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Abstract: Vascular dementia (VaD) is recognised as the second most common cause of dementia after Alzheimer's disease (AD), responsible for around 15% of cases. However, unlike AD, there are currently no licensed treatments for VaD. Progress in the field has been difficult due to uncertainties over nosology and diagnostic criteria, controversy over the exact nature of the relationship between cerebrovascular pathology and cognitive impairment, and the lack of identifiable tractable treatment targets. Though there is an established relationship between vascular and degenerative (Alzheimer) pathology, the mechanistic link between the two has yet to be identified. This review critiques some of the key areas and controversies, summarises treatment trials to date and makes suggestions for what progress is needed to advance our understanding of pathogenesis and so maximise opportunities for the search for new and effective management approaches.

THELANCET-D-15-01740, Vascular Dementia

Dear Helen,

Many thanks indeed for your email and reviewers comments on this. Please find a revised version attached which addresses all the comments made. In our response we have been mindful of the need to fully consider the reviewer's comments, while not significantly extending the length of the paper.

COMMENTS FROM EDITOR

1. *I would be grateful if you could tweak your introduction so that it also briefly states the background for this topic, provides the rationale for the review, and briefly outline what will be covered and the aims for the article.*

We have altered the introduction so that is now states the background, provides the rationale and outlines what's been covered and the aims.

2. *Please could you insert the clinicaltrials.gov registration number or other reference for the AFFECT trial mentioned on page 7.*

We have inserted the trial reference number for the AFFECT study (actually listed on the European clinical trials database).

3. *You mention in your concluding section that potential treatments are currently in clinical trials. Would it be possible to include a short table of any important ongoing trials, including basic details and trial registration numbers?*

The difficulty with including a table is that there are 93 trials listed on clintrials.gov as involving vascular dementia, but many of these are of limited size and the descriptions are generally limited; it would be quite challenging and rather arbitrary to choose a small number for a table. There would also be the issue as to whether to only include pharmacological or also other studies which can be as varied as hyperbaric oxygen and the treatment of associated sleep apnoea. Moreover, in some of the studies it is not entirely clear the extent to which cognition is a primary or secondary outcome. We therefore feel it is probably more appropriate simply to point out that there are studies ongoing, and we have altered the text to signify that these are rather limited in nature (although large in number, the actual size and likely significant advances from these studies would in our estimation be quite small – we know of no other study apart from AFFECT that has significant ambitions in this area).

4. *All reviews and seminars should include a panel entitled "Search strategy and selection criteria", which gives the sources (databases, journal or book reference lists, etc) searched for the references you cite, and the criteria you used to include or exclude studies. Searches should not be limited to English language publications.*

Thank you, we have included a note regarding our search strategy according to the guidance you helpfully sent. This is as follows:

"We searched MEDLINE and EMBASE from start to end 2014 using the search terms "vascular dementia" (both as a single term and also "vascular" AND "dementia") and "vascular cognitive impairment". We largely selected publications in the past 5 years, but did not exclude commonly

referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers."

5. *Please ensure that all disclosures on your COI form match those in your manuscript (eg, financial support from Cytox is mentioned on the form but not in the manuscript for JOB).*

We apologise that the disclosures in the Conflict of Interest form did not match those in the manuscript. This has now been corrected.

6. *Please add each author's contribution to the study in a paragraph entitled Contributions at the end of the manuscript.*

We have added a note of each author's contribution to the study.

7. *Please ensure that high-resolution versions of all images are provided. All submitted photographic images are best supplied 20% larger than they will appear in The Lancet and should have a resolution of 300 dpi. This will ensure high quality processing of your images for print.*

We include high resolution versions of all the images, supplied larger than they will appear in the Lancet with a resolution of 300 dpi.

Reviewer 1

Reviewer #1: The paper is well written and clear. The sections re background, discussion of controversies, diagnostic issues, neuroimaging and neuropathology are concise but clear and provide an excellent presentations of the main issues and key papers.

The treatment section was thorough re RCTs focussing on cognition/function, but could have included more re neuropsychiatric symptoms.

We thank the reviewer for their positive comments regarding the clear and concise nature of our review. Although the reviewer indicates that there could have been more discussion of neuropsychiatric symptoms, Table 2 does contain a column titled "behaviour" which demonstrates that very few studies have investigated this, and with regard to the best evidence base (cholinesterase inhibitors) no significant benefit has been found. Unfortunately, we do not have to the space to discuss other studies which have investigated neuropsychiatric symptoms, there are actually very few and none have produced convincing or positive results. We have therefore altered the labelling in Table 2 to indicate that we are really presenting results from neuropsychiatric symptoms rather than just behaviour, and also altered the text (page 7) to indicate this.

I was slightly disappointed though re the limited scope of the section re prevention - particularly with respect to lifestyle factors - which ignored much of the literature and only briefly mentioned the extremely important FINGER study. There were also some important omissions re the potential impact of management of vascular risk factors from longitudinal studies and it would have been useful to include a section re hypotheses novel targets and possible approaches to move this forward.

We agree there was relatively limited discussion on prevention, but we are very much constrained by the very tight word limit of the article. However, we have tried to expand this within the constraints allowed. We have covered prevention in around 500 words, approximately 20% of the

manuscript is devoted to this. Apart from the FINGER study, we do not feel that there are significant data from other studies to merit a more detailed discussion.

The introduction and conclusion also seemed more pessimistic than the content of the data. Maybe something re opportunities to move the field forward with more investment would have been more upbeat.

We certainly did not intend the article to be entirely pessimistic, but on reflection we understand this concern and have reworded sections of the introduction and conclusion to address this issue.

Reviewer 2

Reviewer #2: This is a well written and well documented review on Vascular Dementia (VaD). The introduction with the history of classification is clear and very useful for the reader. One element should be underlined: should we classify a subject at a given time or on the basis of the history of the patient?. The conditions to classify a case depend of the place of the diagnosis. For instance diagnosis in clinical setting could be different than in population-based study. This is a problem to characterize a clinical entity. Moreover, it seems that the classification of VaD remains transitory and will change with the efficacy of treatment, the biomarkers or neuroimaging progress. It's also true for Alzheimer's Disease (AD) but this fact should be underlined.

We thank reviewer 2 for these positive comments.

Amyloid angiopathy with or without brain haemorrhage was not evoked. Why ?

We have not specifically sought to go into such detail regarding individual syndromes, amyloid angiopathy would be covered in the section on haemorrhagic dementia in Table 1. To clarify this, we have altered Table 1 to make clear that haemorrhagic changes may be associated with amyloid angiopathy.

In the Epidemiology paragraph, the recent drop in incidence and prevalence of Dementia is not discussed. Is it due to a drop in VaD related to an improvement in the management of risk factors ? This point is important to develop for the promotion of prevention.

Thank you for raising this. We agree that this is important, and have now included a brief discussion regarding epidemiological studies such as the Cognitive Function and Ageing (CFAS) study which suggests there may be a reduction in dementia prevalence over time, possibly reflecting an improvement in the management of risk factors – though this does remain somewhat speculative.

In Brain imaging paragraph, the relation between White Matter Hyperintensities (WMH) and VaD should me more developed.

Thank you. We now include a slightly fuller discussion on the role of white matter lesions as predictors of dementia and cognitive decline.

By the same way, the relations between biomarkers of AD and VaD should be evoked.

We have not expanded on the discussion between biomarkers of vascular dementia due to constraints of space, but have now included a brief discussion regarding biomarkers of vascular dementia, an area where some progress has certainly been made but much more is required in terms of validation.

In the Management of VaD, the prognosis of VaD should be presented. This is certainly an important point for the future. To manage a patient and his caregiver, we have to make a good prognosis as a good diagnosis. What is the real interest to make a diagnosis of VaD versus AD for the patient, the caregiver and the Primary Care Practitioner ? Moreover, the interest of non drug treatment should be underlined.

Thank you for this comment. We have now added a sentence regarding the prognosis of vascular dementia. We agree that the importance of making a vascular dementia diagnosis as opposed to Alzheimer's disease for the patient the caregiver and the primary care practitioner an important point but do not feel full discussion of this is within the scope of the current article.

In the conclusion and future direction section, the authors should view the following question : is it really relevant to separate neurodegenerative and vascular entities ?

We agree this is an important question, and have added a sentence in the conclusion to address this.

Reviewer 3

Reviewer #3: The authors wrote a well-considered review or perspective entitled simply, "vascular dementia."

Thank you for this positive comment.

The first line is jarring and attention-grabbing and sets out the theme of the paper which is, the term 'vascular dementia' is controversial. Thus I would expect that the authors will contain or focus the controversy. They ask a couple of questions in that first paragraph but it is not clear that they later answer them. They identify that a challenge in the area is validation of proposed clinical and pathologic concepts. But I don't see later-on where they attempt to show a path forward toward validation.

We thank the reviewer for this comment. We agree the two were not well linked and so we now add a sentence in the conclusions and future directions to attempt to link these, when talking about in vivo biomarkers "such work will also be important to answer the key question as to whether and in what circumstances is relevant to separate out neurodegenerative vascular entities and so, in combination with pathological investigation, provide important validation of our clinical concepts of vascular dementia".

Table 1 is of historical interest listings subtypes of vascular dementia and show that there have been many changes in nosology. In my opinion the authors need to propose a nomenclature that readers can use now. Table 1 would benefit from direct citations and, for some of the conditions, a more detailed description of the imaging and pathology.

Given the complexities of this area, we feel it is beyond the scope of our brief commentary and review to propose a whole new nomenclature for vascular dementia. One has recently been published (Sachdev et al, 2014) which represents a consensus in the area. We already cite this paper and have now made our citation more relevant by clearly signposting readers towards this. So we have altered the paragraph under the table to finish "whilst similar attempts have been made to standardise and operationalise newly proposed sets of diagnostic criteria to provide a common and up to date nomenclature for vascular cognitive disorders (Sachdev et al, 2014)".

I don't see on page 3 a discussion about how one goes about diagnosing vascular cognitive impairment in the first place. Moreover is vascular cognitive impairment a valid diagnosis with adequate sensitivity and specificity or is it simply consensus-based? Either way a reader should be clear on the opinions and guidance of the authors.

Thank you for pointing this out, and we agree. To clarify our position we have now included, during the discussion of VCI, the new sentence "However, there are no clear diagnostic criteria for VCI and it remains a term highlighting the spectrum of pathology, rather than a clearly validated diagnostic entity".

Considering what the authors discussed earlier about the uncertainties of diagnoses, how can they rely on epidemiology if it uses these suspect definitions of vascular dementia? This is especially to say it is the second most common cause of dementia when earlier and later they discuss it is conflated with other pathology such as Alzheimer pathology. Some clarification here would be helpful.

The reviewer is quite right to point out that definitions are key to determining things like accurate epidemiological estimates of prevalence and incidence. However, the term vascular dementia is a particularly narrow term, relying on both the presence of memory impairment and presence of dementia, so while prevalence estimates based on this still place vascular dementia as the second most common type of dementia, any broadening of the concept would, if anything, make vascular dementia more common. We agree that this is an important point to highlight and so have now added a new sentence in the epidemiology section as follows:

"Most epidemiological work to date has used the standard and relatively narrow definition of VaD. This is important because any broader definitions, for example allowing dementia to be diagnosed in the absence of a memory impairment, or use of the wider term VCI, would obviously impact on estimates of prevalence and incidence."

In addition to emphasizing the variable features of vascular dementia the authors might describe the constellation features needed and the clinical history and course expected in order to make a diagnosis. In this section it seems the authors mainly suggested certain screening or cognitive tests be used but not what the findings might be or how they should be interpreted in order to make a diagnosis.

We recognise this as an important point but do not feel that this review article on controversies in the field is the place to have a detailed description on how findings are interpreted and used, the reader would best be referred to the diagnostic papers cited.

The authors might more explicitly or directly discuss the range of expected imaging findings in people with vascular cognitive impairment or dementia; for example, 25% white matter lesion burden and/or hippocampal and other brain atrophy. Are there particular MRI protocols to use and review?

Our paper contains the following discussion of imaging changes:

However, a number of studies have suggested that multiple lacunes, strategic infarcts, substantial burden (often defined as >25%) of white matter lesion or combinations thereof are consistent with (but do not prove) VaD^{35,16} (see Figure 1 for examples).

As this is the only place where they bring up hippocampal sclerosis they might discuss it and also be clear on whether or not it can be imaged.

We do discuss hippocampus sclerosis as a cause for hippocampal atrophy but as we have already breached our word limit and other reviewers have asked us to add further information, do not feel we can begin a discussion on the imaging features of hippocampal sclerosis.

Again considering that the audience is general physicians, under the neuropathology features section, the authors might provide a declarative sentence or two stating the pathology of vascular dementia or that the features of vascular dementia include a, b, c, and d, etc, and then go on to describe variability.

We thank you for this comment and have now added that to the pathology section as follows:

This difficulty reflects the inherent heterogeneous nature of vascular pathology in which large vessel atherosclerosis and small vessel arteriosclerosis (and other vascular diseases, e.g. cerebral amyloid angiopathy) can lead to cortical and sub-cortical infarcts, sub- infarct ischaemic lesions (microinfarcts in grey matter and white matter lesions) and large and small cerebral haemorrhages (microbleeds); reviewed by Thal, Grinberg, Attems).⁵¹ All of these pathologies can occur throughout the brain and can contribute to vascular dementia.⁵² Figures 1 and 2 give examples of some of these lesions.

Under the management section how does one prescribe treatment for a condition that is variably defined? Table 2 could be made more consistent by including the diagnostic or inclusion, the duration, of each, and provide a consistent use of P values or effects.

We thank you for this comment and have added to the table a note regarding the entry criteria and duration of studies, and the magnitude of effects for cognition and the significance values.

In describing why regulators have not approved these drugs for vascular dementia the authors might mention not only the failed primary outcomes in some trials but that the diagnoses were not accepted as valid for the purposes of product labeling. They might also describe the concerns about cardiovascular toxicity with the cholinesterase inhibitors in light of excessive deaths in one of the trials and the increased risks for syncope/falls, hospitalization for cardiovascular reasons, and pacemakers in Alzheimer patients taking these drugs (see the Ontario, Canada group, Rochon and Gill et al)

Thank you. We are very constrained for space but in the paragraph under the table have altered the final sentence to add that “combined with concerns over diagnostic validity and possible side effects” was the reason that led both regulatory bodies guideline groups to conclude they should not be used in patients with VaD.

For the primary prevention studies the authors might point out that vascular dementia or cognitive impairment were not the primary endpoints in these very large trials. If the mean difference in blood pressure reduction of 11 mg was not significant then it should not be mentioned.

Thank you for these points. We agree and have altered the text accordingly. Just to clarify, the blood pressure reduction of 11mg of mercury was significant, it was the impact of this on reducing dementia incidence which was not. We have tried to clarify that in the text.

Without providing criteria for mild cognitive impairment due to cerebrovascular disease alongside criteria for MCI due to Alzheimer's disease it should not be remarkable that both show similar magnitudes of cognitive decline as they would both have about the same level of cognitive decline to start. Much of the current discussion of mild cognitive impairment due to cerebrovascular disease should be moved up to the discussions of epidemiology, risk, imaging and pathology; and in its place

a discussion of the criteria and differences between MCI due to vascular disease and vascular dementia should be provided.

We feel that retaining a separate section on mild cognitive impairment due to cerebrovascular disease is important and the distinction between MCI and vascular dementia is based on the absence of dementia much as the difference between MCI and Alzheimer's disease.

Conclusion and future directions section I don't believe it is true that there has been validation of a range of biomarkers for AD, at least for diagnostic purposes or disease progression. For example, people can have 'positive' Abeta-PET scans, atrophy, or high CSF tau and not have cognitive impairment or Alzheimer disease in particular.

We do agree with the reviewer that there is much more to be done with regards to validating biomarkers for Alzheimer's disease. However, we do not wish to enter into a detailed discussion of the extent to which these have been validated, it is widely recognised that they do at least correlate quite well with pathology, therefore we have changed the text slightly to emphasise the fact that these are biomarkers for degenerative pathologies, rather than Alzheimer's disease per se, and also that the biomarkers require further validation.

For the reasons above I would be circumspect in explicitly recommending cholinesterase inhibitors to treat mixed vascular and Alzheimer's disease.

Thank you for this comment, we have modified the recommendation and rather than clearly recommending cholinesterase inhibitors in those with vascular dementia we have altered the discussion to "cholinesterase inhibitors do not appear to confer benefit in pure vascular dementia, but at least one good RCT suggests they are beneficial in mixed AD/ vascular cases".

Finally, we are pleased to submit as requested:

1. One clean copy of the manuscript
2. One copy where our changes are highlighted using tracked changes
3. Revised images and tables as below.

Figure 1. As suggested we have changed Figure 1D to make it more representative. We have also altered the image to indicate more clearly a lacune.

Figure 2. We have altered Figure 2A to show a micro infarct.

Title: Vascular Dementia

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Abstract:

Vascular dementia (VaD) is recognised as the second most common cause of dementia after Alzheimer's disease (AD), responsible for around 15% of cases. However, unlike AD, there are currently no licensed treatments for VaD. Progress in the field has been difficult due to uncertainties over nosology and diagnostic criteria, controversy over the exact nature of the relationship between cerebrovascular pathology and cognitive impairment, and the lack of identifiable tractable treatment targets. Though there is an established relationship between vascular and degenerative (Alzheimer) pathology, the mechanistic link between the two has yet to be identified. This review critiques some of the key areas and controversies, summarises treatment trials to date and makes suggestions for what progress is needed to advance our understanding of pathogenesis and so maximise opportunities for the search for new and effective management approaches.

Search Strategy and selection criteria

We searched MEDLINE and EMBASE from start to end 2014 using the search terms "vascular dementia" (both as a single term and also "vascular" AND "dementia") and "vascular cognitive impairment". We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

Introduction:

Vascular dementia is the second commonest form of dementia and, while considerable progress has been made over the last decade, there remain several controversies in the field still to be addressed, which this review will discuss. We will outline key areas that remain to be clarified, summarise the current status of treatment trials and make suggestions for future research.

Use of the term vascular dementia (VaD) is controversial. Is dementia an appropriate term, or should vascular cognitive impairment be preferred? Is a dimensional (continuous decline) or categorical (dementia v no dementia) approach most appropriate for classification? How should we begin to understand the relationship between cerebrovascular disease and cognitive impairment, and vascular and degenerative pathology? To understand some of these dilemmas, it is important to place current controversies in their historical context. Up until the late 1960s "senile dementia", as it was known, was thought to be due to cerebral arteriosclerosis. This vascular aetiology was challenged by the classic studies of Blessed, Tomlinson and Roth¹ which established Alzheimer's disease (AD), rather than vascular pathology, as the main cause of dementia in late life. Subsequently, it was thought that cerebrovascular disease only caused dementia when there were multiple large cortical infarcts. This "multi-infarct" dementia concept² was very influential and subsequent classification systems for VaD, including ICD-10 and DSM-IV, were largely based on it.^{3,4} Subsequently, however, it became clear that multi-infarct dementia was just one of many possible causes of VaD, whilst pathological studies from large cohorts showed that subcortical vascular disease, rather than large cortical infarcts, accounted not just for some, but indeed the majority of cases of VaD.⁵ This resulted in competing sets of proposed new criteria for VaD,^{6,7} as well as specific criteria for some subgroups, such as subcortical ischaemic VaD (which largely included subjects with what was known as Binswanger's disease).⁸

One challenge in validating proposed concepts is the lack of a clear consensus on pathological criteria for VaD. Studies that have attempted pathological validation show that the different sets of criteria can indeed identify cases of VaD with reasonable accuracy, with the NINDS/AIREN criteria

arguably the most specific but least sensitive, and DSM and ADDTC criteria more sensitive but less specific.⁹ It is partly for their high specificity that the NINDS/AIREN criteria have been used in the majority of studies in the field thus far.

While these modern criteria allowed new multi-site therapeutic studies to be undertaken, at the same time the utility of the term VaD was questioned.¹⁰ This was largely on the basis that definitions of dementia were based on the concept of Alzheimer’s dementia, and so included not only the need for multiple cognitive deficits, but for memory to be one of the domains affected. Although highly appropriate for AD, memory is variably affected in VaD, so a core criterion of memory disturbance is not necessarily appropriate. Because of this, as well as the increasing recognition that cerebrovascular disease often occurred with other pathologies to cause cognitive impairment, a broader term of vascular cognitive impairment was introduced and preferred by many authors.^{10–12} VCI recognises the heterogeneous nature of the contribution of vascular pathology to dementia, as well as many different subtypes as illustrated in Table 1. However, there are no clear diagnostic criteria for VCI and it remains a term highlighting the spectrum of pathology, rather than a clearly validated diagnostic entity. More recently, classification systems such as DSM-5¹³ (ICD-11 will probably follow the same path) have removed the necessity for memory impairment as one of the criteria for dementia, or as DSM-5 now defines it, “major neurocognitive disorder”.

Table 1

Subtypes of vascular dementia	
Condition	Imaging and pathological changes
Multi-infarct dementia (Cortical VaD)	Multiple cortical infarcts
Small vessel dementia (Subcortical VaD)	Lacunes, extensive white matter lesions; pathologically infarcts, demyelination and gliosis
Strategic infarct dementia	Infarct in strategic location (e.g. thalamus)
Hypoperfusion dementia	Watershed infarcts, white matter lesions; pathologically incomplete infarcts in white matter
Haemorrhagic dementia	Haemorrhagic changes, may be associated with amyloid angiopathy
Hereditary vascular dementia (CADASIL)	Multiple lacunes and white matter lesions, temporal lobe white matter affected
Alzheimer’s disease with CVD	Combination of vascular changes and atrophy, especially medial temporal lobe; pathologically mixture of vascular and degenerative (plaque and tangle) pathology

The multiple changes in the nosology of VaD over the last 25 years, while reflecting new knowledge and progress, have also made harmonised research in the area challenging. Such debates over classification and nosology will almost certainly continue until distinct and tractable pathophysiological mechanisms which underpin VaD can be demonstrated. In the meantime, there is consensus for a standardised approach to assessment of patients with vascular cognitive impairment in relation to research studies,¹¹ to avoid imposition of a priori concepts of categories which may not reflect reality, whilst similar attempts have been made to standardise and operationalise newly proposed sets of diagnostic criteria to provide a common and up to date nomenclature for vascular cognitive disorders.¹⁴

Epidemiology and risk factors for VaD

Most epidemiological work to date has used the standard and relatively narrow definition of VaD. This is important because any broader definitions, for example allowing dementia to be diagnosed in the absence of a memory impairment, or use of the wider term VCI, would obviously impact on estimates of prevalence and incidence. Studies of VaD show it is the second most common cause of dementia after AD. Rates rise with age, risk of VaD approximately doubling every 5.3 years as opposed to AD which doubles every 4.5, so the exponential rise is slightly less pronounced.¹⁵ In

addition, dementia develops in around 15-30% of subjects three months after a stroke.¹⁶ Such “post stroke dementia” is often viewed as a subtype of dementia in its own right, since the pathophysiology of this is also unclear. However, it is heterogeneous in nature and will include the unmasking of already present cognitive impairment or dementia, the emergence of VaD following from a recurrent infarct, and the fact that having a stroke places people at increased risk of dementia in the long term, with around 20-25% of subjects developing a delayed dementia.¹⁶ The close interaction between vascular and Alzheimer pathology has prompted search for whether the pathophysiology of such delayed dementia is due to vascular disease, degenerative pathology, or a combination of the two. Whilst some studies have suggested that AD may be more common in those subjects who have had a stroke, a long term autopsy follow-up study of older stroke survivors, arguably a group at most risk of Alzheimer pathology, found that vascular but not degenerative dementia was the cause of the dementia in over 75% of cases.¹⁷

Risk factors for dementia after stroke include increasing age, low education, female sex, multiple vascular risk factors, stroke location, presence of multiple strokes and both global and medial temporal atrophy on structural imaging.¹⁶ Similar risk factors have been identified for VaD in the absence of stroke, most especially advancing age and vascular risk.¹⁸ A recent meta-analysis demonstrated that late life depression was also a risk factor for VaD, as it is also for AD,¹⁹ a relevant finding as late life depression is associated with a number of vascular abnormalities, demonstrable both on brain imaging^{20,21} and pathology,^{22,23} and vascular mechanisms provide a plausible mechanistic link between depression and VaD. Vascular risk factors have also emerged as major risk factors for AD. As well as age, these include hypertension, smoking, possession of APOE-e4 allele, ischemic heart disease, atrial fibrillation, raised cholesterol and homocysteine diabetes and obesity.²⁴ Interestingly, many of these risk factors have the strongest association with AD when present in mid-life, and the relationship alters with age. So, for example, prior to the onset of dementia blood pressure and weight tend to fall, as does cholesterol, meaning that proximal risk to AD is less clear and in cross-sectional studies there is often no, or even, an inverse relationship.²⁴ The demonstration of common vascular risk factors between AD and VaD is both relevant and important to the known interaction between Alzheimer’s and vascular pathology. Several studies have shown that for a similar burden of Alzheimer’s pathology, clinical expression of dementia is greater when there is comorbid vascular disease.^{25,26}

Clinical features

Cognitive changes in VaD are much more variable than in other conditions such as AD, and are highly dependent on the particular neural substrates affected by the vascular pathology. Because subcortical vascular pathology is frequently present, interrupting frontostriatal circuits, predominant deficits in attention, information processing, and executive function are seen.^{10,27} This is clinically relevant since standard screening tests for dementia, such as the Mini-Mental State Examination which was devised to detect AD,²⁸ may prove relatively insensitive to impairments, especially in these characteristic deficits. Other tests, which highlight attention and executive function, like the Montreal Cognitive Assessment²⁹ or the vascular dementia assessment scale (VADAS-cog),³⁰ are more likely to pick up deficits in this population. Other functions such as memory, language, and praxis are much more variably affected in VaD. As with other dementias, non-cognitive features are frequent and can be particularly distressing both for the patient and their family. Community studies have shown a considerable overlap in neuropsychiatric features between AD and VaD, with a very high burden of all symptoms in both subtypes,³¹ though some symptoms, particularly depression and apathy, are particularly prominent in those with VaD, whilst other features such as delusions and hallucinations, are less frequent.^{31,32} As would be expected from the heterogeneous nature of the condition, outcome is variable, though average rates of cognitive decline are similar in VaD as in AD,

though mortality, largely due to cardiovascular and cerebrovascular causes, is higher with mean survival 3- 5 years.³³

Brain imaging

It is increasingly recognised that an accurate diagnosis of VaD requires demonstration of the presence of sufficient cerebrovascular disease on brain imaging to plausibly account for the degree of cognitive impairment observed clinically.⁶ CT is sufficient to show established infarcts and extensive white matter lesions, though MR is highly preferable to show more precisely the degree, location and extent of cerebrovascular disease. The lack of an obvious relationship between brain vascular disease and dementia is exemplified by a study comparing the imaging criteria for VaD from NINDS/AIREN between post stroke subjects with and without dementia, which found no significant differences.³⁴ However, a number of studies have suggested that multiple lacunes, strategic infarcts, substantial burden (often defined as >25%) of white matter lesion or combinations thereof are consistent with (but do not prove) VaD^{35,16} (see Figure 1 for examples). White matter lesions, which often reflect subcortical vascular disease, may be particularly important here. Some caveats are needed, since white matter lesions can reflect other non-ischaemic aetiologies, but in the context of older people are most likely vascular in origin, and prospective studies show that even if they are not initially associated with cognitive and functional impairment, they are strong predictors of both over the following 3 years.³⁶ It has often been shown in imaging studies that atrophy, both generalised and hippocampal, is as strongly if not more strongly associated with dementia than the extent of vascular pathology.³⁷ Whether this reflects atrophy as a common pathway secondary to vascular disease, or the summed extent of vascular and degenerative changes, is unclear, though the observation that hippocampal atrophy during life can be associated with VaD or hippocampal sclerosis at autopsy^{21,17,38} suggests the contribution of vascular disease to atrophy may often be under-estimated. In terms of assessing the relative contribution of Alzheimer pathology, the availability of in vivo imaging and CSF markers of both amyloid and tau promise to make a significant contribution.^{39,40} Biomarkers of VaD, apart from imaging changes, are less well developed than for AD but candidates have been proposed, including albumen, metalloproteinases and inflammatory markers, but require further validation.⁴¹

Figure 1 here

Genetics

Most genetic research in dementia has been on AD and investigations in VaD have mainly been on rare familial syndromes, especially CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, related to a frameshift mutation in the notch gene on chromosome 19).⁴² Whilst such syndromes may provide important insights into the mechanisms underlying the development of vascular brain ischaemia, it is not clear how relevant such disorders are to the genetics of the majority of later onset VaD. Only one Genome Wide Association Study (GWAS) has been reported.⁴³ This identified only one gene (rs12007229) on the X chromosome and although this association was repeated in replication analyses the odds ratio fell from 3.7 to 1.5, making it possible this is a chance finding, a possibility perhaps increased by the lack of certainty about the biological significance of this locus. A systematic review⁴⁴ of all reported association studies in the broader construct of vascular cognitive impairment included a meta-analysis of six polymorphisms with the strongest associations (APOE, ACT, ACE, MTHFR, PON1, and PSEN-1 genes) but only APOE e4 (OR 1.82, P<0.001) and MTHFR rs1801133 (OR 1.32, P=0.013) remained significant. The association with APOE e4 was also reported in an independent meta-analysis⁴⁵ and this gene is strongly associated with AD, as well as with cardiovascular disease,⁴⁶ making this a plausible association, albeit one not likely to help identify mechanisms or treatments specific to VaD. The cross-association with AD may be due to diagnostic difficulties in accurately identifying and

distinguishing these dementia subtypes or it may point to such shared pathological mechanisms, a possibility increased by reports of common associations of genes between neurodegenerative disorders. Similarly MTHFR polymorphisms, especially C677T, have been identified in previous meta-analyses⁴⁷ and MTHFR is a 'vascular gene' related to homocysteine metabolism suggesting it may be a genuine association, and VaD has been associated with increased homocysteine.⁴⁸ However, effects are modest and again it may not be specific for VaD.⁴⁹ In summary, there are few genetic studies in VaD and only one GWAS analysis, and in other disorders further investigation, including repeated GWAS studies, has nullified such modest evidence as is currently available in VaD.⁵⁰

Neuropathological features

Whilst it seems obvious that cerebrovascular disease causes pathological damage and impairs cognition, determining the exact contribution of cerebrovascular pathology to cognitive decline and dementia is exceedingly difficult. This difficulty reflects the inherent heterogeneous nature of vascular pathology in which large vessel atherosclerosis and small vessel arteriosclerosis (and other vascular diseases, e.g. cerebral amyloid angiopathy) can lead to cortical and sub-cortical infarcts, sub- infarct ischaemic lesions (microinfarcts in grey matter and white matter lesions) and large and small cerebral haemorrhages (microbleeds); reviewed by Thal, Grinberg, Attems).⁵¹ All of these pathologies can occur throughout the brain and can contribute to vascular dementia.⁵² Figures 1 and 2 give examples of some of these lesions. It is also very difficult in autopsy studies to relate cognitive impairments in life to post mortem pathology even when using data from prospective research studies. Whilst AD has a reasonably well defined and predictable pattern of disease progression this is not the case for cerebrovascular disease and there remains no agreed pathological scheme for staging or diagnosing VaD. This means different studies use different criteria to report whether subjects have autopsy evidence of 'significant' cerebrovascular disease.⁵² On the one hand vascular brain pathology is almost universal in older people⁵³ and is thought to contribute to cognitive impairments in mild cognitive impairment as well as more severe dementia.⁵⁴ Small vessel disease, seen on MRI neuroimaging as white matter hyperintense lesions, appears to account for most of this contribution in milder cases.⁵⁵ But on the other hand it seems a large burden of vascular disease pathology is required to produce dementia, in the absence of AD or other degenerative pathology, and so the prevalence of 'pure' VaD appears much lower than previously accepted, accounting for perhaps only about 10% of cases⁵⁶ with most such cases having large infarcts.⁵¹ The burden of such cerebrovascular disease increases with age and with the severity of cognitive impairment. This is also the case for the major neurodegenerative diseases⁵³ and so with ageing and increased dementia severity the presence of multiple cerebral pathologies escalates and the proportion of pure disease cases declines. Thus in the oldest-old 'mixed dementia' is the norm not the exception. Clinically when assessing the contribution of cerebrovascular disease to dementia this all suggests that in the absence of large infarcts (on imaging) and/or a clear relationship of such lesions to the onset or progression of cognitive impairments, it is wisest to regard any vascular pathology as making a contribution to overall impairment rather than being the principal cause (see Figure 2).

Management of VaD

General management principles of dementia including ensuring a timely diagnosis, assessing and treating comorbidities, providing information and support for the person with dementia and their carers and maximising independence apply equally well to VaD as to AD. However, progress towards finding effective treatments for VaD has proved even more elusive than for AD. The best studied treatments are cholinesterase inhibitors and memantine, both of which are licenced and well established drugs for AD, albeit with modest efficacy. The rationale for trialling these drugs in VaD

was largely based on some suggestive evidence showing neuropathological and neurochemical overlap between the two disorders, in particular the suggestion of cholinergic deficit in VaD.⁵⁷ However, this notion has been challenged by subsequent neurochemical analysis which suggested that the cholinergic system might be intact in “pure” VaD, whilst affected to the same extent as in AD in mixed cases.⁵⁸ An early study of galantamine in a group of those with both pure and mixed VaD showed possible benefit.⁵⁹ However, several subsequent large and well-conducted randomised controlled 6 month trials of galantamine, donepezil and rivastigmine either in NINDS-AIREN probable, or probable and possible VaD, have been reported⁶⁰⁻⁶⁴ (see Table 2).

Table 2

Randomised controlled trials of cholinesterase inhibitors in vascular dementia				
	Significant benefits on:			
	Cognition	Global	ADL	Neuropsychiatric symptoms
Galantamine (Gal-INT-06) (n=121 with NINDS/AIREN probable VaD) Erkinjuntti et al ⁵⁹	No (p=0.06) -1.8 points on ADAS-Cog	No	No	No
Galantamine (Gal-INT-26) (n=788 with NINDS/AIREN probable VaD) 26 weeks Auchus et al ⁶⁰	Yes (p<0.001) -1.9 points on ADAS-Cog	No	No	No
Donepezil (307) (n=603 with NINDS/AIREN probable or possible VaD) 24 weeks Black et al ⁶¹	Yes (p<0.001) -2.24 points on ADAS-Cog	No	Yes	N/A
Donepezil (308) (n=616 with NINDS/AIREN probable or possible VaD) Wilkinson et al ⁶²	Yes (p<0.001) -2.09 points of ADAS-Cog	Yes	No	N/A
Donepezil (319) (n=974 with NINDS/AIREN probable or possible VaD) <u>24 weeks</u> Roman et al ⁶³	Yes (P<0.001) -0.91 points on VADAS-Cog	No	No	N/A
Rivastigmine (VantageE) (n=710 with NINDS/AIREN probable VaD) 24 weeks Ballard et al ⁶⁴	Yes (p=0.028) -1.3 points on VADAS-Cog	No	No	No

Although most have shown a small but significant benefit of cholinesterase inhibitors on cognition, the magnitude of this impact has been relatively modest (approximately 2 points on the ADAS-Cog scale, roughly half the benefit seen in the Alzheimer’s studies) and benefits on global functioning, activities of daily living and behaviour have not been consistently seen. This, combined with concerns over diagnostic validity and possible side effects, has led both regulatory bodies and guideline groups, for example NICE, to conclude that cholinesterase inhibitors and memantine should not be used in patients with VaD.⁶⁵

There have been two well-conducted randomised trials run over 6 months of memantine, an NMDA antagonist, in VaD.^{66,67} Similar to the studies of cholinesterase inhibitors, both found a significant but modest effect on cognition that did not appear to generalise as there was no impact on global outcome measures. Meta-analyses of the studies have supported these conclusions.⁶⁸ Unfortunately, there have been few other promising avenues. A study of nimodipine in subcortical VaD missed its primary outcome measures, but did find some secondary improvements in some outcome scales and in terms of memory,⁶⁹ prompting other ongoing studies of calcium channel blockers (e.g. AFFECT; EudraCT Number: 2014-000926-39). There have been some positive trials of cerebrolysin, a putative neurotrophic neuropeptide derived from pigs' brains requiring daily infusion.⁷⁰ A Cochrane review of six studies concluded that there was evidence of a positive effect of cerebrolysin on cognition and global outcome in vascular disease, but that wider use was not recommended due to the small number and short duration of trials, heterogeneity between trials and limited follow-up.⁷¹

There have been some studies of primary prevention, though it should be noted that cognition was not a primary outcome in these studies. In terms of reducing cholesterol, the PROSPER study randomised 6000 people to pravastatin or placebo and found no differences in cognitive outcome between groups after 6 years.⁷² Similarly, the Heart Protection Study randomised 20,537 subjects aged 40 to 80 with vascular disease or diabetes to simvastatin or placebo, but found rates of cognitive impairment at 5 years later were almost identical between the two groups at around 24%, with dementia developing in 0.3% of each group.⁷³ These studies can be criticised for the insensitivity of outcome measures and inclusion of relatively well people with low rates of cognitive decline, but provide no evidence that primary prevention by lowering cholesterol prevents VaD. Studies of reducing blood pressure are more promising, but remain equivocal. One difficulty is that such studies have often been stopped prematurely because end points based on cardiovascular and cerebrovascular outcomes have been reached before there has been adequate ascertainment of dementia outcomes to draw clear conclusions. There appeared to be a trend towards antihypertensive treatment reducing dementia incidence in the HYVET study,⁷⁴ though this was non-significant, and the Syst-Eur study found a significant effect of nitrendipine in reducing dementia compared to placebo, though most of the dementias prevented were actually Alzheimer's rather than VaD.⁷⁵ However, reviews and meta-analyses of these studies have generally shown that antihypertensive treatment can prevent VaD by preventing stroke, but apart from this any effect in reducing dementia incidence is borderline, though in the right direction, and needs to be confirmed in larger, longer term studies.^{74,76} However, the recent SPS3 trial compared a two factorial design with intensive blood pressure (v usual targets) lowering and dual antiplatelet treatment (v single aspirin) in 3200 subjects (mean age 63 years) who had a lacunar infarct. The main outcome, the cognitive assessment and screen instrument (CASI), at a median three years, showed no significant effect of either BP reduction (which was a mean of 11mg of mercury between the groups) or of dual antiplatelet therapy over the control arms.⁷⁷ With regard to antiplatelet agents, the results of SPS3 are very much in accord with other studies which suggest no clear evidence of benefit in preventing cognitive impairment or dementia, whilst the single trial of aspirin in established VaD,⁷⁸ although positive, has been criticised because of methodological limitations including a very small sample size, very high dropout rate, and lack of adequate randomisation.⁷⁶ Overall, therefore, results to date of single pharmacological strategies such as antiplatelet agents, reducing blood pressure or use of statins to prevent or treat VaD do not provide support for these interventions, though of course these remain important treatments for the VaD risk factors themselves. In contrast, ongoing preventative studies are taking a more multi-dimensional approach, for example the FINGER study which combines vascular risk reduction, nutritional advice, cognitive training and exercise in high risk subjects has recently reported promising results with reduced cognitive decline in the active group

at 2 years.⁷⁹ Consistent with this are findings from epidemiological cohort studies suggesting that overall dementia prevalence may actually be decreasing.⁸⁰ While reasons for this are not entirely clear, a reduction in vascular risk is, at least in part, a plausible explanation.

Mild cognitive impairment due to cerebrovascular disease

This has been much less well studied than the syndrome of mild cognitive impairment due to AD, which is largely defined clinically on the basis of an amnesic deficit in the absence of dementia, though diagnostic criteria have been proposed.⁸¹ Far from being a benign condition, the few longitudinal studies of vascular-MCI have reported rates of progression to dementia of similar magnitude to MCI due to AD.⁸² The presentation of early vascular disease is much more heterogeneous as subtle cerebrovascular disease is common with ageing, for example in imaging samples of representative older samples at least 30% have “silent” infarcts on brain imaging,⁸³ with up to 90% of older subjects having varying degrees of white matter lesions.⁸⁴ The clinical significance of such silent white matter lesions had been uncertain, though a large pan-European study (the Leukoaraiosis And DISability or LADIS study) reported in a non-disabled population of older people that the presence at baseline of severe (confluent) white matter lesions conveyed a particularly adverse outcome in terms of a high rate of progression to disability over a three year period (rates around threefold higher than those with only mild white matter disease).³⁶ The study strongly implied the deleterious nature of substantial white matter pathology, even if not currently accompanied by symptoms and disability, and points the need to investigate potential therapeutic approaches which could have significant impact in reducing future disability.

Conclusions and future directions

Though there has been considerable progress in defining and understanding the relationship between cerebrovascular disease and cognitive impairment and dementia, some uncertainties remain. Clinical diagnostic criteria are sufficiently robust to be useful for clinical trials, but need further refinement and validation. For example, , the recent development and validation, while ongoing, of a range of biomarkers for neurodegenerative Alzheimer pathology, including amyloid PET imaging, CSF markers of tau, and amyloid and, more recently, in vivo tau imaging now offer unparalleled opportunities for in vivo subject stratification of those with pure from those with mixed dementia for future naturalistic and therapeutic studies. Such work will also be important to answer the key question as to whether and in what circumstances it is relevant to separate out neurodegenerative and vascular entities and so, in combination with pathological investigation, provide important validation of our clinical concepts of vascular dementia. In these studies we endorse proposals for harmonisation of data capture, avoiding narrow a priori assumptions that may hamper progress. On the other hand, some studies, clinical trials in particular, may need to focus on specific subgroups to ensure a more homogenous population to study. One thing that has clearly been learned from the trials of cholinesterase inhibitors and memantine in VaD is that translation of Alzheimer treatments to VaD on the basis of shared neurochemical mechanisms may not be appropriate. There remains limited research on VaD and its mechanisms compared to other dementias, and there is a clear need for further pathophysiological studies to investigate mechanisms which predispose or accelerate cognitive impairment. Large scale genetic studies, which have been so informative in many other disorders, are in their infancy in relation to VaD and may prove informative, as well as helping understand the shared risk with AD. There are potential treatments currently in clinical trials, including calcium channel blockers, while other agents targeting endothelial function or the renin angiotensin system are putative candidates for further clinical trials.

Current management of VaD should focus on identifying and managing comorbidities, ensuring that vascular risk factors are optimally managed, ensuring appropriate recognition and management of non-cognitive symptoms, and appropriate psychosocial and other support to optimise quality of life

for patients and their carers. Cholinesterase inhibitors do not appear to confer benefit in pure vascular dementia, but at least one good RCT suggests they are beneficial in mixed AD/vascular cases.⁵⁹

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Contributions

Both authors contributed equally to this review

Conflicts of interest

John O'Brien has acted as a consultant for GE Healthcare, Cytos, TauRx and Avid/Lilly, and received honoraria for non-promotional lectures from Pfizer, Lundbeck, Eisai, Novartis and Shire.

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Title: Vascular Dementia

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Abstract:

Vascular dementia (VaD) is recognised as the second most common cause of dementia after Alzheimer's disease (AD), responsible for around 15% of cases. However, unlike AD, there are currently no licensed treatments for VaD. Progress in the field has been difficult due to uncertainties over nosology and diagnostic criteria, controversy over the exact nature of the relationship between cerebrovascular pathology and cognitive impairment, and the lack of identifiable tractable treatment targets. Though there is an established relationship between vascular and degenerative (Alzheimer) pathology, the mechanistic link between the two has yet to be identified. This review critiques some of the key areas and controversies, summarises treatment trials to date and makes suggestions for what progress is needed to advance our understanding of pathogenesis and so maximise opportunities for the search for new and effective management approaches.

Search Strategy and selection criteria

We searched MEDLINE and EMBASE from start to end 2014 using the search terms "vascular dementia" (both as a single term and also "vascular" AND "dementia") and "vascular cognitive impairment". We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers."

Introduction:

Vascular dementia is the second commonest form of dementia and, while considerable progress has been made over the last decade, there remain several controversies in the field still to be addressed, which this review will discuss. We will outline key areas that remain to be clarified, summarise the current status of treatment trials and make suggestions for future research.

Use Even use of the term vascular dementia (VaD) is controversial. Is dementia an appropriate term, or should vascular cognitive impairment be preferred? Is a dimensional (continuous decline) or categorical (dementia v no dementia) approach most appropriate for classification? How should we begin to understand the relationship between cerebrovascular disease and cognitive impairment, and vascular and degenerative pathology? To understand some of these dilemmas **and uncertainties**, it is important to place current controversies in their historical context. Up until the late 1960s "senile dementia", as it was known, was thought to be due to cerebral arteriosclerosis. This vascular aetiology was challenged by the classic studies of Blessed, Tomlinson and Roth¹ which established Alzheimer's disease (AD), rather than vascular pathology, as the main cause of dementia in late life. Subsequently, it was thought that cerebrovascular disease only caused dementia when there were multiple large cortical infarcts. This "multi-infarct" dementia concept² was very influential and subsequent classification systems for VaD, including ICD-10 and DSM-IV, were largely based on it.^{3,4} Subsequently, however, it became clear that multi-infarct dementia was just one of many possible causes of VaD, whilst pathological studies from large cohorts showed that subcortical vascular disease, rather than large cortical infarcts, accounted not just for some, but indeed the majority of cases of VaD.⁵ This resulted in competing sets of proposed new criteria for VaD,^{6,7} as well as specific criteria for some subgroups, such as subcortical ischaemic VaD (which largely included subjects with what was known as Binswanger's disease).⁸

One challenge in validating the area is accurate validation of proposed concepts is the, a major problem being the lack of a clear consensus on pathological criteria for VaD. Studies that have attempted pathological validation show that the different sets of criteria can indeed identify cases of

VaD with reasonable accuracy, with the NINDS/AIREN criteria arguably the most specific but least sensitive, and DSM and ADDTC criteria more sensitive but less specific.⁹ It is partly for their high specificity that the NINDS/AIREN criteria have been used in the majority of studies in the field thus far.

While these modern criteria allowed new multi-site therapeutic studies to be undertaken, at the same time the utility of the term VaD was questioned.¹⁰ This was largely on the basis that definitions of dementia were based on the concept of Alzheimer’s dementia, and so included not only the need for multiple cognitive deficits, but for memory to be one of the domains affected. Although highly appropriate for AD, memory is variably affected in VaD, so a core criterion of memory disturbance is not necessarily appropriate. Because of this, as well as the increasing recognition that cerebrovascular disease often occurred with other pathologies to cause cognitive impairment, a broader term of vascular cognitive impairment was introduced and preferred by many authors.^{10–12} VCI recognises the heterogeneous nature of the contribution of vascular pathology to dementia, as well as many different subtypes as illustrated in Table 1. However, there are no clear diagnostic criteria for VCI and it remains a term highlighting the spectrum of pathology, rather than a clearly validated diagnostic entity. More recently, classification systems such as DSM-5¹³ (ICD-11 will probably follow the same path) have removed the necessity for memory impairment as one of the criteria for dementia, or as DSM-5 now defines it, “major neurocognitive disorder”.

Table 1

Subtypes of vascular dementia	
Condition	Imaging and pathological changes
Multi-infarct dementia (Cortical VaD)	Multiple cortical infarcts
Small vessel dementia (Subcortical VaD)	Lacunae, extensive white matter lesions; pathologically infarcts, demyelination and gliosis
Strategic infarct dementia	Infarct in strategic location (e.g. thalamus)
Hypoperfusion dementia	Watershed infarcts, white matter lesions; pathologically incomplete infarcts in white matter
Haemorrhagic dementia	Haemorrhagic changes, <u>may be associated with amyloid angiopathy</u>
Hereditary vascular dementia (CADASIL)	Multiple lacunae and white matter lesions, temporal lobe white matter affected
Alzheimer’s disease with CVD	Combination of vascular changes and atrophy, especially medial temporal lobe; pathologically mixture of vascular and degenerative (plaque and tangle) pathology

The multiple changes in the nosology of VaD over the last 25 years, while reflecting new knowledge and progress, have also made harmonised research in the area challenging. Such debates over classification and nosology will almost certainly continue until distinct and tractable pathophysiological mechanisms which underpin VaD can be demonstrated. In the meantime, there is consensus for a standardised approach to assessment of patients with vascular cognitive impairment in relation to research studies,¹¹ to avoid imposition of a priori concepts of categories which may not reflect reality, whilst similar attempts have been made to standardise and operationalise newly proposed sets of diagnostic criteria to provide a common and up to date nomenclature for ~~for other~~ vascular cognitive disorders.¹⁴

Epidemiology and risk factors for VaD

Most epidemiological work to date has used the standard and relatively narrow definition of VaD. This is important because any broader definitions, for example allowing dementia to be diagnosed in the absence of a memory impairment, or use of the wider term VCI, would obviously impact on estimates of prevalence and incidence. Studies of VaD show it is the second most common cause of dementia after AD. Rates rise with age, risk of VaD approximately doubling every 5-3 years as

opposed to AD which doubles every 4-5, so the exponential rise is slightly less pronounced.¹⁵ In addition, dementia develops in around 15-30% of subjects three months after a stroke.¹⁶ Such “post stroke dementia” is often viewed as a subtype of dementia in its own right, since the pathophysiology of this is also unclear. However, it is heterogeneous in nature and will include the unmasking of already present cognitive impairment or dementia, the emergence of VaD following from a recurrent infarct, and the fact that having a stroke places people at increased risk of dementia in the long term, with around 20-25% of subjects developing a delayed dementia.¹⁶ The close interaction between vascular and Alzheimer pathology has prompted search for whether the pathophysiology of such delayed dementia is due to vascular disease, degenerative pathology, or a combination of the two. Whilst some studies have suggested that AD may be more common in those subjects who have had a stroke, a long term autopsy follow-up study of older stroke survivors, arguably a group at most risk of Alzheimer pathology, found that vascular but not degenerative dementia was the cause of the dementia in over 75% of cases.¹⁷

Risk factors for dementia after stroke include increasing age, low education, female sex, multiple vascular risk factors, stroke location, presence of multiple strokes and both global and medial temporal atrophy on structural imaging.¹⁶ Similar risk factors have been identified for VaD in the absence of stroke, most especially advancing age and vascular risk.¹⁸ A recent meta-analysis demonstrated that late life depression was also a risk factor for VaD, as it is also for AD,¹⁹ a relevant finding as late life depression is associated with a number of vascular abnormalities, demonstrable both on brain imaging^{20, 21} and pathology,^{22, 23} and vascular mechanisms provide a plausible mechanistic link between depression and VaD. Vascular risk factors have also emerged as major risk factors for AD. As well as age, these include hypertension, smoking, possession of APOE-e4 allele, ischemic heart disease, atrial fibrillation, raised cholesterol and homocysteine diabetes and obesity.²⁴ Interestingly, many of these risk factors have the strongest association with AD when present in mid-life, and the relationship alters with age. So, for example, prior to the onset of dementia blood pressure and weight tend to fall, as does cholesterol, meaning that proximal risk to AD is less clear and in cross-sectional studies there is often no, or even, an inverse relationship.²⁴ The demonstration of common vascular risk factors between AD and VaD is both relevant and important to the known interaction between Alzheimer’s and vascular pathology. Several studies have shown that for a similar burden of Alzheimer’s pathology, clinical expression of dementia is greater when there is comorbid vascular disease.^{25,26}

Clinical features

Cognitive changes in VaD are much more variable than in other conditions such as AD, and are highly dependent on the particular neural substrates affected by the vascular pathology. Because subcortical vascular pathology is frequently present, interrupting frontostriatal circuits, predominant deficits in attention, information processing, and executive function are seen.^{10,27} This is clinically relevant since standard screening tests for dementia, such as the Mini-Mental State Examination which was devised to detect AD,²⁸ may prove relatively insensitive to impairments, especially in these characteristic deficits. Other tests, which highlight attention and executive function, like the Montreal Cognitive Assessment²⁹ or the vascular dementia assessment scale (VADAS-cog),³⁰ are more likely to pick up deficits in this population. Other functions such as memory, language, and praxis are much more variably affected in VaD. As with other dementias, non-cognitive features are frequent and can be particularly distressing both for the patient and their family. Community studies have shown a considerable overlap in neuropsychiatric features between AD and VaD, with a very high burden of all symptoms in both subtypes,³¹ though some symptoms, particularly depression and apathy, are particularly prominent in those with VaD, whilst other features such as delusions and hallucinations, are less frequent.^{31,32} As would be expected from the heterogeneous nature of the condition, outcome is variable, though average rates of cognitive decline are similar in VaD as in AD,

[though mortality, largely due to cardiovascular and cerebrovascular causes, is higher with mean survival 3- 5 years Kua et al, 2014.](#)³³

Brain imaging

It is increasingly recognised that an accurate diagnosis of VaD requires demonstration of the presence of sufficient cerebrovascular disease on brain imaging to plausibly account for the degree of cognitive impairment observed clinically.⁶ CT is sufficient to show established infarcts and extensive white matter lesions, though MR is highly preferable to show more precisely the degree, location and extent of cerebrovascular disease. The lack of an obvious relationship between brain vascular disease and dementia is exemplified by a study comparing the imaging criteria for VaD from NINDS/AIREN between post stroke subjects with and without dementia, which found no significant differences.³⁴ However, a number of studies have suggested that multiple lacunes, strategic infarcts, substantial burden (often defined as >25%) of white matter lesion or combinations thereof are consistent with (but do not prove) VaD^{35,16} (see Figure 1 for examples). [White matter lesions, which often reflect subcortical vascular disease, may be particularly important here. Some caveats are needed, since white matter lesions can reflect other non-ischaemic aetiologies, but in the context of older people are most likely vascular in origin, and prospective studies show that even if they are not initially associated with cognitive and functional impairment, they are strong predictors of both over the following 3 years.](#)³⁶ It has often been shown in imaging studies that atrophy, both generalised and hippocampal, is as strongly if not more strongly associated with dementia than the extent of vascular pathology.³⁷ Whether this reflects atrophy as a common pathway secondary to vascular disease, or the summed extent of vascular and degenerative changes, is unclear, though the observation that hippocampal atrophy during life can be associated with VaD or hippocampal sclerosis at autopsy^{21,17,38} suggests the contribution of vascular disease to atrophy may often be under-estimated. In terms of assessing the relative contribution of Alzheimer pathology, the availability of in vivo imaging and CSF markers of both amyloid and tau promise to make a significant contribution.^{39,40} [Biomarkers of VaD, apart from imaging changes, are less well developed than for AD but candidates have been proposed, including albumen, metalloproteinases and inflammatory markers, but require further validation.](#)⁴¹

Figure 1 here

Genetics

Most genetic research in dementia has been on AD and investigations in VaD have mainly been on rare familial syndromes, especially CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, related to a frameshift mutation in the notch gene on chromosome 19).⁴² Whilst such syndromes may provide important insights into the mechanisms underlying the development of vascular brain ischaemia, it is not clear how relevant such disorders are to the genetics of the majority of later onset VaD. Only one Genome Wide Association Study (GWAS) has been reported.⁴³ This identified only one gene (rs12007229) on the X chromosome and although this association was repeated in replication analyses the odds ratio fell from 3.7 to 1.5, making it possible this is a chance finding, a possibility perhaps increased by the lack of certainty about the biological significance of this locus. A systematic review⁴⁴ of all reported association studies in the broader construct of vascular cognitive impairment included a meta-analysis of six polymorphisms with the strongest associations (APOE, ACT, ACE, MTHFR, PON1, and PSEN-1 genes) but only APOE e4 (OR 1.82, P<0.001) and MTHFR rs1801133 (OR 1.32, P=0.013) remained significant. The association with APOE e4 was also reported in an independent meta-analysis⁴⁵ and this gene is strongly associated with AD, as well as with cardiovascular disease,⁴⁶ making this a plausible association, albeit one not likely to help identify mechanisms or treatments specific to VaD. The

cross-association with AD may be due to diagnostic difficulties in accurately identifying and distinguishing these dementia subtypes or it may point to such shared pathological mechanisms, a possibility increased by reports of common associations of genes between neurodegenerative disorders. Similarly MTHFR polymorphisms, especially C677T, have been identified in previous meta-analyses⁴⁷ and MTHFR is a 'vascular gene' related to homocysteine metabolism suggesting it may be a genuine association, and VaD has been associated with increased homocysteine.⁴⁸ However, effects are modest and again it may not be specific for VaD.⁴⁹ In summary, there are few genetic studies in VaD and only one GWAS analysis, and in other disorders further investigation, including repeated GWAS studies, has nullified such modest evidence as is currently available in VaD.⁵⁰

Neuropathological features

Whilst it seems obvious that cerebrovascular disease causes pathological damage and impairs cognition, determining the exact contribution of cerebrovascular pathology to cognitive decline and dementia is exceedingly difficult. This difficulty reflects the inherent heterogeneous nature of vascular pathology in which large vessel atherosclerosis and small vessel arteriosclerosis (and other vascular diseases, e.g. cerebral amyloid angiopathy) can lead to cortical and sub-cortical infarcts, sub-infarct ischaemic lesions (microinfarcts in grey matter and white matter lesions) and large and small cerebral haemorrhages (microbleeds); reviewed by Thal, Grinberg, Attems).⁵¹ All of these pathologies can occur throughout the brain and can contribute to vascular dementia.⁵² Figures 1 and 2 give examples of some of these lesions. (such as atherosclerosis, small vessel arteriosclerosis, arteriolosclerosis, and lipohyalinosis, and cerebral amyloid angiopathy; reviewed by Thal, Grinberg, Attems)⁵³ and the wide anatomical variation in brain areas and neural circuits damaged by such pathology.⁵² It is also very difficult in autopsy studies to relate cognitive impairments in life to post mortem pathology even when using data from prospective research studies. Whilst AD has a reasonably well defined and predictable pattern of disease progression this is not the case for cerebrovascular disease and there remains no agreed pathological scheme for staging or diagnosing VaD. This means different studies use different criteria to report whether subjects have autopsy evidence of 'significant' cerebrovascular disease.⁵² On the one hand vascular brain pathology is almost universal in older people⁵³ and is thought to contribute to cognitive impairments in mild cognitive impairment as well as more severe dementia.⁵⁴ Small vessel disease, seen on MRI neuroimaging as white matter hyperintense lesions, appears to account for most of this contribution in milder cases.⁵⁵ But on the other hand it seems a large burden of vascular disease pathology is required to produce dementia, in the absence of AD or other degenerative pathology, and so the prevalence of 'pure' VaD appears much lower than previously accepted, accounting for perhaps only about 10% of cases⁵⁶ with most such cases having large infarcts.⁵¹ The burden of such cerebrovascular disease increases with age and with the severity of cognitive impairment. This is also the case for the major neurodegenerative diseases⁵³ and so with ageing and increased dementia severity the presence of multiple cerebral pathologies escalates and the proportion of pure disease cases declines. Thus in the oldest-old 'mixed dementia' is the norm not the exception. Clinically when assessing the contribution of cerebrovascular disease to dementia this all suggests that in the absence of large infarcts (on imaging) and/or a clear relationship of such lesions to the onset or progression of cognitive impairments, it is wisest to regard any vascular pathology as making a contribution to overall impairment rather than being the principal cause (see Figure 2).

Management of VaD

General management principles of dementia including ensuring a timely diagnosis, assessing and treating comorbidities, providing information and support for the person with dementia and their

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carers and maximising independence apply equally well to VaD as to AD. However, progress towards finding effective treatments for VaD has proved even more elusive than for AD. The best studied treatments are cholinesterase inhibitors and memantine, both of which are licenced and well established drugs for AD, albeit with modest efficacy. The rationale for trialling these drugs in VaD was largely based on some suggestive evidence showing neuropathological and neurochemical overlap between the two disorders, in particular the suggestion of cholinergic deficit in VaD.⁵⁷ However, this notion has been challenged by subsequent neurochemical analysis which suggested that the cholinergic system might be intact in “pure” VaD, whilst affected to the same extent as in AD in mixed cases.⁵⁸ An early study of galantamine in a group of those with both pure and mixed VaD showed possible benefit.⁵⁹ However, several subsequent large and well-conducted randomised controlled **6 month** trials of galantamine, donepezil and rivastigmine **either in NINDS-AIREN probable, or probable and possible VaD**, have been reported⁶⁰⁻⁶⁴ (see Table 2).

Table 2

Randomised controlled trials of cholinesterase inhibitors in vascular dementia				
	Significant benefits on:			
	Cognition	Global	ADL	Neuropsychiatric symptoms Behaviour
Galantamine (Gal-INT-06) (n=121 with NINDS/AIREN probable VaD) Erkinjuntti et al ⁵⁹	No (p=0.06) -1.8 points on ADAS-Cog	No	No	No
Galantamine (Gal-INT-26) (n=788 with NINDS/AIREN probable VaD) 26 weeks Auchus et al ⁶⁰	Yes (p<0.001) -1.9 points on ADAS-Cog	No	No	No
Donepezil (307) (n=603 with NINDS/AIREN probable or possible VaD) 24 weeks Black et al ⁶¹	Yes (p<0.001) -2.24 points on ADAS-Cog	No	Yes	N/A
Donepezil (308) (n=616 with NINDS/AIREN probable or possible VaD) Wilkinson et al ⁶²	Yes (p<0.001) -2.09 points of ADAS-Cog	Yes	No	N/A
Donepezil (319) (n=974 with NINDS/AIREN probable or possible VaD) 24 weeks Roman et al ⁶³	Yes (P<0.001) -0.91 points on VADAS-Cog	No	No	N/A
Rivastigmine (VantageE) (n=710) with NINDS/AIREN probable VaD) 24 weeks Ballard et al ⁶⁴	Yes (p=0.028) -1.3 points on VADAS-Cog	No	No	No

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Although most have shown a small but significant benefit of cholinesterase inhibitors on cognition, the magnitude of this impact has been relatively modest (approximately **2 points on the ADAS-Cog scale, roughly half the benefit at** seen in the Alzheimer’s studies) and benefits on global functioning,

activities of daily living and behaviour have not been consistently seen. This, combined with concerns over diagnostic validity and possible side effects, has led both regulatory bodies and guideline groups, for example NICE, to conclude that cholinesterase inhibitors and memantine should not be used in patients with VaD.⁶⁵

There have been two well-conducted randomised trials run over 6 months of memantine, an NMDA antagonist, in VaD.^{66,67} Similar to the studies of cholinesterase inhibitors, both found a significant but modest effect on cognition that did not appear to generalise as there was no impact on global outcome measures. Meta-analyses of the studies have supported these conclusions.⁶⁸ Unfortunately, there have been few other promising avenues. A study of nimodipine in subcortical VaD missed its primary outcome measures, but did find some secondary improvements in some outcome scales and in terms of memory,⁶⁹ prompting other ongoing studies of calcium channel blockers (e.g. AFFECT; [EudraCT Number: 2014-000926-39](#) [clinicaltrials.gov](#)). There have been some positive trials of cerebrolysin, a putative neurotrophic neuropeptide derived from pigs' brains requiring daily infusion.⁷⁰ A Cochrane review of six studies concluded that there was evidence of a positive effect of cerebrolysin on cognition and global outcome in vascular disease, but that wider use was not recommended due to the small number and short duration of trials, heterogeneity between trials and limited follow-up.⁷¹

There have been some studies of primary prevention, though it should be noted that cognition was not a primary outcome in these studies. In terms of reducing cholesterol, the PROSPER study randomised 6000 people to pravastatin or placebo and found no differences in cognitive outcome between groups after 6 years.⁷² Similarly, the Heart Protection Study randomised 20,537 subjects aged 40 to 80 with vascular disease or diabetes to simvastatin or placebo, but found rates of cognitive impairment at 5 years later were almost identical between the two groups at around 24%, with dementia developing in 0.3% of each group.⁷³ These studies can be criticised for the insensitivity of outcome measures and inclusion of relatively well people with low rates of cognitive decline, but provide no evidence that primary prevention by lowering cholesterol prevents VaD. Studies of reducing blood pressure are more promising, but remain equivocal. One difficulty is that such studies have often been stopped prematurely because end points based on cardiovascular and cerebrovascular outcomes have been reached before there has been adequate ascertainment of dementia outcomes to draw clear conclusions. There appeared to be a trend towards antihypertensive treatment reducing dementia incidence in the HYVET study,⁷⁴ though this was non-significant, and the Syst-Eur study found a significant effect of nitrendipine in reducing dementia compared to placebo, though most of the dementias prevented were actually Alzheimer's rather than VaD.⁷⁵ However, reviews and meta-analyses of these studies have generally shown that antihypertensive treatment can prevent VaD by preventing stroke, but apart from this any effect in reducing dementia incidence is borderline, though in the right direction, and needs to be confirmed in larger, longer term studies.^{74,76} However, the recent SPS3 trial compared a two factorial design with intensive blood pressure (v usual targets) lowering and dual antiplatelet treatment (v single aspirin) in 3200 subjects (mean age 63 years) who had a lacunar infarct. The main outcome, the cognitive assessment and screen instrument (CASI), at a median three years, showed no significant effect of either BP reduction (which was a mean of 11mg of mercury between the groups) or of dual antiplatelet therapy over the control arms.⁷⁷ With regard to antiplatelet agents, the results of SPS3 are very much in accord with other studies which suggest no clear evidence of benefit in preventing cognitive impairment or dementia, whilst the single trial of aspirin in established VaD,⁷⁸ although positive, has been criticised because of methodological limitations including a very small sample size, very high dropout rate, and lack of adequate randomisation.⁷⁶ Overall, therefore, results to date of single pharmacological strategies such as antiplatelet agents, reducing blood pressure or use of statins to prevent or treat VaD do not provide support for these interventions, though of course

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these remain important treatments for the VaD risk factors themselves. In contrast, ongoing preventative studies are taking a more multi-dimensional approach, for example the FINGER study which combines vascular risk reduction, nutritional advice, cognitive training and exercise in high risk subjects has recently reported promising results with reduced cognitive decline in the active group at 2 years.⁷⁹ Consistent with this are findings from epidemiological cohort studies suggesting that overall dementia prevalence may actually be decreasing.⁸⁰ While reasons for this are not entirely clear, a reduction in vascular risk is, at least in part, a plausible explanation.

Mild cognitive impairment due to cerebrovascular disease

This has been much less well studied than the syndrome of mild cognitive impairment due to AD, which is largely defined clinically on the basis of an amnesic deficit in the absence of dementia, though diagnostic criteria have been proposed.⁸¹ Far from being a benign condition, the few longitudinal studies of vascular-MCI have reported rates of progression to dementia of similar magnitude to MCI due to AD.⁸² The presentation of early vascular disease is much more heterogeneous as subtle cerebrovascular disease is common with ageing, for example in imaging samples of representative older samples at least 30% have “silent” infarcts on brain imaging,⁸³ with up to 90% of older subjects having varying degrees of white matter lesions.⁸⁴ The clinical significance of such silent white matter lesions had been uncertain, though a large pan-European study (the Leukoaraiosis And DISability or LADIS study) reported in a non-disabled population of older people that the presence at baseline of severe (confluent) white matter lesions conveyed a particularly adverse outcome in terms of a high rate of progression to disability over a three year period (rates around threefold higher than those with only mild white matter disease).³⁶ The study strongly implied the deleterious nature of substantial white matter pathology, even if not currently accompanied by symptoms and disability, and points the need to investigate potential therapeutic approaches which could have significant impact in reducing future disability.

Conclusions and future directions

Though there has been considerable progress in defining and understanding the relationship between cerebrovascular disease and cognitive impairment and dementia, ~~some~~ many uncertainties remain, ~~which hamper progress in the field.~~ Clinical diagnostic criteria are sufficiently robust to be useful for clinical trials, but need further refinement and still need to be refined and validation. ~~For example, and until recently, it has not been possible to determine the relative contribution of Alzheimer and vascular pathology to cognitive impairment in life, since imaging measures such as medial temporal atrophy can also be due to vascular (as well as Alzheimer) change. However, the recent development and validation, while ongoing, of a range of biomarkers for neurodegenerative Alzheimer pathology, AD,~~ including amyloid PET imaging, CSF markers of tau, and amyloid and, more recently, in vivo tau imaging now offer unparalleled opportunities for in vivo subject stratification of those with pure from those with mixed dementia for future naturalistic and therapeutic studies. Such work will also be important to answer the key question as to whether and in what circumstances it is relevant to separate out neurodegenerative and vascular entities and so, in combination with pathological investigation, provide important validation of our clinical concepts of vascular dementia. ~~In these such~~ studies we endorse proposals for harmonisation of data capture, avoiding narrow a priori assumptions that may hamper progress. On the other hand, some studies, clinical trials in particular, may need to focus on specific subgroups to ensure a more homogenous population to study. One thing that has clearly been learned from the trials of cholinesterase inhibitors and memantine in VaD is that translation of Alzheimer treatments to VaD on the basis of shared neurochemical mechanisms may not be appropriate. ~~has not proved fruitful.~~ There remains ~~very~~ limited research on VaD and its mechanisms compared to other dementias, and there is a clear need for further pathophysiological studies to investigate mechanisms which predispose or accelerate cognitive impairment. Large scale genetic studies, which have been so informative in many other disorders, are in their infancy in relation to VaD and may prove informative, as well as

helping understand the shared risk with AD. There are potential treatments currently in clinical trials, including calcium channel blockers, while other agents targeting endothelial function or the renin angiotensin system are putative candidates for further clinical trials.

~~Current~~ ~~Until better treatments are available,~~ management of VaD should focus on identifying and managing comorbidities, ensuring that vascular risk factors are optimally managed, ~~prescribing cholinesterase inhibitors for mixed (but not pure vascular) dementia,~~ ensuring appropriate recognition and management of non-cognitive symptoms, and appropriate psychosocial and other support to optimise quality of life for patients and their carers. ~~Cholinesterase inhibitors do not appear to confer benefit in pure vascular dementia, but at least one good RCT suggests they are beneficial in mixed AD/vascular cases.~~⁵⁹

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Contributions

[Both authors contributed equally to this review](#)

Conflicts of interest

John O'Brien has acted as a consultant for GE Healthcare, [Cytos](#), TauRx and Avid/Lilly, and received honoraria for non-promotional lectures from Pfizer, Lundbeck, Eisai, Novartis and Shire.

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Figure 1 overview

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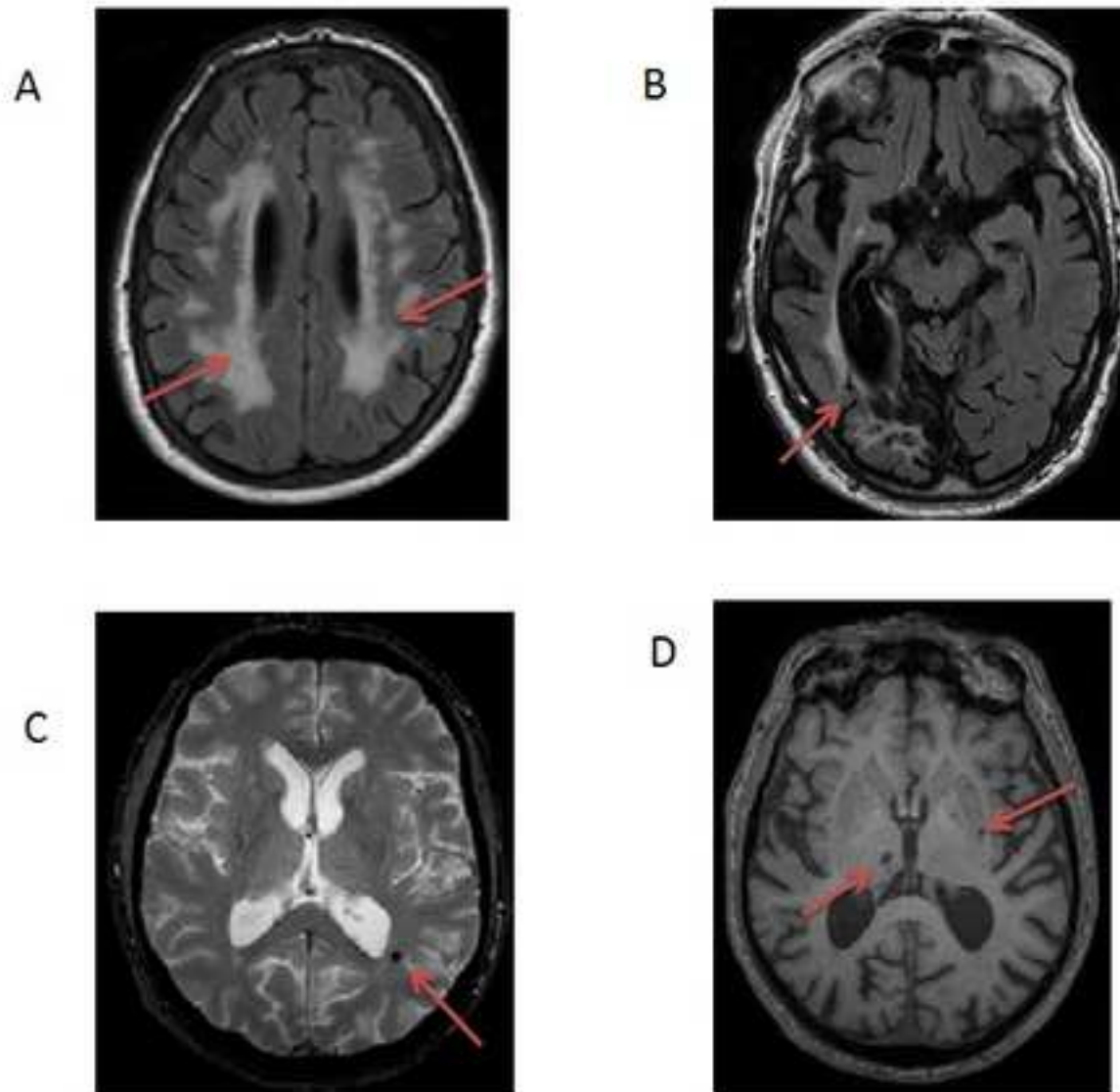


Figure 1. vascular imaging changes on MRI. A Extensive (>25%) white matter lesions (FLAIR image). B Large cortical infarction (FLAIR image). C Microbleed (T2* image). D Multiple lacunar infarcts (T1 image)

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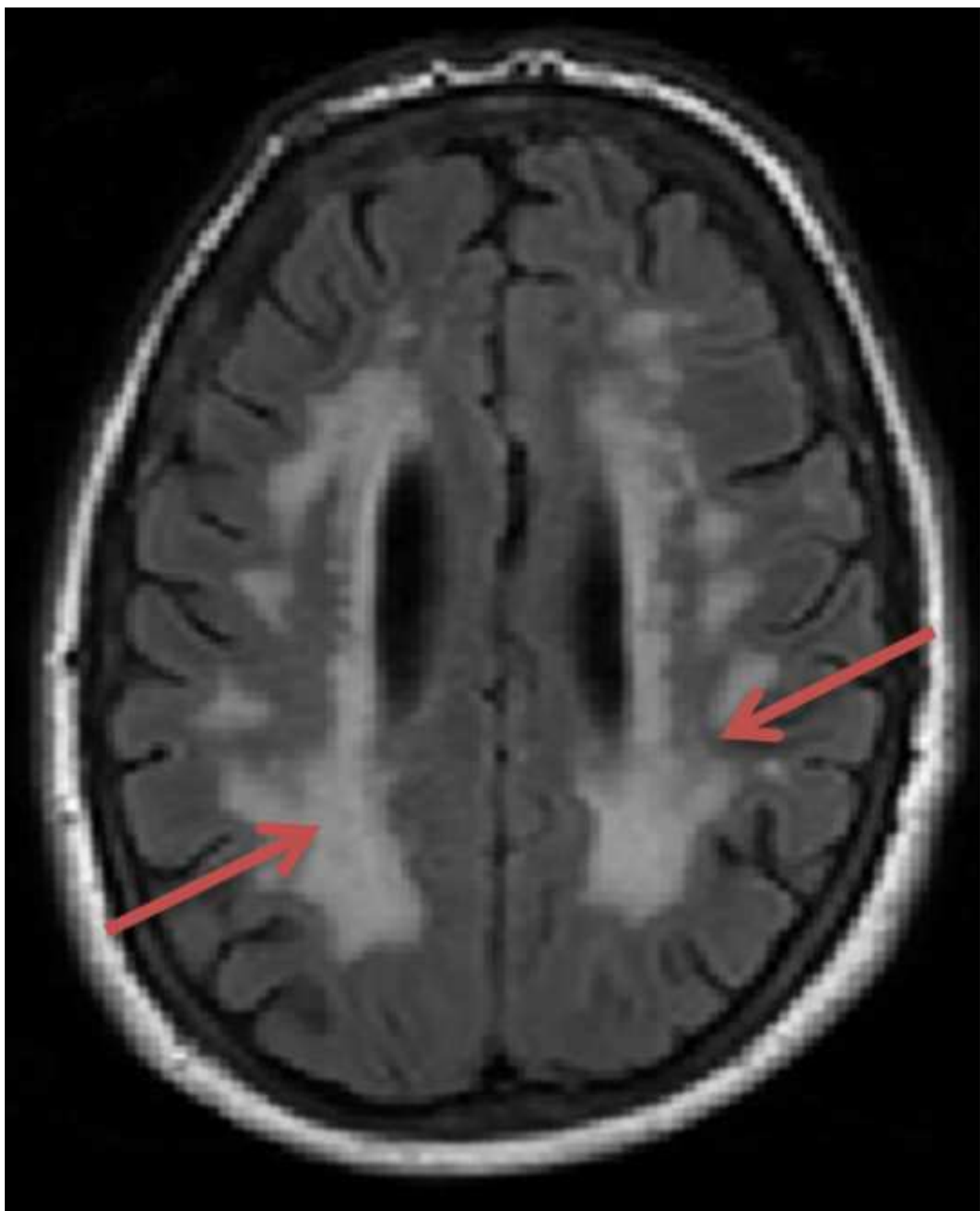


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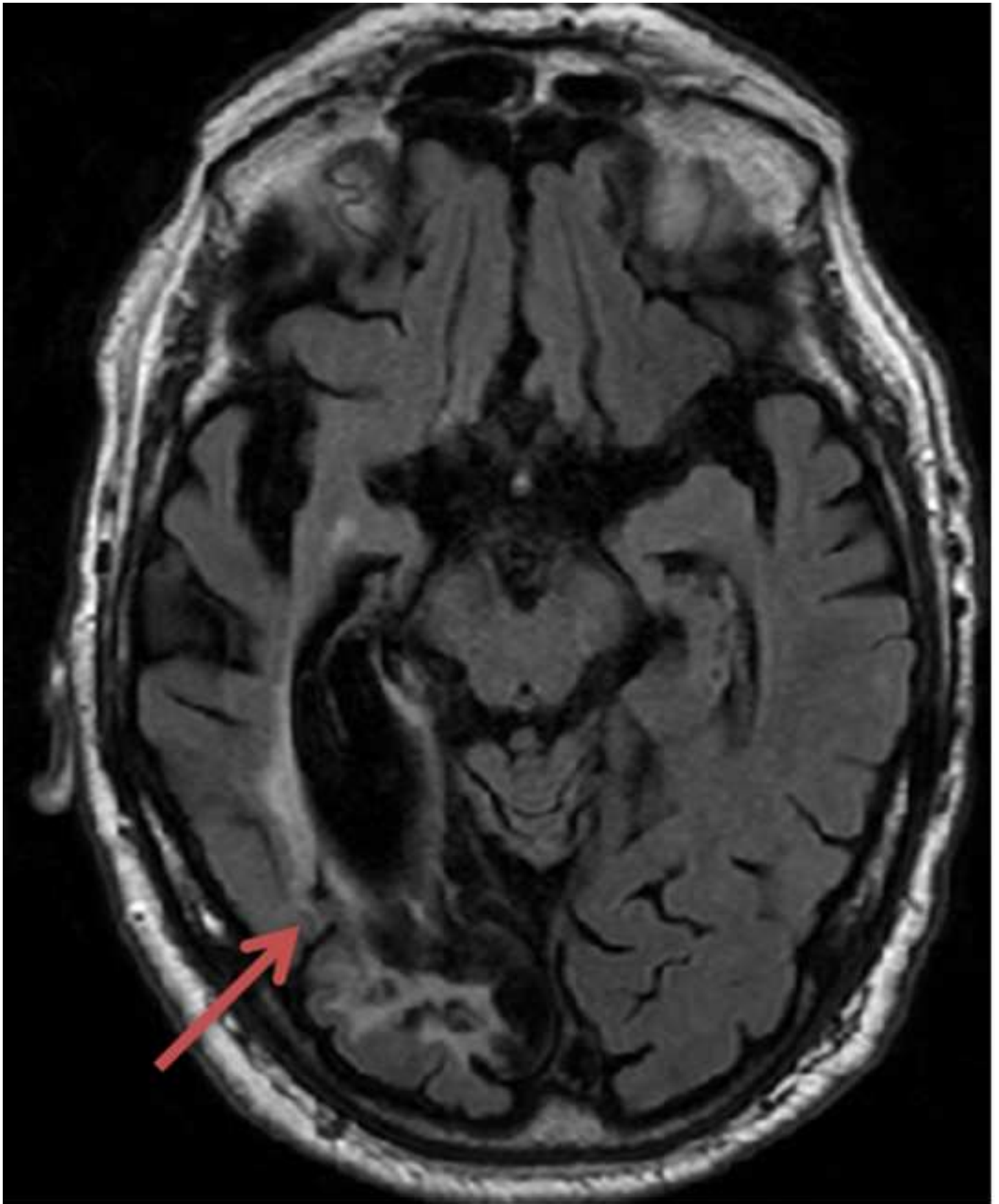


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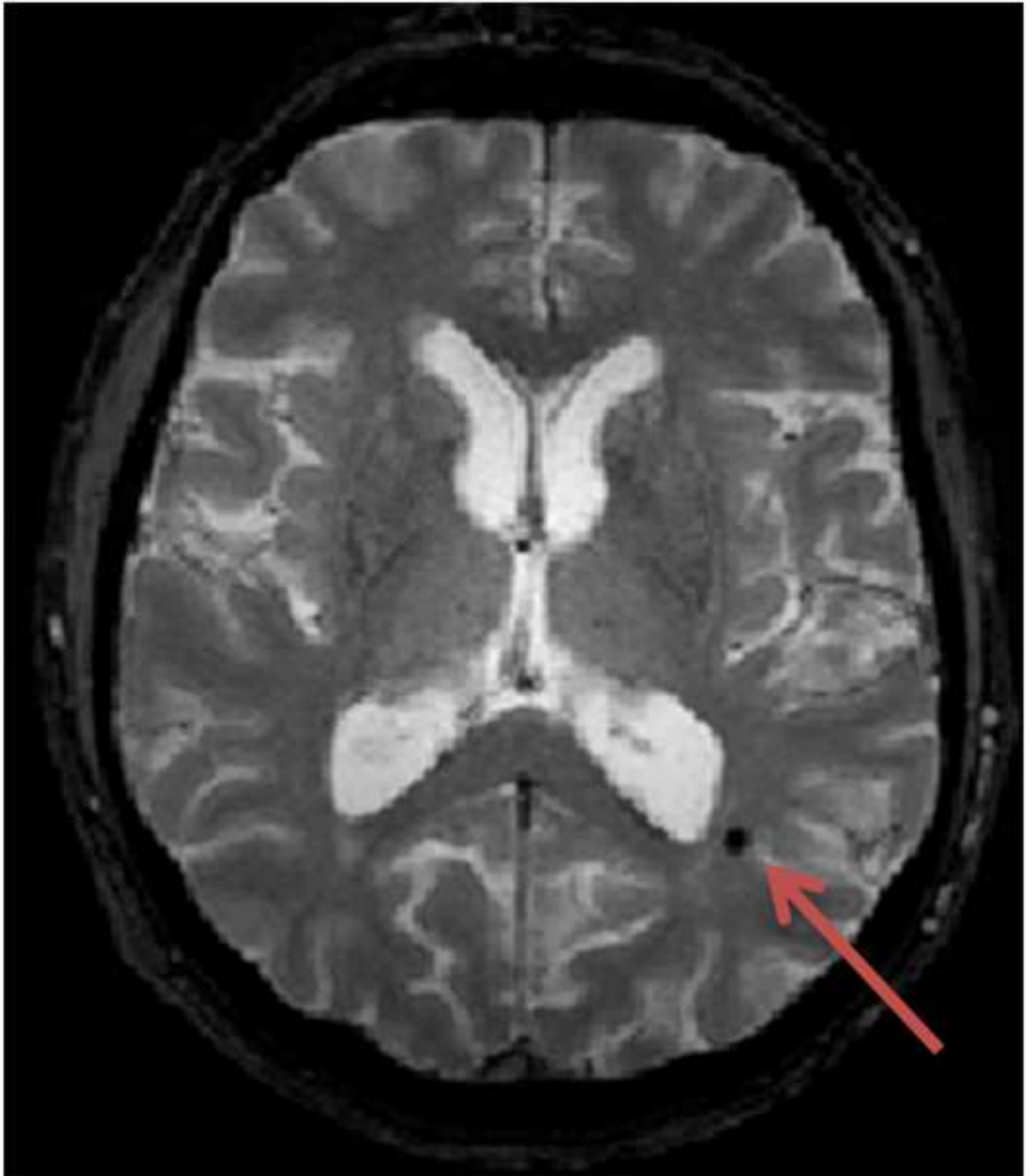
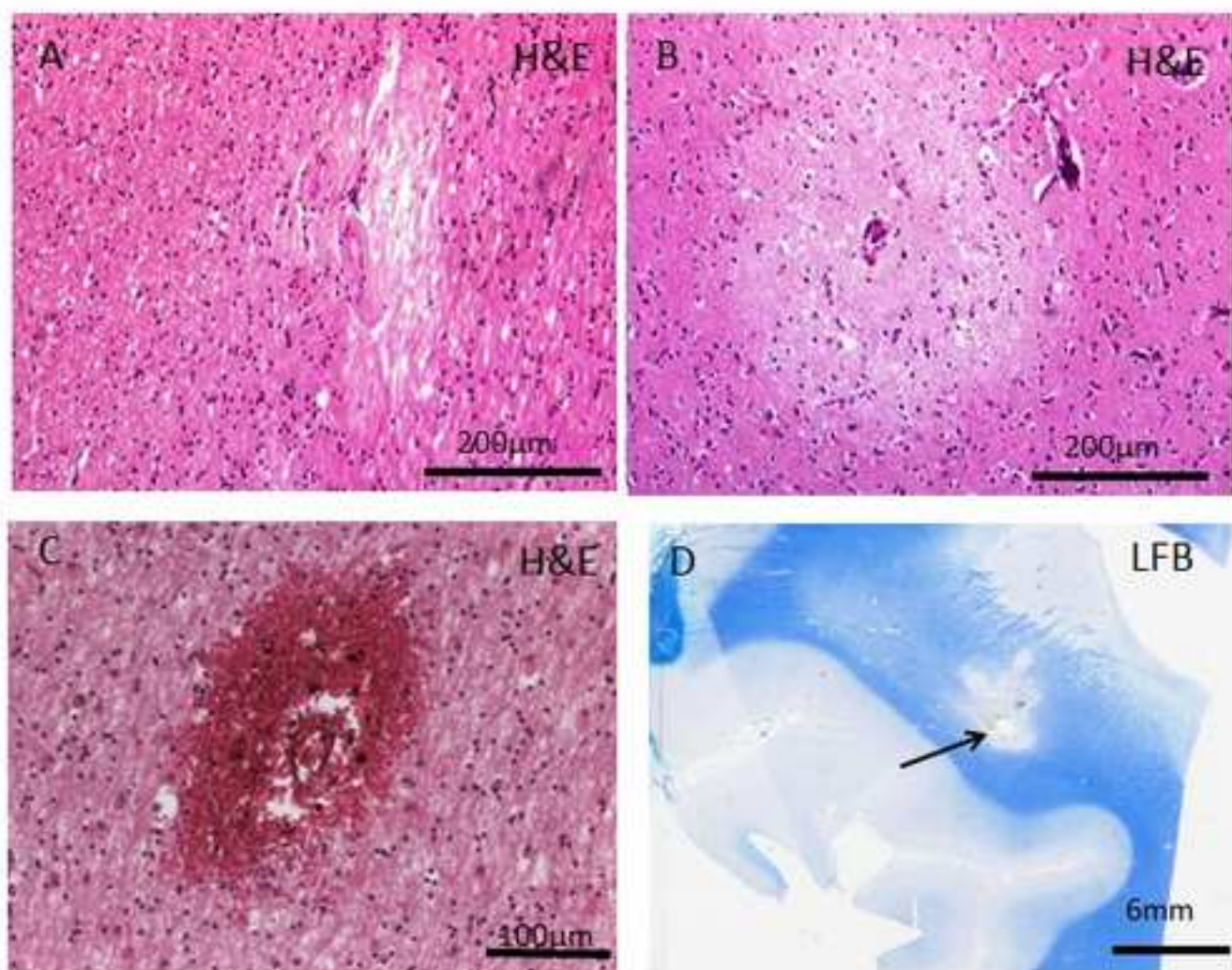


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A Microinfarct in cingulate white matter

B Micro-infarct in frontal cortex

C Micro-bleed in white matter from occipital lobe

D Lacunar Infarct (arrow) in frontal white matter with associated pallor

Sections were cut at a thickness of 100µm and stained with H&E (A,B and C) and Luxol fast blue (D)

Figure 2: Pathological vascular changes which can be associated with vascular dementia

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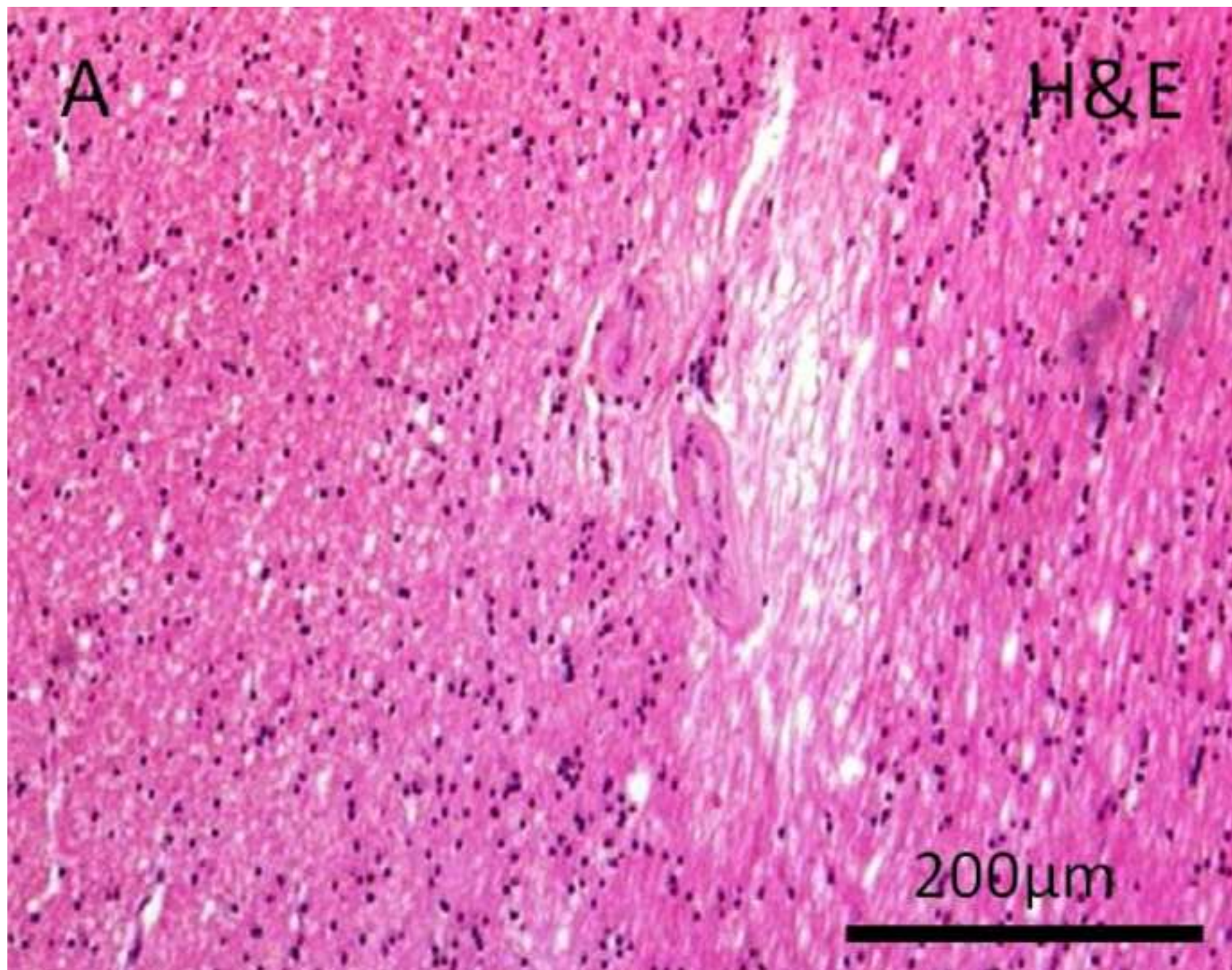


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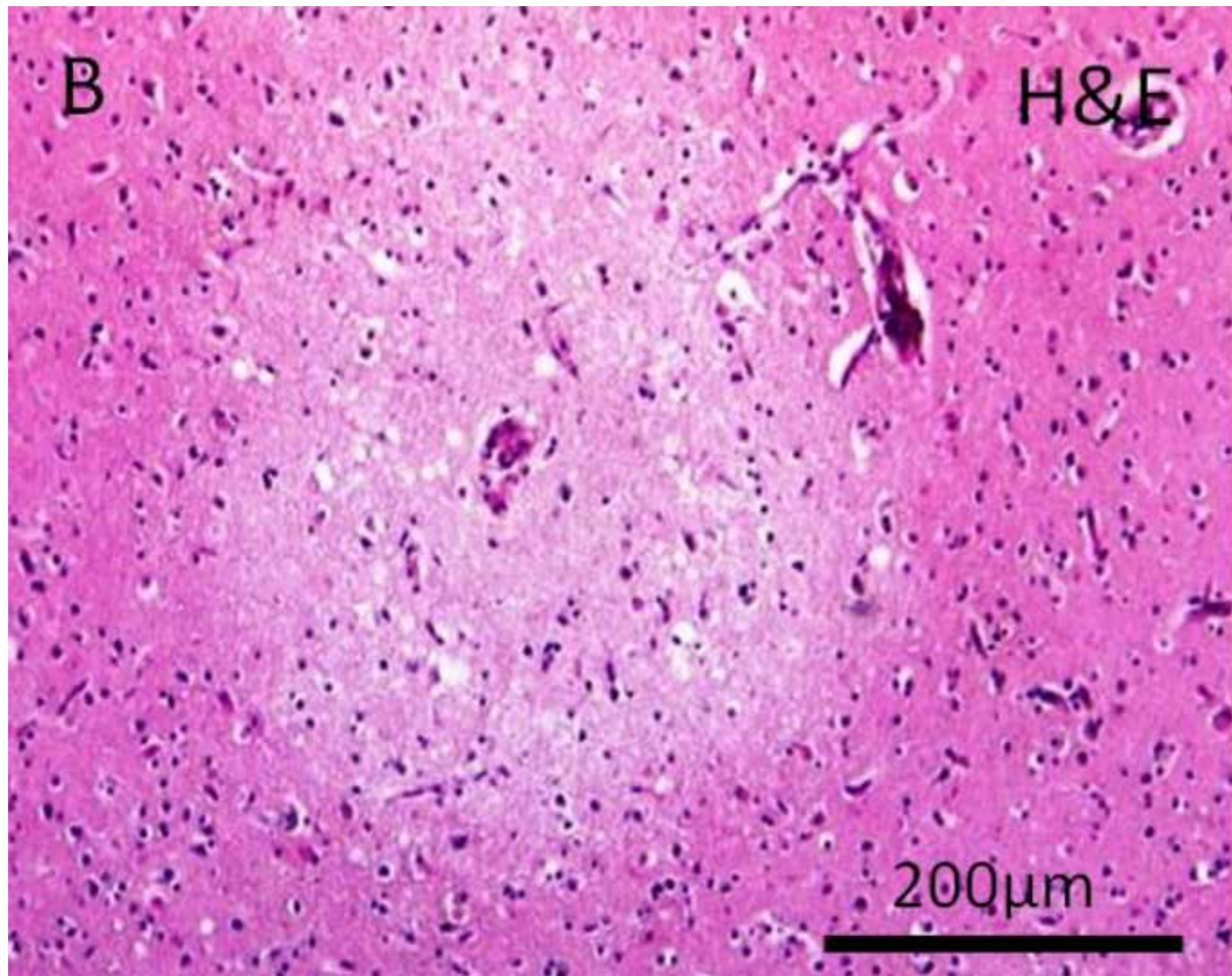


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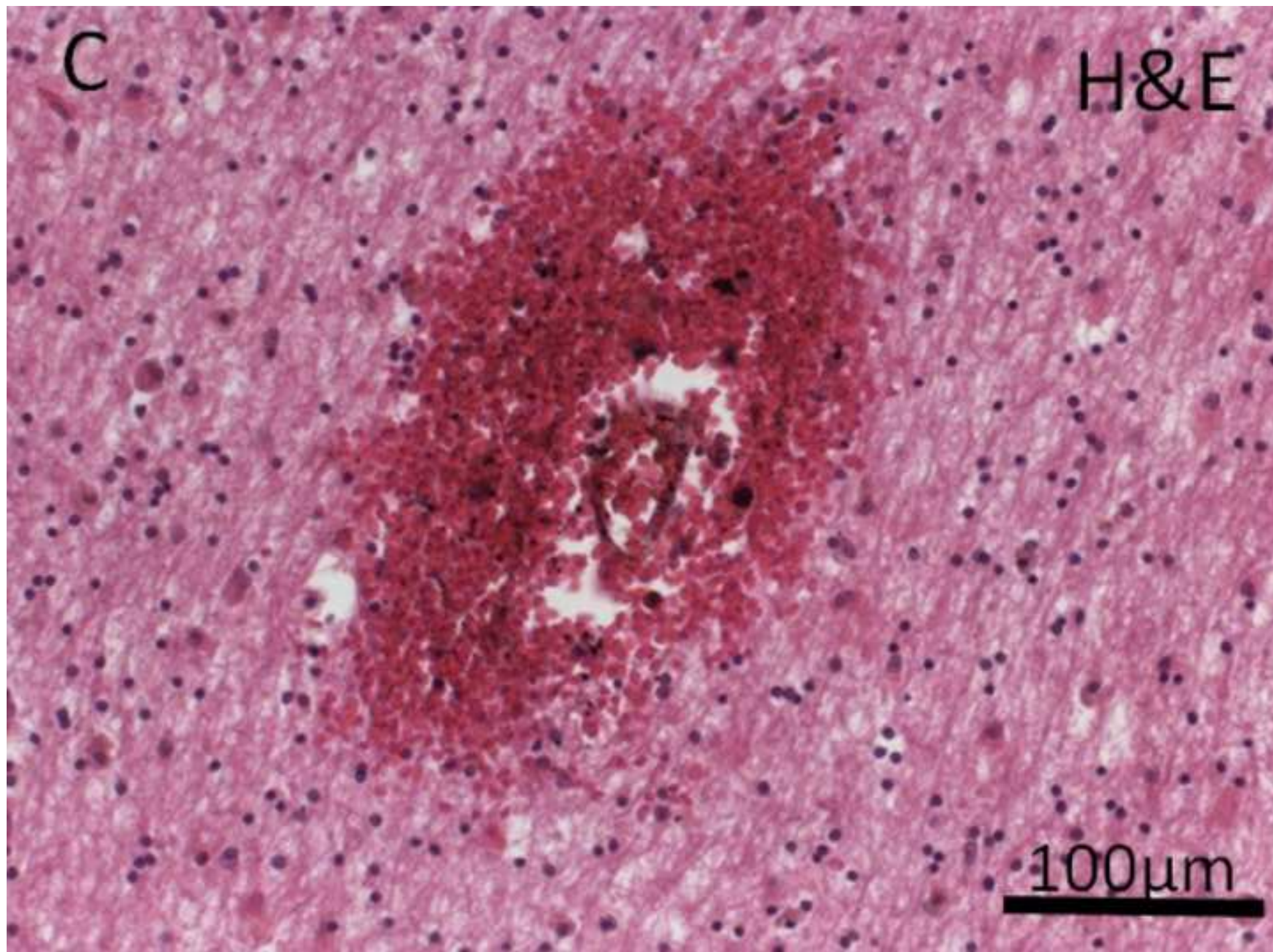


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