History of Vascular Cognitive Impairment and Dementia

Lukas Sveikata and Frédéric Assal

Abstract: Over the years, the definition of vascular cognitive impairment and dementia (VCID) has become a "moving target" due to demographic changes, advancements in the management of vascular risk factors, and neuroimaging. Since Sir Thomas Willis described the anatomy of brain blood supply (1664), "cerebral congestion" has become the main cause of dementia for several centuries. Later, the spotlight was on hypertensive arteriopathy, but as the population aged and hypertension management improved, the focus shifted to cerebral amyloid angiopathy and its contributions to dementia. The seminal pathological descriptions in the 1900s by Alzheimer and Binswanger put cerebrovascular disease on the map as one of the main drivers of cognitive dysfunction under the umbrella term of arteriosclerosis. It was not until the 1970s, with the advent of modern brain imaging, that the concept of vascular dementia (VaD) became widely accepted. The term VCID, on the other hand, was a result of developments in the understanding of a broad clinical spectrum of vascular disease, ranging from minor to major cognitive decline. The imaging revolution has led to the phenotyping of small-vessel disease, including the in vivo diagnosis of cerebral amyloid angiopathy, a key driver of VCID. Cerebrovascular disease has become widely recognized as the second most common form of dementia. In recent decades, the incidence of dementia was decreasing, leading to the recognition of vascular health as a major factor in brain health. We provide an overview of the field's evolution, from Sir Thomas Willis to our current understanding of VCID.

1. 17th to 19th Century—Apoplexy or the Concept of "Cerebral Congestion"

In the 17th century, stroke, referred to as the most typical form of apoplexy (from ancient Greek, "striking away"), was attributed to "cerebral congestion". Therefore, bloodletting was a common therapy until the introduction of the sphygmomanometer by Riva-Roci (1896) and Korotkov (1905) and the recognition of arterial hypertension as the primary cause of stroke.

The descriptions of Sir Thomas Willis (1621–1675) trace the origins of vascular dementia (VaD). In his work *De Anima Brutorum* [1], Willis wrote about his first case series of post-stroke dementia, describing the spectrum of clinical presentations from "dullness of mind and forgetfulness" to "stupidity and foolishness" accompanied by hemiplegia. He was also the first to recognize the ischemic nature of apoplexy. In *Cerebri Anatome* (1662) [2] he described an occlusion of the carotid artery and persistent collateral brain circulation —"The nature had substituted a sufficient remedy against the danger of Apoplexy", referring to the principal brain supplying arteries forming an anastomotic circle, named after him (Figure 1). Etienne Esquirol

(1772–1840) provided an anatomo-pathological report on 232 cases, identifying apoplexy as a potential cause of dementia [3]. Amédée Dechambre (1812–1886), a French physician, was the first to characterize "lacunes" (1838) in stroke survivors as small "cerebral softenings" (*ramollissement cérébral*) [4]. Five years later, Maxime Durand-Fardel (1843), the father of gerontology in France, independently postulated the pathogenesis of lacunes [5]. In 1854, Durand-Fardel described interstitial atrophy of the brain (compatible with modern-day *leukoaraiosis*) and *état criblé* (cribriform state, sieve-like state) reflecting chronic "cerebral congestion" [6].

In 1878, William Alexander Hammond (1828–1900), an American military physician and neurologist, stated the following:

> *Cerebral congestion is more common . . . than any other affection of the nervous system . . . the result of mental strain or emotional disturbance . . . an outgrowth of our civilization, and of the restless spirit of enterprise and struggle for wealth . . .* [7]

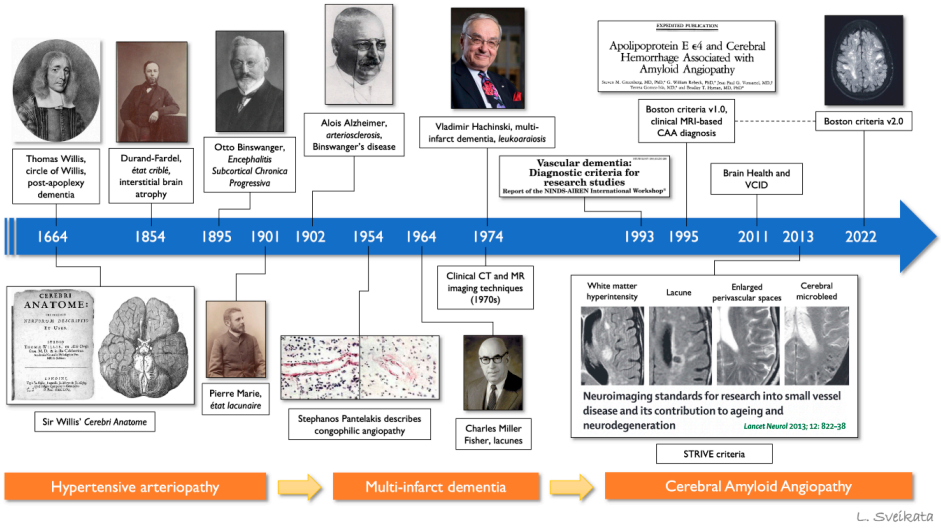

Figure 1. Principal clinician–scientists, their contributions, and major developments in vascular cognitive impairment and dementia (VCID). Over time, the field's focus has shifted from hypertensive arteriopathy to cerebral amyloid angiopathy as the primary pathology of interest, driven by population aging and better care for vascular risk factors. Source: Adapted from personal collection (V.H.) as well as Wardlaw et al. 2013 Lancet Neurol and Charidimou et al. 2022 Lancet Neurol, with permission from Elsevier.

2. 20th Century—Arteriosclerosis Confusion and the Dawn of Vascular Dementia

The modern history of VaD starts with Otto Binswanger (1852–1929) and Alois Alzheimer (1864–1915). The latter characterized arteriosclerotic brain atrophy

(*arteriosclerotische Hirnatrophie*) and separated it from neurosyphilitic progressive paralysis (Table 1) [8]. In 1902, Alzheimer coined the name Binswanger's disease after the latter's description of white matter pallor as well as atrophy in one of his demented patients:

> *The disease has an insidious onset, with mild tiredness, headache, dizziness, decrease in sleep, followed by severe irritability and memory deficit. Alternatively, sudden onset with an apoplectiform attack and one-sided paralysis could initiate the picture*. [9]

Table 1. Historical terms used to describe vascular cognitive impairment and dementia. Source: Authors' compilation based on references provided in the table. Abbreviations: AHA/ASA, American Heart Association, American Stroke Association; AIREN, Association Internationale pour la Recherche et 1'Enseignement en Neuroscience, NINDS, Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke.

Term	Main Reference
Cerebral congestion	17th century
Post-apoplexy dementia	Thomas Willis (1672) [1]
Cerebral softenings (*ramollissement cérébral*), lacunes	Amédée Dechambre (1838) [4] and Durand-Fardel (1843) [5]
Interstitial brain atrophy and *etat criblé*	Durand-Fardel (1843) [5]
General arthritic pseudoparalysis (Klippel's disease)	Maurice Klippel (1892) [10]
Chronic progressive subcortical encephalopathy (*Encephalitis subcorticalis chronica progressiva*)	Otto Binswanger (1894) [11]
Arteriosclerotic dementia	Alois Alzheimer (1897) [12]
Etat lacunaire et criblé	Pierre Marie (1901) [13]
Binswanger's disease	Alois Alzheimer (1902) [9]
Senile dementia, arteriosclerosis	Emil Kraepelin (1910) [14]
Multi-infarct dementia	Vladimir Hachinski et al. (1974) [15]
Leukoaraiosis	Vladimir Hachinski et al. (1987) [16]
Vascular dementia	Gustavo Román et al. NINDS-AIREN criteria (1993) [17]
Vascular leukoencephalopathy	Unknown, but mostly derived from older CADASIL literature [18]
Subcortical ischemic vascular dementia	Gustavo Román et al. (2002) [19]
Post-stroke dementia	Didier Leys et al. (2005) [20]
Vascular cognitive impairment and dementia	Philip Gorelick et al. AHA/ASA Scientific Statement (2011) [21]

Alzheimer wondered whether white matter changes might be the result of secondary degeneration due to small infarcts, but he did not offer clear proof. He distinguished four clinicopathological variants of VaD: dementia post-apoplexy (later known as post-stroke dementia), arteriosclerotic brain degeneration (*état lacunaire* or *criblé*), senile cortical atrophy (granular atrophy), and subcortical encephalopathy (Binswanger's disease, later known as small-vessel disease). Interestingly, in the more severe forms of progressive arteriosclerotic brain degeneration, Alzheimer described multiple bleedings and softenings in the cerebral cortex as well as hemispheric white matter, possibly corresponding to microbleeds related to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or cerebral amyloid angiopathy (CAA).

Stephanos Pantelakis, a neuropathologist from Geneva Brain Collection, provided one of the first detailed pathological descriptions of congophilic angiopathy in 1954, known as modern-day CAA [22,23]. Subsequent studies supported Pantelakis' original discoveries that CAA impacts cortical and leptomeningeal vessels, that it was associated with age, dementia, its predilection for occipital lobes, and its absence of relation to arteriosclerosis. These findings paved the way for CAA as a unique disease entity, although it remained a pathological entity for several decades until its clinical manifestations of brain hemorrhaging and cognitive decline were attributed to the disease at the turn of the 21st century.

In the decades to come, Olszewski (1962) and Hachinski (1991) were skeptical of the existence of "so-called Binswanger's Disease" [24,25]. To them, Binswanger's description seemed to resemble leukodystrophies, Schilder's disease (currently a form of multiple sclerosis), or especially syphilitic changes. Notwithstanding, Binswanger also described two other forms of VaD: arteriosclerotic brain disease and dementia post-apoplexia, compatible with hypertensive arteriopathy and multi-infarct dementia, respectively [26]. One of the earliest illustrations of Binswanger's disease was published in the chapter on "Senile and Presenile Dementia" in the 1910 edition of Emil Kraepelin's seminal psychiatry textbook [14]. Kraepelin's influence was so prominent that, after the description of arteriosclerotic dementia and cerebral arteriosclerosis, the term "sclerosis" became synonymous with senile dementia for the next 70 years [27].

Pierre Marie (1853–1940), from the Hospice for the Elderly in Bicêtre, Paris, presented on *état lacunaire et criblé* at the 1901 congress in Paris [13]. For several decades there was some confusion between lacunes and *état criblé* until Charles Miller Fisher (1913–2012) published his landmark observations on lacunes in the 1960s [28,29]. He noted the frequent step-wise progression affecting speech, producing dysarthria, pseudobulbar signs, gait and instability problems, diplopia, aphasia, and confusion. He noted that "by the time the full course has been run, the patient may be immobilized by bilateral hemiparesis, incontinent, mute, and mindless" [30].

With the advent of neuroimaging, leukoaraiosis, derived from Greek root *leukos*, "white", and *araios*, "rarefied", was coined by Vladimir Hachinski and colleagues in 1987 [16]. The assumption of hypoperfusion causing vascular brain lesions led to decades of "blanket" treatment with vasodilation drugs, but all in vain [31]. Even upon detailed histopathological examination, Fisher did not observe vascular occlusions in penetrating arteries of the white matter, discarding the hypothesis that white matter disease was due to an occlusive mechanism [29,30]. Modern-era advanced neuroimaging techniques were also unable to demonstrate occlusion of a single artery leading to white matter injury [32].

3. End of the 20th and 21st Century: Neuroimaging Revolution

3.1. 1970s: From Multi-Infarct Dementia to VaD Subtypes

The advent of CT and, later, MRI imaging allowed for the in vivo identification of vascular contributions to dementia. In 1968, Charles Miller Fisher provided a lucid description of vascular dementia from his extensive experience, summarizing that "it is a matter of strokes large and small" [33]. The old and confusing term cerebral arteriosclerosis was replaced by multi-infarct dementia by Hachinski and colleagues in 1974 [15]. The latter concept was based on the mechanism that multiple brain infarcts of varying sizes ultimately cause cognitive deterioration. Although multi-infarct dementia and tools, such as the ischemic score, suggested a person's cerebrovascular burden, neither a causal nor temporal relation between vascular lesions and dementia was established [34].

A standardized diagnostic approach was required to advance the VaD field. The ADDTC criteria unified clinical and imaging criteria exclusively for ischemic VaD, requiring one or two strokes and a clear temporal relationship between a stroke and dementia onset [35]. DSM-IV and ICD-10 criteria were less restrictive but did not specify neuroimaging standards. VaD was recognized to have a much broader clinical spectrum than multi-infarct dementia under the 1993 NINDS-AIREN criteria, which included a subtype due to small-vessel disease [17]. Later, to emphasize the need for early detection and prevention, the term mild cognitive impairment of vascular origin or vascular cognitive impairment (VCI)—no dementia was proposed [36]. Next, because of relatively intact memory in VCI (relatively preserved integrity of mesial temporal lobes and thalami), the 2011 AHA/ASA criteria no longer required memory impairment to diagnose vascular dementia. The concept of brain health was also introduced [21]. The most recent VICCCS guidelines provided standardization of the VCI diagnosis based on MRI imaging, neuropsychological testing, and clinical components [37]. They encompassed a broad clinical spectrum, from mild to major VCI, and acknowledged subtypes of VCI, including mixed pathologies.

MRI became the gold standard and allowed for better phenotyping of small-vessel [38]. The delineation of ischemic and hemorrhagic imaging markers became possible. Iron-sensitive imaging allowed for the clinical identification of

CAA [39]. This was clinically relevant, as CAA was increasingly recognized as being highly prevalent in older adults. Importantly, combined vascular and AD pathologies lead to a higher likelihood of dementia than either pathology alone [40,41]. The most recent update of the Boston criteria v2.0, incorporated non-hemorrhagic imaging markers and improved diagnostic accuracy across a spectrum of clinical settings, including cognitive impairment without previous hemorrhage [42].

3.2. Diffuse White Matter Disease

Ischemic brain injury, commonly detected in pathology as macro- or microinfarcts related to small-vessel disease, was increasingly recognized as a driver of cognitive decline. Leveraging the arrival of MRI, Franz Fazekas and colleagues unified the WMH grading system in 1984 [43]. Later, Wahlund and colleagues developed a widely used clinical scale to rate age-related white matter changes [44]. In 2013, the STRIVE guidelines brought standardization to small-vessel disease imaging and terminology and, thus, made a significant advancement in the field [18]. White matter hyperintensities (WMHs) were proposed as an umbrella term to encompass different terms previously used to describe white matter changes, e.g., vascular leukoencephalopathy, Binswanger's disease, leukoaraiosis, etc. The WMHs term had a major advantage in terms of being purely descriptive and not attempting to delineate underlying tissue alteration mechanisms, as they are now known to be highly variable.

3.3. Mechanisms of Vascular Pathology

In recent decades, diffusion-weighted imaging has made it possible to recognize microinfarcts that despite their small size have significant effects on cognitive decline [45]. Microinfarcts became a marker of widespread vascular damage leading to disconnection syndrome [46]. As the underlying cellular function was better understood, the concepts of the blood–brain barrier [47] and neurovascular unit dysfunction [48] came to light.

The discovery of the NOTCH 3 gene related to CADASIL in 1996 greatly advanced research and understanding of the pathophysiology of small-vessel disease [49]. The discovery improved our understanding of the clinical and radiologic manifestations of "pure" vascular disease, independent of Alzheimer's disease [50].

Multiple neuropathological effects of the apolipoprotein E (ApoE) e4 allele have been identified, including decreased amyloid clearance, the loss of cerebrovascular integrity, and blood–brain barrier disintegration. In 1995, Greenberg and colleagues discovered that the presence of the ApoE ε4 allele raises the levels of both plaque and vascular amyloid, suggesting major implications for VCID [51]. Adults who were more likely to develop AD or CAA were able to be identified thanks to APOE genotyping. Contrarily, ApoE ε2 was found to be protective in AD but a risk factor for hemorrhagic CAA (for a review of this, see Greenberg et al. 2020 [52]).

4. Conclusions

The history of VCID starts with Sir Thomas Willis' description of post-apoplexy dementia, described as "dullness of mind and forgetfulness". In the two centuries that followed, the initial approach was focused on "brain congestion" and bloodletting. Over the years, the definition of VCID has become a "moving target" and shifted due to changes in population demography, improving vascular risk factor control, and advancement in neuroimaging. The vascular alterations in patients with dementia have been extensively discussed in seminal works by Alzheimer and Binswanger; however, the concepts of senile dementia (akin to Alzheimer's disease) and arteriosclerotic disease were used interchangeably for several decades. In the modern era, a subclassification of vascular dementia subtypes arose. This was followed by the concepts of vascular cognitive impairment and dementia, which were more inclusive and encompassed both ischemic and hemorrhagic vascular brain alterations. The identification of small-vessel disease, including CAA in vivo, expanded the boundaries of our knowledge of the linkages between vascular and Alzheimer's disease. As a result of better blood pressure control and improved vascular health, the incidence of dementia has been declining in recent years [44]. This intriguing finding suggests that vascular dementia may be the most curable and, possibly, most fascinating type of dementia. The evolution of VCID has proven once again that "The problems are immense, but the opportunities are even greater" [53].

Author Contributions: L.S. drafted the manuscript, while both authors revised and approved the published version. All authors have read and agreed to the published version of the manuscript.

Funding: Lukas Sveikata was supported by the Swiss National Science Foundation postdoctoral award (P2GEP3_191584). Frédéric Assal was supported by the FNS Sinergia CRSII5_202228, FNS 4078P0_198438/1].

Acknowledgments: We thank Andreas Charidimou for his critical review and suggestions to the manuscript. The figure elements were reproduced with permission from Vladimir Hachinski and Elsevier.

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Willis, T. *De anima brutorum*; Davis: London, UK, 1672.
2. Willis, T. *Cerebri anatome: Cui accessit nervorum descriptio et usus*; Martin & Allestry by University College London: London, UK, 1664.
3. Esquirol, E. *Des Maladies Mentales Considérées Sous les Rapports Médical, Hygiénique et Médico-Légal*; J.-B. Baillière: Paris, France, 1938.
4. Dechambre, A. Mémoire sur la curabilité du ramollissement cérébral. *Gazette Medicale de Paris* **1838**, *6*, 305–314.
5. Durand-Fardel, M. *Traité du ramollissement du cerveau*; J.-B. Baillière: Paris, France, 1843.
6. Durand-Fardel, M. *Traité clinique et pratique des maladies des vieillards*; G. Baillière: Paris, France, 1854.

7. Hammond, W.A. *Cerebral Hyperæmia; The Result of Mental Strain or Emotional Disturbance*; G.P. Putnam's Sons: New York, NY, USA, 1879.
8. Alzheimer, A. Die arteriosklerotische atrophie des gehirns. *Neurol Cent.* **1894**, *51*, 1809–1812.
9. Alzheimer, A. Die Seelenstörungen auf arteriosclerotischer Grundlage. *Allg. Z Psychiatr. Psych.-Gerichtl. Med.* **1902**, *59*, 695–711.
10. Klippel, M. De la pseudoparalysie générale arthritique. *Rev. De Méd.* **1892**, *12*, 280–285.
11. Binswanger, O. Die Abgrenzung der allgemeinen progressiven Paralyse. *Berl. Klin Wochenschr.* **1894**, *49*, 1103–1105, 1137–1139, 1180–1186.
12. Alzheimer, A. Ueber perivasculaere Gliose. *Allg. Z Psychiatr. Psych. Med.* **1897**, *53*, 863–865.
13. Marie, P. Des foyers lacunaires de désintégration et de différents autres états cavitaires du cerveau. *Rev. Méd.* **1901**, *21*, 281–298.
14. Kraepelin, E. *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. II. Band*; Johann Ambrosius Barth: Leipzig, Germany, 1910.
15. Hachinski, V.C.; Lassen, N.A.; Marshall, J. Multi-infarct dementia a cause of mental deterioration in the elderly. *Lancet* **1974**, *304*, 207–209. [CrossRef]
16. Hachinski, V.C.; Potter, P.; Merskey, H. Leuko-Araiosis. *Arch. Neurol.-Chic.* **1987**, *44*, 21–23. [CrossRef]
17. Roman, G.C.; Tatemichi, T.K.; Erkinjuntti, T.; Cummings, J.L.; Masdeu, J.C.; Garcia, J.H.; Amaducci, L.; Orgogozo, J.-M.; Brun, A.; Hofman, A.; et al. Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. *Neurology* **1993**, *43*, 250. [CrossRef]
18. Wardlaw, J.M.; Smith, E.E.; Biessels, G.J.; Cordonnier, C.; Fazekas, F.; Frayne, R.; Lindley, R.I.; O'Brien, J.T.; Barkhof, F.; Benavente, O.R.; et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* **2013**, *12*, 822–838. [CrossRef] [PubMed]
19. Román, G.C.; Erkinjuntti, T.; Wallin, A.; Pantoni, L.; Chui, H.C. Subcortical ischaemic vascular dementia. *Lancet Neurol.* **2002**, *1*, 426–436. [CrossRef] [PubMed]
20. Leys, D.; Hénon, H.; Mackowiak-Cordoliani, M.-A.; Pasquier, F. Poststroke dementia. *Lancet Neurol.* **2005**, *4*, 752–759. [CrossRef]
21. Gorelick, P.B.; Scuteri, A.; Black, S.E.; DeCarli, C.; Greenberg, S.M.; Iadecola, C.; Launer, L.J.; Laurent, S.; Lopez, O.L.; Nyenhuis, D.; et al. Vascular Contributions to Cognitive Impairment and Dementia. *Stroke* **2011**, *42*, 2672–2713. [CrossRef] [PubMed]
22. Kövari, E.; Hof, P.R.; Bouras, C. The Geneva brain collection. *Ann. N. Y. Acad. Sci.* **2011**, *1225*, E131–E146. [CrossRef]
23. Pantelakis, S. Un type particulier d'angiopathie sénile du système nerveux central: L'angiopathie congophile. Topographie et fréquence; pp. 219–237. *Eur. Neurol.* **1954**, *128*, 219–237. [CrossRef]
24. Hachinski, V. Binswanger's disease: Neither Binswanger's nor a disease. *J. Neurol. Sci.* **1991**, *103*, 1. [CrossRef]
25. Olszewski, J. Subcortical arteriosclerotic encephalopathy. Review of the literature on the so-called Binswanger's disease and presentation of two cases. *World Neurol.* **1962**, *3*, 359–375.

26. Mast, H.; Tatemichi, T.K.; Mohr, J.P. Chronic brain ischemia: The contributions of Otto Binswanger and Alois Alzheimer to the mechanisms of vascular dementia. *J. Neurol. Sci.* **1995**, *132*, 4–10. [CrossRef]
27. Román, G. Vascular Dementia: A Historical Background. *Int. Psychogeriatr.* **2003**, *15*, 11–13. [CrossRef]
28. Fisher, C.M. Lacunes Small, deep cerebral infarcts. *Neurology* **1965**, *15*, 774. [CrossRef] [PubMed]
29. Fisher, C.M. The arterial lesions underlying lacunes. *Acta Neuropathol.* **1969**, *12*, 1–15. [CrossRef] [PubMed]
30. Fisher, C.M. Binswanger's encephalopathy: A review. *J. Neurol.* **1989**, *236*, 65–79. [CrossRef] [PubMed]
31. Frackowiak, R.S.J.; Pozzilli, C.; Legg, N.J.; Boulay, G.H.; Marshall, J.; Lenzi, G.L.; Jones, T. Regional cerebral oxygen supply and utilization in dementia: A clinical and physiological study with oxygen-15 and positron tomography a clinical and physiological study with oxygen-15 and positron tomography. *Brain* **1981**, *104*, 753–778. [CrossRef] [PubMed]
32. Wardlaw, J.M.; Dennis, M.S.; Warlow, C.P.; Sandercock, P.A. Imaging appearance of the symptomatic perforating artery in patients with lacunar infarction: Occlusion or other vascular pathology? *Ann. Neurol.* **2001**, *50*, 208–215. [CrossRef] [PubMed]
33. Fisher, C.M. Dementia in cerebral vascular disease. In *Cerebral Vascular Diseases: Sixth Princeton Conference*; Toole, J.F., Siekert, R.G., Whisnant, J.P., Eds.; Grune & Stratton: New York, NY, USA, 1968; pp. 232–236.
34. Hachinski, V.C.; Iliff, L.D.; Zilhka, E.; Boulay, G.H.D.; McAllister, V.L.; Marshall, J.; Russell, R.W.R.; Symon, L. Cerebral Blood Flow in Dementia. *Arch. Neurol.-Chic.* **1975**, *32*, 632–637. [CrossRef]
35. Chui, H.C.; Victoroff, J.I.; 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. [CrossRef]
36. Bowler, J.; Hachinski, V. Vascular cognitive impairment: A new approach to vascular dementia. In *Bailliere's Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, 1995; Volume 4, pp. 357–376.
37. Skrobot, O.A.; Black, S.E.; Chen, C.; DeCarli, C.; Erkinjuntti, T.; Ford, G.A.; Kalaria, R.N.; O'Brien, J.; Pantoni, L.; Pasquier, F.; et al. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. *Alzheimer's Dement.* **2018**, *14*, 280–292. [CrossRef]
38. Zotin, M.C.Z.; Sveikata, L.; Viswanathan, A.; Yilmaz, P. Cerebral small vessel disease and vascular cognitive impairment: From diagnosis to management. *Curr. Opin. Neurol.* **2021**, *34*, 246–257. [CrossRef]
39. Greenberg, S.M.; Vonsattel, J.P.G.; Stakes, J.W.; Gruber, M.; Finklestein, S.P. The clinical spectrum of cerebral amyloid angiopathy: Presentations without lobar hemorrhage. *Neurology* **1993**, *43*, 2073. [CrossRef]
40. Viswanathan, A.; Greenberg, S.M. Cerebral amyloid angiopathy in the elderly. *Ann. Neurol.* **2011**, *70*, 871–880. [CrossRef] [PubMed]

41. Zekry, D.; Duyckaerts, C.; Moulias, R.; Belmin, J.; Geoffre, C.; Herrmann, F.; Hauw, J.-J. Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. *Acta Neuropathol.* **2002**, *103*, 481–487. [CrossRef] [PubMed]
42. Charidimou, A.; Boulouis, G.; Frosch, M.P.; Baron, J.-C.; Pasi, M.; Albucher, J.F.; Banerjee, G.; Barbato, C.; Bonneville, F.; Brandner, S.; et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: A multicentre, retrospective, MRI–neuropathology diagnostic accuracy study. *Lancet Neurol.* **2022**, *21*, 714–725. [CrossRef] [PubMed]
43. Fazekas, F.; Chawluk, J.; Alavi, A.; Hurtig, H.; Zimmerman, R. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am. J. Roentgenol.* **1987**, *149*, 351–356. [CrossRef]
44. Wahlund, L.O.; Barkhof, F.; Fazekas, F.; Bronge, L.; Augustin, M.; Sjögren, M.; Wallin, A.; Ader, H.; Leys, D.; Pantoni, L.; et al. A New Rating Scale for Age-Related White Matter Changes Applicable to MRI and CT. *Stroke* **2001**, *32*, 1318–1322. [CrossRef]
45. Van Veluw, S.J.; Shih, A.Y.; Smith, E.E.; Chen, C.; Schneider, J.A.; Wardlaw, J.M.; Greenberg, S.M.; Biessels, G.J. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol.* **2017**, *16*, 730–740. [CrossRef]
46. Ter Telgte, A.; van Leijsen, E.M.C.; Wiegertjes, K.; Klijn, C.J.M.; Tuladhar, A.M.; de Leeuw, F.-E. Cerebral small vessel disease: From a focal to a global perspective. *Nat. Rev. Neurol.* **2018**, *14*, 387–398. [CrossRef]
47. Wardlaw, J.M.; Sandercock, P.A.G.; Dennis, M.S.; Starr, J. Is Breakdown of the Blood-Brain Barrier Responsible for Lacunar Stroke, Leukoaraiosis, and Dementia? *Stroke J. Am. Heart Assoc.* **2003**, *34*, 806–812. [CrossRef]
48. Iadecola, C. The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron* **2017**, *96*, 17–42. [CrossRef]
49. Joutel, A.; Corpechot, C.; Ducros, A.; Vahedi, K.; Chabriat, H.; Mouton, P.; Alamowitch, S.; Domenga, V.; Cécillion, M.; Maréchal, E.; et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* **1996**, *383*, 707–710. [CrossRef]
50. Buffon, F.; Porcher, R.; Hernandez, K.; Kurtz, A.; Pointeau, S.; Vahedi, K.; Bousser, M.-G.; Chabriat, H. Cognitive profile in CADASIL. *J. Neurol. Neurosurg. Psychiatry* **2006**, *77*, 175. [CrossRef] [PubMed]
51. Greenberg, S.M.; Rebeck, G.W.; Vonsattel, J.P.G.; Gomez-Isla, T.; Hyman, B.T. Apolipoprotein E ϵ4 and cerebral hemorrhage associated with amyloid angiopathy. *Ann. Neurol.* **1995**, *38*, 254–259. [CrossRef] [PubMed]
52. Greenberg, S.M.; Bacskai, B.J.; Hernandez-Guillamon, M.; Pruzin, J.; Sperling, R.; van Veluw, S.J. Cerebral amyloid angiopathy and Alzheimer disease—One peptide, two pathways. *Nat. Rev. Neurol.* **2020**, *16*, 30–42. [CrossRef] [PubMed]
53. Hachinski, V. Vascular Dementia: A Radical Redefinition. *Dement. Geriatr. Cogn.* **1994**, *5*, 130–132. [CrossRef] [PubMed]