational epidemiological studies have suggested that vascular risk factors contribute to cognitive decline and dementia, not only for VCI, but also in Alzheimer's disease[104]. Livingston and colleagues had previously found that up to 40% of dementia cases could be attributed to potentially modifiable factors, most of which were vascular risk factors[105]. Recently, in the update of this same document produced by the *Lancet Commission*, the addition of two more risk factors to the twelve previously identified led the authors to conclude that up to 45.3% of dementias could be attributed to risk factors, most of which were vascular and modifiable[106]. Several studies have been carried out, in populations at high vascular risk and with combined intervention strategies in various areas[107-110]. However, evidence that modifying these factors actually translates into dementia prevention has been more difficult to obtain[111,112], with promising results, but not yet sufficient to produce robust recommendations[113]. The difficulty in generating this evidence has led to the recent proposal by the FINESSE group (mentioned above) to consider more selected populations, with very early vascular disease and characteristic and specific profiles in future clinical trials[71]. Again citing the LADIS study, we found that hypertension, diabetes and stroke were associated with worse cognitive performance - particularly in executive functions, attention and mental processing speed, in autonomous people with evidence of cerebral small vessel disease[65], and among these risk factors, diabetes remained an independent factor predicting cognitive decline and dementia over time[75], an effect that is not unrelated to the already known association between diabetes and cerebral amyloid deposition[114].

Several factors have been identified as protective of cognitive decline. In the LADIS study, we confirmed that a low level of education is associated with a higher risk of cognitive decline[50]. On the other hand, participation in leisure activities, both physical and cognitive, plays a preventive role in the incidence and progression of dementia[106, 115]. The recent *Lancet Commission* review reinforces the importance of cognitive reserve and staying socially active as protective factors against developing dementia of any etiology[106]. Several studies have suggested that physical activity can delay or prevent the functional decline associated with ageing and promote overall health. In the European observational study LADIS, physical activity was found to be associated with better cognitive performance among autonomous people[116] and also as a factor associated with less progression to cognitive impairment of any etiology and particularly to Vascular Dementia[117]. Recently, in a systematic review, we showed that physical activity has a protective role, particularly in cognitive impairment and vascular dementia[118], but these results were based only on observational studies. In this context, we carried out the AFIVASC study[6]. The AFIVASC study aimed to assess the impact of a six-month physical activity intervention on people diagnosed with vascular mild cognitive impairment in

6 AFIVASC stands for "Physical Activity and Vascular Cognitive Impairment", a randomized study funded by FCT[2014]. The AFIVASC study was approved by the Ethics Committee of Hospital Santa Maria and Hospital Santo António do Porto. AFIVASC was registered on ClinicalTrials.gov (NCT03578614).

terms of their cognitive performance, quality of life, functional status and physical function[119]. The inclusion criteria consisted of having a diagnosis of vascular mild cognitive impairment[13], being fluent in reading and writing in Portuguese, with no relevant functional alterations. The exclusion criteria were contraindication (due to medical or orthopedic pathology) to physical activity. In this population, we showed how physical activity, even before randomization and active intervention, was associated with better ability to perform cognitive tests[120]. We found that participants were unable to accurately assess their own physical capacity subjectively, compared to a standard of objective measures (use of accelerometry)[120]. It is worth noting that, in general, physical activity has been described as safe in people with cognitive decline and dementia[118]. The AFIVASC study showed an improvement in the physical capacity of the participants and showed how it was possible and safe to carry out a randomized study with physical activity in patients with Vascular Cognitive Impairment. Although the main objective of the study was not achieved, a *post-hoc* analysis showed cognitive improvement in participants who met the World Health Organization's recommendations for physical activity, measured objectively[121].

Therapeutics

There is currently no specific therapy for Vascular Cognitive Impairment. Therapy for Vascular Cognitive Impairment largely involves general health promotion measures, optimizing the correction of vascular risk factors and stroke prevention[122]. In stroke patients, the recommended secondary prevention measures should be implemented[43]. Treatment should always be individualized, depending on the underlying cerebrovascular disease. In all cases, control of hypertension, hypercholesterolemia and smoking, as well as measures to reduce obesity and treat diabetes should be considered, as these factors are associated with an increased risk of cardio-cerebrovascular diseases in general. Contrary to what happens in the secondary prevention of ischemic stroke, there is no evidence that antithrombotic or anticoagulant therapy is effective in preventing the progression of VCI[123]. Although there is no evidence that patients with "pure" VaD benefit from drugs approved for symptomatic therapy of Alzheimer's disease, the frequent co-existence of vascular pathology with amyloid-type degenerative pathology could lead to their use for symptomatic benefit[18,124].

The lack of specific therapeutic measures for cognitive impairment due to vascular pathology led our group to try an intervention mediated by physical activity, which has already been mentioned[120,121], but also an intervention directly aimed at cognitive rehabilitation specifically for patients with Vascular Cognitive Impairment. Together with the Faculty of Sciences of the University of Lisbon, we developed a *software program* centered on a common activity - shopping in a supermarket, which was aimed at training attention skills, processing speed and action planning and programming[125-128]. While can be done autonomously in mild stages of the disease, it will require help in more advanced stages and is aimed at everyday activities[127].

In a simplified outline, the approach to these patients should always include: 1. Identifying vascular risk factors; 2. Optimizing therapy for vascular risk factors, with a special focus on hypertension, diabetes, lipid profile, vascular events, control of systemic pathologies that may compromise correct cerebral oxygenation (e.g. heart failure, obstructive sleep apnea syndrome); 3. Advising on a healthy lifestyle, including regular physical activity and preventing social isolation; 4. Promoting cognitive activities and monitoring cognitive complaints that can be corrected (e.g. reduced initiative, attention training) in individuals with vascular risk factors, taking special care in individuals with a combination of several risk factors; 5. Assessing the impact of symptoms on the person's life, using non-pharmacological interventions applicable to other cognitive pathologies, including support for the caregiver, depending on the person's specific needs. We refer to two recent recommendations produced in a European context and in which we participated, which are a useful tool in the management of these patients[124,129].

CHAPTER 4
FUTURE PROSPECTS FOR RESEARCH INTO VASCULAR COGNITIVE DEFECTS

Despite the advances in knowledge of Vascular Cognitive Defect, many aspects remain to be clarified. These include the identification of biomarkers, particularly accessible serum markers, and advanced imaging techniques for earlier identification. In the field of genetics, considerable progress has been made in recent years, with the identification of various monogenic forms of cerebral small vessel disease[130-132]. The fact that these pathologies share clinical and neuroim-

aging characteristics with sporadic forms has helped to improve our understanding of the pathogenesis of small vessel disease and to identify potential therapeutic targets[132]. The identification of several genes associated with a higher risk of developing the disease can also identify high-risk individuals who will also be good therapeutic targets[71]. Some recent studies have addressed the application of drug-genomic tests[7] and there are already published trials with drugs commonly used in clinical practice for the prevention of vascular events associated with cerebral small vessel disease[133,134].

There is also a need for better knowledge of the determinants of the different sub-types of Vascular Cognitive Defect. For example, data linking cholesterol levels throughout life and the risk of developing dementia has been controversial. Very recently, a longitudinal study showed that low serum HDL (high-density lipoprotein) cholesterol values were associated with an increased risk of subcortical vascular dementia, due to damage to small cerebral vessels, but not Alzheimer's disease or dementia with mixed characteristics[135]. Progress in clarifying the particularities of the subtypes of Vascular Cognitive Defect could be decisive in deciding on therapeutic targets. Finally, there is some data suggesting that regression of vascular lesions of the cerebral white matter is possible, particularly in patients who do not have alterations in the microstructural integrity of the white matter [136], with a controversial mechanism that remains unexplained. The possibility of regression further promotes the need to invest in prevention, which should cover the interaction between risk factors and protective factors at different stages of life. Recently, an open clinical trial showed a potential benefit of drugs with potential effects as vascular endothelium stabilizers in cognitive impairment caused by lacunar vascular events, but the results of a more robust design are still awaited[137].

Our work group is continuing its research aimed at better understanding the clinical expression of the disease and trying to modify its evolution. In this sense, the study OSTOAP (*Age-Related White Matter Changes and Lower Urinary Tract Dysfunction - One Step Towards OverActive Bladder Phenotyping*) aims to assess the relationship between small vessel disease and urinary function, with a clinical aspect that includes an exhaustive neuro- and urological assessment, and a more fundamental research aspect, with research into potential biomarkers in blood, urine and cerebrospinal fluid.

Another of our group's lines of research deals with the impact of physical activity on vascular cognitive impairment. The results of the AFIVASC randomized study[121], already commented on, instigate a need to reflect on the implementation of clinical trials with physical activity, and make it urgent to improve the available evidence on the relationship between physical activity and cognitive ability, including the assessment of adherence to physical activity itself. Notably, there is a lack of information on how the brain of elderly individuals with cerebrovascular disease responds to exercise. In this context, we feel the need to add better evidence on this topic, and it is in this context that our future research is situated.

Following the articles published in recent years, studies on prevention and adherence to preventive measures are expanding and will certainly be, in the absence of curative drugs, a viable way of changing health parameters, particularly in cognitive health and cognitive impairment caused by vascular pathology.

7 Pharmacogenomic tests (also known as pharmacogenetics) are part of precision medicine technologies and make it possible to assess the specific response of each individual and their genetic profile to the metabolism of a given drug.) The field is expanding rapidly and can target a single or several genes simultaneously and evaluate the response to a drug or combinations of drugs.

BIBLIOGRAFIA

1. Román GC. On the history of lacunes, etat criblé, and the white matter lesions of vascular dementia. Cerebrovasc Dis. 2002;13 Suppl 2:1-6. doi: 10.1159/000049142.
2. Fontoura, F. A prática neurológica nas Centúrias de Amatus Lusitanus, Sinapse, 2007, volume 7, nº2, página 90.
3. Schneider R, Wieczorek V, Historical aspects of neurosciences Otto Binswanger [1852–1929], Journal of the Neurological Sciences. Volume 103, Issue 1, 1991, Pages 61-64,ISSN 0022-510X,https://doi.org/10.1016/0022-510X[91]90285-F.
4. Mast H, Tatemichi TK, Mohr JP. Chronic brain ischemia: the contributions of Otto Binswanger and Alois Alzheimer to the mechanisms of vascular dementia, Journal of the Neurological Sciences, Volume 132, Issue 1, 1995, Pages 4-10, ISSN 0022-510X, https://doi.org/10.1016/0022-510X[95]00116-J.
5. Caplan LR. Binswanger's disease--revisited. Neurology. 1995;45[4]:626-33. doi: 10.1212/wnl.45.4.626. PMID: 7723946.
6. Engelhardt E, Grinberg LT. Alois Alzheimer and vascular brain disease: Arteriosclerotic atrophy of the brain. Dement Neuropsychol. 2015;9[1]:81-84. doi: 10.1590/S1980-57642015DN91000013. PMID: 29213946; PMCID: PMC5618996.
7. Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet. 1974;2 [7874]:207-10. doi: 10.1016/s0140-6736[74]91496-2. PMID: 4135618.
8. Hachinski VC. The decline and resurgence of vascular dementia. CMAJ. 1990;142[2]:107-11.
9. American Psychiatric Association. Diagnostic and statistical

manual of mental disorders, 5th ed (DSM-5). Washington, DC: American Psychiatric Association, 2013.

10. International Statistical Classification of Diseases and Related Health Problems. 11th ed,; ICD-World Health Organization, 2019.
11. Román GC, Sachdev P, Royall DR, et al. Vascular cognitive disorder. A new diagnostic category updating vascular cognitive impairment and vascular dementia. J Neurol Sci 2004;226:81–87. doi:10.1016/j.jns.2004.09.016.
12. Skrobot OA, O'Brien J, Black S, Chen C, DeCarli C, Erkinjuntti T, Ford GA, Kalaria RN, Pantoni L, Pasquier F, Roman GC, Wallin A, Sachdev P, Skoog I; VICCCS group; Ben-Shlomo Y, Passmore AP, Love S, Kehoe PG. The Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement. 2017:13[6]:624-633. doi: 10.1016/j.jalz.2016.10.007.
13. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2011;42:2672–2713. doi: 10.1161/STR.0b013e3182299496.
14. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, Dichgans M. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019;73[25]:3326-3344.
15. Jellinger KA. Prevalence of vascular lesions in dementia with Lewy bodies. A postmortem study. J Neural Transm (Vienna). 2003 Jul;110[7]:771-8. doi: 10.1007/s00702-003-0824-x. PMID: 12811637.
16. Agrawal S, Leurgans SE, Nag S, Oveisgharan S, Barnes LL, Bennett DA, Buchman AS, Schneider JA. Effects of Cerebrovascular and Lewy Body Pathology on Parkinsonian Signs in Community- Dwelling Older Adults. Neurology. 2023;101[7]:e754-e763. doi: 10.1212/WNL.0000000000207497.
17. Dichgans M, Zietemann V. Prevention of vascular cognitive impairment. Stroke. 2012;43:3137–3146. doi: 10.1161/STROKEAHA.112.651778.
18. Verdelho, A., Biessels, G. J., Chabriat, H., Charidimou, A., Duering, M., Godefroy, O., Pantoni, L., Pavlovic, A., & Wardlaw, J. Cerebrovascular disease in patients with cognitive impairment: A white paper from the ESO dementia committee - A practical point of view with suggestions for the management of cerebrovascular diseases in memory clinics. European stroke journal, 2021;6[2], 111–119. https://doi.org/10.1177/2396987321994294
19. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. Neurology. 1993; 43: 250–260.
20. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the state of California Alzheimer's disease diagnostic and treatment centers. Neurology. 1992; 42: 473–480.
21. Hachinski VC, Iliff LD, Zilhka E. Cerebral blood flow in dementia, Arch Neurol, 1975, vol. 32: 632-637.
22. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National institute of neurological disorders and stroke-association internationale pour la recherche et l'enseignement en neurosciences. Stroke. 2000; 31: 2952–2957.
23. Gold G, Bouras C, Canuto A, Bergallo MF, Herrmann FR, Hof PR, Mayor PA, Michel JP, Giannakopoulos P. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. Am J Psych. 2002; 159: 82–87.
24. Lopez OL, Kuller LH, Becker JT, Jagust WJ, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos C, Kawas C, Carlson M. Classification of vascular dementia in the cardiovascular health study cognition study. Neurology. 2005; 64: 1539–1547.
25. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST. Vascular cognitive impairment. Lancet Neurol. 2003; 2: 89–98.
26. Chui HC, Mack W, Jackson JE, et al. Clinical Criteria for the Diagnosis of Vascular Dementia: A Multicenter Study of Comparability and Interrater Reliability. Arch Neurol. 2000;57[2]:191–196. doi:10.1001/archneur.57.2.191
27. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord 2014;28[3]:206–218. doi:10.1097/WAD.0000000000000034.
28. Skrobot OA, Black SE, Chen C, DeCarli C, Erkinjuntti T, Ford GA, Kalaria RN, O'Brien J, Pantoni L, Pasquier F, Roman GC, Wallin A, Sachdev P, Skoog I; VICCCS group; Ben-Shlomo Y, Passmore AP, Love S, Kehoe PG. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement. 2018;14[3]:280-292. doi: 10.1016/j.jalz.2017.09.007.
29. Jellinger KA. The pathology of "vascular dementia": a critical update. J Alzheimers Dis. 2008 May;14[1]:107-23.
30. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54:S4–S9.
31. Ganguli M. Epidemiology of dementia. chap 38., Abou-Saleh MT, Katona C, Kumar A. eds. Principles and Practice of Geriatric Psychiatry. 3rd ed. Hoboken, NJ: Wiley; 2011.
32. Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology. 2000;54:447–451.
33. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69[24]:2197–2204.
34. Schneider JA, Aggarwal NT, Barnes L, et al. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis 2009;18[3]:691–701
35. Gonçalves-Pereira M, Cardoso A, Verdelho A, Alves da Silva J, Caldas de Almeida M, Fernandes A, Ferri C, Prince M, Xavier M. Implementação em Portugal de um estudo de prevalência da demência e da depressão geriátrica: a metodologia do 10/66 Dementia Research Group[Implementing a prevalence study of dementia and geriatric depression in Portugal: The 10/66 DRG methodology]. Revista Portuguesa de Saúde Pública, 2016; 34[2]: 134-143. http://doi.org/10.1016/j.rpsp.2016.03.002
36. Gonçalves-Pereira M, Cardoso A, Verdelho A, Alves da Silva J, Caldas de Almeida M, Fernandes A, Raminhos C, Ferri CP, Prina AM, Prince M, Xavier M. The prevalence of dementia in a Portuguese community sample: a 10/66 Dementia Research Group study. BMC geriatrics, 2017:17[1], 261. https://doi.org/10.1186/s12877-017-0647-5.
37. Ruano L, Araújo N, Branco M, Barreto R, Moreira S, Pais R, Cruz VT, Lunet N, Barros H. Prevalence and Causes of Cognitive Impairment and Dementia in a Population-Based Cohort From Northern Portugal. Am J Alzheimers Dis Other Demen. 2019;34[1]:49-56. doi: 10.1177/1533317518813550.
38. Nunes B, Silva RD, Cruz VT, Roriz JM, Pais J, Silva MC. Prevalence and pattern of cognitive impairment in rural and urban populations from Northern Portugal. BMC Neurol. 2010;10[1]:42.
39. Yanagihara T Vascular dementia in Japan. Ann N Y Acad Sci. 2002;977:24-8.
40. Brunnström H, et al. Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports. Arch Gerontol Geriatr. 2009;49[1]:146-9.
41. Knopman DS, Parisi JE, Boeve BF, et al. Vascular dementia in a population-based autopsy study. Arch Neurol 2003;60[4]:569–575. doi:10.1001/archneur.60.4.569.
42. Weaver NA, Kuijf HJ, Aben HP, Abrigo J, Bae HJ, Barbay M, Best JG, Bordet R, Chappell FM, Chen CPLH, Dondaine T, van der Giessen RS, Godefroy O, Gyanwali B, Hamilton OKL, Hilal S, Huenges Wajer IMC, Kang Y, Kappelle LJ, Kim BJ, Köhler S, de Kort PLM, Koudstaal PJ, Kuchcinski G, Lam BYK, Lee BC, Lee KJ, Lim JS, Lopes R, Makin SDJ, Mendyk AM, Mok VCT, Oh MS, van Oostenbrugge RJ, Roussel M, Shi L, Staals J, Del C Valdés-Hernández M, Venketasubramanian N, Verhey FRJ, Wardlaw JM, Werring DJ, Xin X, Yu KH, van Zandvoort

MJE, Zhao L, Biesbroek JM, Biessels GJ. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. Lancet Neurol. 2021;20[6]:448-459. doi: 10.1016/S1474-4422[21]00060-0.

43. Verdelho A, Wardlaw J, Pavlovic A, Pantoni L, Godefroy O, Duering M, Charidimou A, Chabriat H, Biessels GJ. Cognitive impairment in patients with cerebrovascular disease: A white paper from the links between stroke ESO Dementia Committee. European stroke journal, 2021:6[1], 5–17. https://doi.org/10.1177/23969873211000258

44. Hamilton OKL, Backhouse EV, Janssen E, Jochems ACC, Maher C, Ritakari TE, Stevenson AJ, Xia L, Deary IJ, Wardlaw JM. Cognitive impairment in sporadic cerebral small vessel disease: A systematic review and meta-analysis. Alzheimers Dement. 2021;17[4]:665-685. doi: 10.1002/alz.12221.

45. Salvadori E, Brambilla M, Cova I, Pomati S, Pantoni L. Cognitive evaluation in cerebral small vessel disease: towards an evidence-based identification of the reference standards. Part 1. A systematic review and qualitative data synthesis. J Neurol. 2021;268[12]:4563-4572. doi: 10.1007/s00415-020-10262-2

46. Clancy U, Gilmartin D, Jochems ACC, Knox L, Doubal FN, Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. Lancet Psychiatry. 2021;8[3]:225-236. doi: 10.1016/S2215-0366[20]30431-4.

47. Miranda, B., Madureira, S., Verdelho, A., Ferro, J., Pantoni, L., Salvadori, E., Chabriat, H., Erkinjuntti, T., Fazekas, F., Hennerici, M., O'Brien, J., Scheltens, P., Visser, M. C., Wahlund, L. O., Waldemar, G., Wallin, A., Inzitarion, D., & LADIS Study. Self-perceived memory impairment and cognitive performance in an elderly independent population with age-related white matter changes. Journal of neurology, neurosurgery, and psychiatry, 2008;79[8],869–873. https://doi.org/10.1136/jnnp.2007.131078

48. Verdelho A, Madureira S, Moleiro C, Santos CO, Ferro JM, Erkinjuntti T, Poggesi A, Pantoni L, Fazekas F, Scheltens P, Waldemar G, Wallin A, Inzitari D; LADIS Study. Self-perceived memory complaints predict progression to Alzheimer disease. The LADIS study. J Alzheimers Dis.2011;27[3]:491-8. doi: 10.3233/JAD-2011-110494.

49. Verdelho A, Ferro JM. Late onset depressive symptoms can be a marker of cerebral vascular pathology. J Neurol Neurosurg Psychiatry. 2008;79[9]:977. doi: 10.1136/jnnp.2007.142364. PMID: 18708565.

50. Verdelho A, Madureira S, Moleiro C, Ferro JM, O'Brien JT, Poggesi A, Pantoni L, Fazekas F, Scheltens P, Waldemar G, Wallin A, Erkinjuntti T, Inzitari D; LADIS Study. Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study. J Neurol Neurosurg Psychiatry. 2013;84[11]:1250-4. doi: 10.1136/jnnp-2012-304191.

51. Folstein M, Folstein S, McHugh PJ. Mini-Mental State: a practical method for grading the cognitive state of patients for clinicians. J Psychiatr Res 1975;12:189–98.

52. Nasreddine Z, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: A brief screening tool for Mild Cognitive Impairment. American Geriatrics Society. 2005:53, 695-699.

53. Madureira S, Verdelho A, Ferro J, Basile AM, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M, O'brien J, Pantoni L, Salvadori E, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D; LADIS Study Group. Development of a neuropsychological battery for the Leukoaraiosis and Disability in the Elderly Study (LADIS): experience and baseline data. Neuroepidemiology. 2006;27[2]:101-16. doi: 10.1159/000095381.

54. Moleiro C, Madureira S, Verdelho A, Ferro JM, Poggesi A, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M, O'Brien J, Pantoni L, Salvadori E, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D; LADIS Study. Confirmatory factor analysis of the Neuropsychological Assessment Battery of the LADIS study: a longitudinal analysis. J Clin Exp Neuropsychol. 2013;35[3]:269-78. doi: 10.1080/13803395.2013.770822.

55. Madureira S, Verdelho A, Moleiro C, Ferro JM, Erkinjuntti T, Jokinen H, Pantoni L, Fazekas F, Van der Flier W, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D. Neuropsychological predictors of dementia in a three-year follow-up period: data from the LADIS study. Dement Geriatr Cogn Disord. 2010;29[4]:325-34. doi: 10.1159/000278333.

56. Madureira S, Verdelho A, Moleiro C, Santos C, Scheltens P, Gouw A, Ferro J. White Matter Changes and Cognitive Decline in a Ten-Year Follow-Up Period: A Pilot Study on a Single-Center Cohort from the Leukoaraiosis and Disability Study. Dement Geriatr Cogn Disord. 2016;41[5-6]:303-13. doi: 10.1159/000447121.

57. Kancheva AK, Wardlaw JM, Lyall DM, Quinn TJ. Clinical Phenotypes Associated With Cerebral Small Vessel Disease: An Overview of Systematic Reviews. Neurology. 2024;102[8]:e209267. doi: 10.1212/WNL.0000000000209267.

58. Poggesi A, Gouw A, van der Flier W, Pracucci G, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, Langhorne P, O'Brien JT, Visser MC, Wahlund LO, Waldemar G, Wallin A, Scheltens P, Inzitari D, Pantoni L. Cerebral white matter changes are associated with abnormalities on neurological examination in non-disabled elderly: the LADIS study. J Neurol. 2013;260[4]:1014-21. doi: 10.1007/s00415-012-6748-3.

59. Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Langhorne P, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Hennerici MG; LADIS Study Group. Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology. 2008;70[12]:935-42. doi: 10.1212/01.wnl.0000305959.46197.e6. PMID: 18347315.

60. Poggesi A, Pracucci G, Chabriat H, Erkinjuntti T, Fazekas F, Verdelho A, Hennerici M, Langhorne P, O'Brien J, Scheltens P, Visser MC, Crisby M, Waldemar G, Wallin A, Inzitari D, Pantoni L; Leukoaraiosis And DISability Study Group. Urinary complaints in nondisabled elderly people with age-related white matter changes: the Leukoaraiosis And DISability (LADIS) Study. J Am Geriatr Soc. 2008;56[9]:1638-43. doi: 10.1111/j.1532-5415.2008.01832.x.

61. Silva RPE, Sousa DA, Lopes FA, Silva-Ramos M, Verdelho A. Age-related white matter hyperintensities and overactive bladder: A systematic review. Neurourol Urodyn. 2023 Jun;42[5]:1088-1100. doi: 10.1002/nau.25174.

62. Silva RPE, Sousa DA, Lopes FA, Silva-Ramos M, Verdelho A. Age-related white matter hyperintensities and overactive bladder: A systematic review. Neurourol Urodyn. 2023;42[5]:1088-1100. doi: 10.1002/nau.25174.

63. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149[2]:351–6

64. Benisty S, Gouw AA, Porcher R, Madureira S, Hernandez K, Poggesi A, van der Flier WM, Van Straaten EC, Verdelho A, Ferro J, Pantoni L, Inzitari D, Barkhof F, Fazekas F, Chabriat H; LADIS Study group. Location of lacunar infarcts correlates with cognition in a sample of non-disabled subjects with age-related white-matter changes: the LADIS study. J Neurol Neurosurg Psychiatry. 2009;80[5]:478-83. doi: 10.1136/jnnp.2008.160440.

65. Verdelho A, Madureira S, Ferro JM, Basile AM, Chabriat H, Erkinjuntti T, Fazekas F, Hennerici M, O'Brien J, Pantoni L, Salvadori E, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Inzitari D; LADIS Study. Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. J Neurol Neurosurg Psychiatry. 2007;78[12]:1325-30. doi: 10.1136/jnnp.2006.110361.

66. van der Flier WM, van Straaten EC, Barkhof F, Verdelho A, Madureira S, Pantoni L, Inzitari D, Erkinjuntti T, Crisby M, Waldemar G, Schmidt R, Fazekas F, Scheltens P. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. Stroke. 2005;36[10]:2116-20. doi: 10.1161/01.STR.0000179092.59909.42.

67. Frederiksen KS, Garde E, Skimminge A, Barkhof F, Scheltens P, van Straaten EC, Fazekas F, Baezner H, Verdelho A, Ferro JM, Erkinjuntti T, Jokinen H, Wahlund LO, O'Brien JT, Basile AM, Pantoni L, Inzitari D, Waldemar G. Corpus callosum tissue loss and development of motor and global cognitive impairment: the LADIS study. Dement Geriatr Cogn Disord. 2011;32[4]:279-86. doi: 10.1159/000334949.

68. Jokinen H, Frederiksen KS, Garde E, Skimminge A, Siebner H, Waldemar G, Ylikoski R, Madureira S, Verdelho A, van Straaten EC, Barkhof F, Fazekas F, Schmidt R, Pantoni L, Inzitari D, Erkinjuntti T. Callosal tissue loss parallels subtle decline in psychomotor speed. a longitudinal quantitative MRI study. The LADIS Study. Neuropsychologia. 2012;50[7]:1650-5. doi: 10.1016/j.neuropsychologia.2012.03.020.

69. Jokinen H, Lipsanen J, Schmidt R, Fazekas F, Gouw AA, van der Flier WM, Barkhof F, Madureira S, Verdelho A, Ferro JM, Wallin A, Pantoni L, Inzitari D, Erkinjuntti T; LADIS Study Group. Brain atrophy accelerates cognitive decline in cerebral small vessel disease: the LADIS study. Neurology. 2012;78[22]:1785-92. doi: 10.1212/WNL.0b013e3182583070.

70. Jokinen H, Schmidt R, Ropele S, Fazekas F, Gouw AA, Barkhof F, Scheltens P, Madureira S, Verdelho A, Ferro JM, Wallin A, Poggesi A, Inzitari D, Pantoni L, Erkinjuntti T; LADIS Study Group.Diffusion changes predict cognitive and functional outcome: the LADIS study. Ann Neurol. 2013;73[5]:576-83. doi: 10.1002/ana.23802.

71. Markus HS, van Der Flier WM, Smith EE, Bath P, Biessels GJ, Briceno E, Brodtman A, Chabriat H, Chen C, de Leeuw FE, Egle M, Ganesh A, Georgakis MK, Gottesman RF, Kwon S, Launer L, Mok V, O'Brien J, Ottenhoff L, Pendlebury S, Richard E, Sachdev P, Schmidt R, Springer M, Tiedt S, Wardlaw JM, Verdelho A, Webb A, Werring D, Duering M, Levine D, Dichgans M. Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE): A Review. JAMA Neurol. 2022;79[11]:1187-1198. doi: 10.1001/jamaneurol.2022.2262.

72. Pinter D, Gattringer T, Fandler-Höfler S, Kneihsl M, Eppinger S, Deutschmann H, Pichler A, Poltrum B, Reishofer G, Ropele S, Schmidt R, Enzinger C. Early Progressive Changes in White Matter Integrity Are Associated with Stroke Recovery. Transl Stroke Res. 2020;11[6]:1264-1272. doi: 10.1007/s12975-020-00797-x.

73. Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, Debette S, Frayne R, Jouvent E, Rost NS, Ter Telgte A, Al-Shahi Salman R, Backes WH, Bae HJ, Brown R, Chabriat H, De Luca A, deCarli C, Dewenter A, Doubal FN, Ewers M, Field TS, Ganesh A, Greenberg S, Helmer KG, Hilal S, Jochems ACC, Jokinen H, Kuijf H, Lam BYK, Lebenberg J, MacIntosh BJ, Maillard P, Mok VCT, Pantoni L, Rudilosso S, Satizabal CL, Schirmer MD, Schmidt R, Smith C, Staals J, Thrippleton MJ, van Veluw SJ, Vemuri P, Wang Y, Werring D, Zedde M, Akinyemi RO, Del Brutto OH, Markus HS, Zhu YC, Smith EE, Dichgans M, Wardlaw JM. Neuroimaging standards for research into small vessel disease-advances since 2013. Lancet Neurol. 2023;22[7]:602-618.

74. Ferro JM, Verdelho A, Madureira S. The cognitive consequences of cerebral small vessel diseases. In: Leonardo Pantoni, Philip B. Gorelick, editors. (Eds.). Cerebral Small Vessels Diseases. 2014, p. 371. Cambridge University Press, Cambridge. UK ISBN: 978-1-107-03166-1. doi: 10.1017/CBO9781139382694.

75. Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, Pantoni L, Fazekas F, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D; LADIS Study. White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. Neurology. 2010;75[2]:160-7. doi: 10.1212/WNL.0b013e3181e7ca05.

76. Jokinen H, Gouw AA, Madureira S, Ylikoski R, van Straaten EC, van der Flier WM, Barkhof F, Scheltens P, Fazekas F, Schmidt R, Verdelho A, Ferro JM, Pantoni L, Inzitari D, Erkinjuntti T; LADIS Study Group. Incident lacunes influence cognitive decline: the LADIS study. Neurology. 2011;76[22]:1872-8. doi: 10.1212/WNL.0b013e31821d752f.

77. Jokinen H, Koikkalainen J, Laakso HM, Melkas S, Nieminen T, Brander A, Korvenoja A, Rueckert D, Barkhof F, Scheltens P, Schmidt R, Fazekas F, Madureira S, Verdelho A, Wallin A, Wahlund LO, Waldemar G, Chabriat H, Hennerici M, O'Brien J, Inzitari D, Lötjönen J, Pantoni L, Erkinjuntti T. Global Burden of Small Vessel Disease-Related Brain Changes on MRI Predicts Cognitive and Functional Decline. Stroke. 2020;51[1]:170-178. doi: 10.1161/STROKEAHA.119.026170.

78. Erkinjuntti T. Vascular cognitive deterioration and stroke. Cerebrovasc Dis. 2007;24 Suppl 1:189-94.

79. Inzitari D, Erkinjuntti T, Wallin A, Del Ser T, Romanelli M, Pantoni L. Subcortical vascular dementia as a specific target for clinical trials. Ann N Y Acad Sci. 2000 Apr;903:510-21.

80. Jokinen H, Kalska H, Ylikoski R, Madureira S, Verdelho A, Gouw A, Scheltens P, Barkhof F, Visser MC, Fazekas F, Schmidt R, O'Brien J, Hennerici M, Baezner H, Waldemar G, Wallin A, Chabriat H, Pantoni L, Inzitari D, Erkinjuntti T; LADIS group. MRI-defined subcortical ischemic vascular disease: baseline clinical and neuropsychological findings. The LADIS Study. Cerebrovasc Dis. 2009;27[4]:336-44. doi: 10.1159/000202010.

81. Jokinen H, Kalska H, Ylikoski R, Madureira S, Verdelho A, van der Flier WM, Scheltens P, Barkhof F, Visser MC, Fazekas F, Schmidt R, O'Brien J, Waldemar G, Wallin A, Chabriat H, Pantoni L, Inzitari D, Erkinjuntti T; LADIS group. Longitudinal cognitive decline in subcortical ischemic vascular disease--the LADIS Study. Cerebrovasc Dis. 2009;27[4]:384-91. doi: 10.1159/000207442.

82. Pendlebury ST, Rothwell PM; Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. Lancet Neurol. 2019 Mar;18[3]:248-258. doi: 10.1016/S1474-4422[18]30442-3.

83. Verdelho A, Hénon H, Lebert F, Pasquier F, Leys D. Depressive symptoms after stroke and relationship with dementia: A three-year follow-up study. Neurology. 2004;62[6]:905-11. doi: 10.1212/01.wnl.0000115107.66957.8c.

84. Bernhardt J, Hayward K, Kwakkel G et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. Int J Stroke. 2017;12[5]:444-50. doi:10.1177/1747493017711816

85. Droś J, Kowalska K, Pasińska P, et al. Transient cognitive impairment in the acute phase of stroke – prevalence, risk factors and influence on long-term prognosis in population of patients with stroke (research study – part of the PROPOLIS study). BMC Neurol 23, 75[2023]. https://doi.org/10.1186/s12883-023-03120-x

86. Pendlebury ST, Wadling S, Silver LE, Mehta Z, Rothwell PM. Transient cognitive impairment in TIA and minor stroke. Stroke. 2011;42[11]:3116–21.

87. Ferro JM, Caeiro L, Verdelho A. Delirium in acute stroke. Curr Opin Neurol. 2002 Feb;15[1]:51-5. doi: 10.1097/00019052-200202000-00009

88. Pendlebury ST, Poole D, Burgess A, et al. APOE-e4 genotype and dementia before and after transient ischemic attack and stroke: population-based cohort study. Stroke 2020; 51: 751–758

89. Casolla B, Caparros F, Cordonnier C, Bombois S, Hénon H, Bordet R, Orzi F, Leys D. Biological and imaging predictors of cognitive impairment after stroke: a systematic review. J Neurol. 2019;266[11]:2593-2604. doi: 10.1007/s00415-018-9089-z.

90. Puy L, Barbay M, Roussel M, Canaple S, Lamy C, Arnoux A, Leclercq C, Mas JL, Tasseel-Ponche S, Constans JM, Godefroy O; GRECogVASC Study Group. Neuroimaging Determinants of Poststroke Cognitive Performance. Stroke. 2018 Nov;49[11]:2666-2673. doi: 10.1161/STROKEAHA.118.021981. PMID: 30355190.

91. Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, Wadley VG. Trajectory of Cognitive Decline After Incident Stroke. JAMA. 2015;314[1]:41-51. doi: 10.1001/jama.2015.6968. PMID: 26151265; PMCID: PMC4655087.

92. Lo JW, Crawford JD, Desmond DW, Bae HJ, Lim JS, Godefroy O, Roussel M, Kang Y, Jahng S, Köhler S, Staals J, Verhey F, Chen C, Xu X, Chong EJ, Kandiah N, Yatawara C, Bordet R, Dondaine T, Mendyk AM, Brodaty H, Traykov L, Mehrabian S, Petrova N, Kim KW, Bae JB, Han JW, Lipnicki DM, Lam B, Sachdev PS; Stroke and Cognition (STROKOG) Collaboration. Long-Term Cognitive Decline After Stroke: An Individual Participant Data Meta-Analysis. Stroke. 2022;53[4]:1318-1327. doi: 10.1161/STROKEAHA.121.035796.

93. Mok VCT, Lam BYK, Wang Z, Liu W, Au L, Leung EYL, Chen S, Yang J, Chu WCW, Lau AYL, Chan AYY, Shi L, Fan F, Ma SH, Ip V, Soo YOY, Leung TWH, Kwok TCY, Ho CL, Wong LKS, Wong A. Delayed-onset dementia after stroke or transient ischemic attack. Alzheimers Dement. 2016;12[11]:1167-1176. doi: 10.1016/j.jalz.2016.05.007.

94. Lee JH, Kim SH, Kim GH, et al. Identification of pure subcortical vascular dementia using 11C- Pittsburgh compound B. Neurology 2011;77[1]:18–25.

95. Hagberg G, Ihle-Hansen H, Fure B, Thommessen B, Ihle-Hansen H, Øksengård AR, Beyer MK, Wyller TB, Müller EG, Pendlebury ST, Selnes P. No evidence for amyloid pathology as a key mediator of neurodegeneration post-stroke - a seven-year follow-up study. BMC Neurol. 2020;20[1]:174. doi: 10.1186/s12883-020-01753-w.

96. Duering M, Righart R, Wollenweber FA, Zietemann V, Gesierich B, Dichgans M. Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts. Neurology. 2015;84:1685–1692.

97. Schroeter M, Zickler P, Denhardt DT, Hartung HP, Jander S. Increased

thalamic neurodegeneration following ischaemic cortical stroke in osteopontin-deficient mice. Brain. 2006;129:1426–1437.

98. Jindahra P, Petrie A, Plant GT. The time course of retrograde trans-synaptic degeneration following occipital lobe damage in humans. Brain. 2012;135:534–54185.

99. Li H, Jacob MA, Cai M, Duering M, Chamberland M, Norris DG, Kessels RPC, de Leeuw FE, Marques JP, Tuladhar AM. Regional cortical thinning, demyelination and iron loss in cerebral small vessel disease. Brain. 2023;146[11]:4659-4673. doi: 10.1093/brain/awad220. PMID: 37366338; PMCID: PMC10629800.

100. Lim JS, Lee JJ, Woo CW. Post-Stroke Cognitive Impairment: Pathophysiological Insights into Brain Disconnectome from Advanced Neuroimaging Analysis Techniques. J Stroke. 2021;23[3]:297-311. doi: 10.5853/jos.2021.02376. Epub 2021 Sep 30. PMID: 34649376; PMCID: PMC8521255.

101. Ouyang F et al. Is Cerebral Amyloid-β Deposition Related to Post-stroke Cognitive Impairment? Transl Stroke Res. 2021;12:946-957

102. Rasquin SM, Lodder J, Verhey FR. Predictors of reversible mild cognitive impairment after stroke: a 2-year follow-up study. J Neurol Sci. 2005;229-230:21–25.

103. Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS. Heart failure and cognitive impairment: challenges and opportunities. Clin Interv Aging. 2007;2:209–218.

104. Verdelho A. Role of Cerebrovascular Disease in cognitive Decline. In: Galimberti D and Scarpini E (Editors). Neurodegeneration: Clinical Aspects, Molecular Genetics and Biomarkers for Early Diagnosis and Treatment. 2014. Springer

105. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020:396, 413-446.

106. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C, Fox NC, Ferri CP, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Nakasujja N, Rockwood K, Samus Q, Shirai K, Singh-Manoux A, Schneider LS, Walsh S, Yao Y, Sommerlad A, Mukadam N. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet. 2024:S0140-6736[24]01296-0. doi: 10.1016/S0140-6736[24]01296-0.

107. Ngandu T, Lehtisalo J, Solomon A, et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at- risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385[9984]:2255-2263.

108. Teuschl Y, Ihle-Hansen H, Matz Ket al. Aspis Study Group. Multidomain intervention for the prevention of cognitive decline after stroke - a pooled patient-level data analysis. Eur J Neurol 2018, 25: 1182-88.

109. Teuschl Y, Matz K, Firlinger B, et al. Aspis Study Group. Preventive effects of multiple domain interventions on lifestyle and risk factor changes in stroke survivors: Evidence from a two-year randomized trial. Int J Stroke 2017; 12: 976-84.

110. Noach S, Witteman B, Boss HM, Janse A. Effects of multidomain lifestyle interventions on cognitive decline and Alzheimer's disease prevention: A literature review and future recommendations. Cereb Circ Cogn Behav. 2023;4:100166. doi: 10.1016/j.cccb.2023.100166. PMID: 37215433; PMCID: PMC10199401.

111. Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. Cochrane Database Syst Rev. 2021;11[11]:CD013572. doi:10.1002/14651858.CD013572.pub2. PMID: 34748207; PMCID: PMC8574768.

112. Van Dalen, Willem J, Moll EP et al. Effect of Long-Term Vascular Care on Progression of Cerebrovascular Lesions: Magnetic Resonance Imaging Substudy of the PreDIVA Trial (Prevention of Dementia by Intensive Vascular Care). Stroke 2017; 48: 1842-48.

113. World Health Organization. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. Geneva: World Health Organization 2019. PMID: 31219687.

114. van Arendonk J, Neitzel J, Steketee RME, van Assema DME, Vrooman HA, Segbers M, Ikram MA, Vernooij MW. Diabetes and hypertension are related to amyloid-beta burden in the population-based Rotterdam Study. Brain. 2023;146[1]:337-348. doi: 10.1093/brain/awac354. PMID: 36374264; PMCID: PMC9825526.

115. Grande G, Qiu C, Fratiglioni L. Prevention of dementia in an ageing world: Evidence and biological rationale. Ageing Res Rev. 2020;64:101045. doi: 10.1016/j.arr.2020.101045.

116. Frederiksen KS, Verdelho A, Madureira S, Bäzner H, O'Brien JT, Fazekas F, Scheltens P, Schmidt R, Wallin A, Wahlund LO, Erkinjunttii T, Poggesi A, Pantoni L, Inzitari D, Waldemar G; LADIS Study. Physical activity in the elderly is associated with improved executive function and processing speed: the LADIS Study. Int J Geriatr Psychiatry. 2015;30[7]:744-50. doi: 10.1002/gps.4220.

117. Verdelho A, Madureira S, Ferro JM, Baezner H, Blahak C, Poggesi A, Hennerici M, Pantoni L, Fazekas F, Scheltens P, Waldemar G, Wallin A, Erkinjuntti T, Inzitari D; LADIS Study. Physical activity prevents progression for cognitive impairment and vascular dementia: results from the LADIS (Leukoaraiosis and Disability) study. Stroke. 2012;43[12]:3331-5. doi:10.1161/STROKEAHA.112.661793.

118. Vítor J, Melita C, Rodrigues M, de Sousa DA, Costa J, Ferro JM, Verdelho A. Physical activity in vascular cognitive impairment: Systematic review with meta-analysis. J Stroke Cerebrovasc Dis. 2023;32[8]:107133. doi: 10.1016/j.jstrokecerebrovasdis.2023.107133

119. Verdelho A, Madureira S, Correia M, Ferro JM, Rodrigues M, Gonçalves-Pereira M, Gonçalves M, Santos AC, Vilela P, Bárrios H, Borges M, Santa-Clara H. Impact of physical activity in vascular cognitive impairment (AFIVASC): study protocol for a randomised controlled trial. Trials. 2019;20[1]:114. doi: 10.1186/s13063-019-3174-1.

120. Verdelho A, Correia M, Ferro JM, Madureira S, Vilela P, Rodrigues M, Borges M, Oliveira V, Santos AC, Gonçalves-Pereira M, Santa-Clara H. Physical Activity Self-Report Is Not Reliable Among Subjects with Mild Vascular Cognitive Impairment: The AFIVASC Study. J Alzheimers Dis. 2022;87[1]:405-414. doi: 10.3233/JAD-215381.

121. Verdelho A, Correia M, Gonçalves-Pereira M, Madureira S, Vilela P, Santos AC, Rodrigues M, Borges M, Ferro JM, Santa-Clara H. Physical activity in Mild Vascular Cognitive Impairment: Results of the AFIVASC randomized controlled trial at 6 months. Journal of Alzheimer disease. In press, accepted in 31 july 2024.

122. Verdelho A, Gonçalves-Pereira M. Management of vascular risk factors in dementia. In: Frideriksen KS, Waldemar G (Eds). Management of patients with dementia: The role of the physician. Springer, Cham; 2021(pp. 155-178). https://doi.org/10.1007/978-3-030-77904-7_8

123. Kwan J, Hafdi M, Chiang LLW, Myint PK, Wong LS, Quinn TJ. Antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia. Cochrane Database Syst Rev. 2022;7[7]:CD012269. doi:10.1002/14651858.CD012269.pub2. PMID: 35833913; PMCID: PMC9281623.

124. Quinn TJ, Richard E, Teuschl Y, Gattringer T, Hafdi M, O'Brien JT, Merriman N, Gillebert C, Huygelier H, Verdelho A, Schmidt R, Ghaziani E, Forchammer H, Pendlebury ST, Bruffaerts R, Mijajlovic M, Drozdowska BA, Ball E, Markus HS. European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment. European journal of neurology. 2021:28[12], 3883–3920. https://doi.org/10.1111/ene.15068

125. Ferreira-Brito F, Fialho M, Virgolino A, Neves I, Miranda AC, Sousa-Santos N, Caneiras C, Carriço L, Verdelho A, Santos O. Game-based interventions for neuropsychological assessment, training and rehabilitation: Which game-elements to use? A systematic review. J Biomed Inform. 2019 Oct;98:103287. doi: 10.1016/j.jbi.2019.103287.

126. Ferreira-Brito F, Alves S, Santos O, Guerreiro T, Caneiras C, Carriço L, Verdelho A. Photo- Realistic Interactive Virtual Environments for Neurorehabilitation in Mild Cognitive Impairment (NeuroVRehab. PT): A Participatory Design and Proof-of-Concept Study. J Clin Med. 2020;9[12]:3821. doi: 10.3390/jcm9123821.

127. Ferreira-Brito F, Ribeiro F, Aguiar de Sousa D, Costa J, Caneiras C, Carriço L, Verdelho A. Are Video Games Effective to Promote Cognition and Everyday Functional Capacity in Mild Cognitive Impairment/Dementia Patients? A Meta-

Analysis of Randomized Controlled Trials. J Alzheimers Dis. 2021;84[1]:329-341. doi: 10.3233/JAD-210545.

128. Ferreira-Brito F, Alves S, Guerreiro T, Santos O, Caneiras C, Carriço L, Verdelho A. Digital health and patient adherence: A qualitative study in older adults. Digit Health. 2024 Jan 12;10:20552076231223805. doi: 10.1177/20552076231223805.

129. Frederiksen KS, Cooper C, Frisoni GB, Frölich L, Georges J, Kramberger MG, Nilsson C, Passmore P, Mantoan Ritter L, Religa D, Schmidt R, Stefanova E, Verdelho A, Vandenbulcke M, Winblad B, Waldemar G. A European Academy of Neurology guideline on medical management issues in dementia. Eur J Neurol. 2020;27[10]:1805-1820. doi: 10.1111/ene.14412.

130. Mancuso M, Arnold M, Bersano A, Burlina A, Chabriat H, Debette S, Enzinger C, Federico A, Filla A, Finsterer J, Hunt D, Lesnik Oberstein S, Tournier-Lasserve E, Markus HS. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. Eur J Neurol. 2020;27[6]:909-927. doi: 10.1111/ene.14183.

131. Manini A, Pantoni L. Genetic Causes of Cerebral Small Vessel Diseases: A Practical Guide for Neurologists. Neurology. 2023 Apr 18;100[16]:766-783. doi: 10.1212/WNL.0000000000201720.

132. Bhagat R, Marini S, Romero JR. Genetic considerations in cerebral small vessel diseases. Front Neurol. 2023;14:1080168. doi: 10.3389/fneur.2023.1080168. PMID: 37168667; PMCID: PMC10164974.

133. Swen JJ, van der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, Böhringer S, Cambon-Thomsen A, Cecchin E, Cheung KC, Deneer VH, Dupui M, Ingelman- Sundberg M, Jonsson S, Joefield-Roka C, Just KS, Karlsson MO, Konta L, Koopmann R, Kriek M, Lehr T, Mitropoulou C, Rial-Sebbag E, Rollinson V, Roncato R, Samwald M, Schaeffeler E, Skokou M, Schwab M, Steinberger D, Stingl JC, Tremmel R, Turner RM, van Rhenen MH, Dávila Fajardo CL, Dolžan V, Patrinos GP, Pirmohamed M, Sunder-Plassmann G, Toffoli G, Guchelaar HJ; Ubiquitous Pharmacogenomics Consortium. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 2023;401[10374]:347-356. doi: 10.1016/S0140-6736[22]01841-4.

134. Liu H, Jing J, Wang A, Xu Q, Meng X, Li H, Li Z, Wang Y. Genotype-Guided Dual Antiplatelet Therapy in Minor Stroke or Transient Ischemic Attack With a Single Small Subcortical Infarction. Neurology. 2023;100[16]:e1643-e1654. doi: 10.1212/WNL.0000000000206775.

135. Axelsson Andrén E, Safi D, Wallin A, Svensson J. Low serum HDL-cholesterol is associated with increased risk of the subcortical small vessel type of dementia. Cereb Circ Cogn Behav. 2024 ;6:100229. doi: 10.1016/j.cccb.2024.100229.

136. Jochems ACC, Muñoz Maniega S, Clancy U, Arteaga C, Jaime Garcia D, Chappell FM, Hewins W, Locherty R, Backhouse EV, Barclay G, Jardine C, McIntyre D, Gerrish I, Kampaite A, Sakka E, Valdés Hernández M, Wiseman S, Bastin ME, Stringer MS, Thrippleton MJ, Doubal FN, Wardlaw JM. Magnetic Resonance Imaging Tissue Signatures Associated With White Matter Changes Due to Sporadic Cerebral Small Vessel Disease Indicate That White Matter Hyperintensities Can Regress. J Am Heart Assoc. 2024;13[3]:e032259. doi: 10.1161/JAHA.123.032259.

137. Wardlaw JM, Woodhouse LJ, Mhlanga II, Oatey K, Heye AK, Bamford J, Cvoro V, Doubal FN, England T, Hassan A, Montgomery A, O'Brien JT, Roffe C, Sprigg N, Werring DJ, Bath PM; Lacunar Intervention Trial-2 (LACI-2) Investigator Group. Isosorbide Mononitrate and Cilostazol Treatment in Patients With Symptomatic Cerebral Small Vessel Disease: The Lacunar Intervention Trial-2 (LACI-2) Randomized Clinical Trial. JAMA Neurol. 2023;80[7]:682-692. doi:10.1001/jamaneurol.2023.1526. PMID: 37222252; PMCID: PMC10209826.

ANNEX 1

Etiologies of Vascular Cognitive Impairment

- Disease of the small cerebral vessels due to arteriosclerosis of the small caliber arteries (penetrating or perforating arteries), referred to as lipo-hyalinosis. It manifests as white matter changes, lacunae and micro-hemorrhages (typically deep).
- Infarcts (cortical, cortico-subcortical, single or multiple, of different sizes) resulting from pathology in larger caliber arteries.
- Strategically located infarcts (e.g. in the angular circumvolution, in the territory of the posterior cerebral artery, in the territory of the anterior cerebral artery, in the thalamus).
- Hypoxia/anoxia/hemodynamic effect.
- Hemorrhagic vascular accidents, including subarachnoid hemorrhage.
- Cerebral venous thrombosis.
- Cerebral amyloid angiopathy.
- Congenital/genetically determined pathology that can lead to multiple vascular lesions of different types (coagulation disorders, metabolic diseases).
- Monogenic vascular diseases (such as CADASIL).

ANNEX 2

Schematic representation of the information that each MRI sequence can provide.

The following table was taken from the article Verdelho et al, 2021 ESJ; and as such kept in the original version[1].

Table 2. MRI sequences in CI due to CVD should include

Sequence	Provides information on:
T1-weighted	brain morphology, focal or diffuse atrophy
T2-weighted or fluid-attenuated inversion recovery (FLAIR)	white-matter hyperintensities, old vascular lesions
Diffusion-weighted imaging (DWI)	number, size and location of most recent ischemic lesions
Susceptibility-weighted imaging (SWI)/GRE-T2*	microbleeds, cortical superficial siderosis

1. Verdelho, A., Wardlaw, J., Pavlovic, A., Pantoni, L., Godefroy, O., Duering, M., Charidimou, A., Chabriat, H., & Biessels, G. J.[2021]. Cognitive impairment in patients with cerebrovascular disease: A white paper from the links between stroke ESO Dementia Committee. European stroke journal, 6[1], 5-17.

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