The state of play in vascular dementia research: a lay summary

1. Introduction

Vascular dementia was highlighted as a research priority in the Stroke Association's Research Strategy 2014-2019. Despite the devastating impact of this disease, there is a lack of treatments or preventive measures to stop it's progression in people who develop it and an urgent need for more knowledge and research in this area.

Vascular dementia is of particular concern to the Stroke Association, as up to 30% of stroke survivors will develop it. Stroke doubles the risk of developing dementia and there is still a lack of knowledge around the pathology, risk factors, markers and other links between stroke and dementia. The co-existence and co-development of these two conditions presents a very complex picture.

At the Stroke Association, we want to work in collaboration with researchers, other funders, people with dementia and stroke and their carers to identify the big issues that we can start to tackle with research.

Our aim is to lead a programme of work around vascular dementia. Firstly, to identify the difficulties, priorities and next steps for research in this field, and to work in partnership with others to ensure we fund a research programme that takes our knowledge and understanding of this disease forward.

Dementia UK's report for the Alzheimer's Society suggested that by 2025 there will be 250,000 people living with vascular dementia in the UK. We must act now to make some long overdue progress in our basic understanding of how this devastating condition develops, as well as how to diagnose, treat and prevent it.

On 29 January 2015 we brought together a group of experts working in the field of vascular dementia, to discuss the latest research and summarise the state of play in this field: what we know, what we don't know and the next priorities for research. The agenda from this roundtable discussion can be found in Appendix 1 and an attendance list from the day can be found in Appendix 2.

Sections 2–4 of this report provide a brief summary of the topics covered during the discussion and the current state of play in vascular dementia research. The overall priorities that were discussed and agreed at the round table event on 29 January 2015

are listed in section 5. Finally, we outline the next steps for this programme of work in section 6.

There is a Glossary in Appendix 3, this will cover all terms throughout the text that are highlighted in **bold italics.**

2. Overview of the state of play in vascular dementia research

Classification and diagnosis of vascular dementia

In 1968, alzheimer's disease (AD) was recognised as the main cause of dementia in later life.[1] This was also previously referred to as 'senile dementia' and in 1974 the term '**multi-infarct** dementia' (MID) was established.[2] In the 1980s and 1990s MID was recognised to be just one of many causes of vascular dementia (VaD). In 1993 consensus diagnostic criteria were published for VaD.[3] They outlined a set of criteria to help doctors diagnose the condition and included levels of certainty (definite, probable and possible).

By 2003 the broader terms vascular cognitive impairment or vascular cognitive disorder (VCID) were preferred to 'dementia', which included a range of subtypes, such as multi-infarct dementia, small vessel dementia and haemorrhagic dementia. Descriptions of mild and severe vascular cognitive disorder have also been proposed [4]. A combination of mixed cases, pure vascular dementia and pure alzheimer's disease has been emerging more recently and a so-called 'mixed dementia' is recognised as being very common in older people who have dementia.

Several sets of criteria to diagnose VaD have been published since the 1960s. The continuing uncertainty around these criteria needed a critical re-examination. The Vas-Cog Society was established in 2002 and set up a working group to address diagnostic criteria. Following their critique of the criteria in 2009, a broader, more inclusive set of changes have now been established as diagnostic criteria, although this is still yet to be validated in large cohorts.[4]

Recent advances in **neuroimaging** and systematic neuropathological examination have led to better definitions of clinically diagnosed **cerebrovascular** disorders, which cause cognitive impairment and result in VaD. Like AD, the definitive diagnosis of VaD requires **neuropathological** examination. However, it is often difficult to define which neuropathological changes are relevant and to what degree they contribute to VaD. The cause and type of blockage in the blood vessels, presence of a **haemorrhage**, distribution of arteries and the size of blood vessels all play a role in diagnosing VaD.

Multiple brain regions have been linked to VaD and it is not possible to diagnose VaD based only on the location of changes in the brain.

Early or mild changes in the brain, such as **small vessel disease** (SVD) or the presence of **'white matter'**, that can be linked to relevant cognitive changes (such as slower memory processing or memory difficulties) would usually lead to a diagnosis of mild vascular cognitive disorder or impairment[4]. The Oxford Project to Investigate Memory and Ageing (OPTIMA) study has shown that severe SVD is linked to low cognitive scores and 43% of those with high SVD scores were confirmed to have dementia.[5]

In many cases stroke will lead to VaD. People who have had a stroke are more likely to develop dementia than those who have not had stroke, and many stroke survivors who are treated in the acute stages of their stroke will eventually develop dementia. Those with small vessel disease may also survive to an older age and eventually develop VaD. Post-stroke dementia (PSD) may occur immediately after the stroke, or a year or more later. Estimates of PSD developing less than one year after a stroke range from 7% to 41%. Over 75% of PSD cases are classified as VaD. Therefore, most of the dementia that develops in stroke survivors is VaD.

People with VaD usually experience major changes in their concentration, ability to process information and **executive function**; however, this varies, especially between the subtypes of VaD.

In conclusion, the criteria for clinically diagnosing VaD are still debated and need further refinement and validation. However, they are robust enough to be used by clinical studies and research trials. There is also a possibility that markers used to diagnose AD could help to identify mixed cases of dementia. Current evidence shows that small vessel disease is often linked to VaD and that most cases of dementia after stroke are VaD. Hereditary conditions (such as **CADASIL**) are also known to cause VaD. Age-related changes in the brain are also likely to contribute to dementia.

Risk factors

Several risk factors for VaD are also risk factors for 'pure' AD, such as high blood pressure, smoking, raised cholesterol, diabetes, obesity and atrial fibrillation. Depression is a risk factor for VaD as well as for AD and for 'all-cause' dementia.

Vascular dementia is the second most common cause of dementia. AD causes 60% of dementia cases, VaD causes 20% and Dementia with Lewy Bodies (DLB) causes

15%. Similar to AD, rates of VaD rise with age[6]; therefore, age is the strongest risk factor for VaD.

New data is starting to emerge that is beginning to give a picture of the genes that may make people more likely to develop dementia.[7]

Dementia after stroke occurs in approximately 15-30% of stroke survivors. A further 20-25% will develop dementia later in life. The estimated incidence of new onset dementia after stroke is 7% after one year and 48% after 25 years[8].

Treatment and management of vascular dementia

The main way of treating and managing vascular dementia so far has been to use drugs developed for AD. However, recent trials have shown that these are largely ineffective. The use of these drugs has been based on the assumption that the underlying causes and development of AD and VaD are similar; however, it has since been discovered that this is not the case and this approach does not work.

There is limited clinical research to date on VaD and out of the randomised controlled trials (RCTs) that have been completed, there has been no successful outcome for people with this disease. Many drug trials have taken place and have failed to find any treatment options. Long-term observational studies, to understand the natural course of the disease, alongside trials of the best treatment strategies are required. This would be valuable in deciding how best to manage and treat the disease. The UK can and should do more to address this and develop a better strategy for managing VaD.

A Cochrane review (2013) looked at six studies of a treatment called Cerebrolysin and found that it showed positive effects on cognition and outcome in people with VaD. However, this treatment cannot be widely recommended due to the small number of trials that have been completed, the differences in treatment and limited follow-up.

Other RCTs that looked at the use of Galantamine, Donepezil and Rivastigminend all resulted in no effects on outcome for people with VaD. There is a clear need to identify new treatments for this disease.

3. Animal research models of vascular dementia

At present there isn't a model that replicates all the relevant features of VaD well enough to be used in research.[9,10] Systematic reviews of the available literature have concluded that existing animal models of VaD are far from ideal and do not accurately reflect the human disease. There is a need for new model systems that can more

authentically replicate the disease in humans. Rodents are not ideal and progress with larger models may be needed to more closely replicate the disease in humans.

There may be a benefit in looking at species that aren't mammals (such as zebrafish, fruit flies and round worms) although any findings that came from this would still need to be confirmed in larger animals. *In vitro* (laboratory cell culture) systems may also show a benefit, although it is clear that animal models cannot be replaced with laboratory cell models for stroke research, due to the complex processes within the human brain. The involvement of the pharmaceutical industry would be key to progressing this work, as pharmaceutical companies have huge sets of data from their research using rodents. They also have primate and large mammal data that would be relevant to VaD.

4. MRI and *biomarkers* to detect and diagnose VaD

Conventional magnetic resonance imaging (MRI) is very sensitive and can detect the individual features of SVD and VaD. Because MRI is sensitive enough to detect small changes that can be matched against cognitive changes in patients, it's suggested that MRI could be a useful marker for clinical trials.[11,12] It has been shown that it is much easier to detect change using MRI than it is with cognitive testing, which appears relatively insensitive to smaller structural changes in the brain.

It may also be worth considering combinations of **imaging features**. Some studies have shown it is possible to miss risk factors when only looking at one individual feature.[13]

However further work is required before these MRI markers can be widely used in clinical practice. In particular, this includes:

1. Studies to show that identifying MRI markers and changes in MRI markers over time can predict which patients will progress to cognitive decline and dementia.

2. Studies to determine which MRI markers, or combination of markers, are most sensitive to change and also match best with the clinical condition of patients.

3. Clinical trials in which MRI is used to determine if it can provide similar information (but in smaller sample sizes) to that obtained by measuring other clinical factors.

Much more research is needed to validate existing biomarkers, including using MRI markers and other types of biomarkers together. Areas for future priority research are outlined in the research priorities in section 5.

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9) Snyder HM, Corriveau RA, Craft S et al. (2014) Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimers Dement

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12) Schmidt R, Scheltens P, Erkinjuntti T, et al. White matter lesion progression: a surrogate endpoint for trials in cerebral small-vessel disease. Neurology. 2004 Jul 13;**63**(1):139-44.

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5. Research priorities

In reviewing the state of play in VaD research we identified some areas of work, which we organised into six overall research priorities as follows:

i) Further refinement and larger scale validation of the criteria for clinical diagnosis of VaD.

ii) Long-term observational studies are needed to understand the natural course of VaD, alongside trials to test the best ways to treat it.

iii) Define the guidelines and criteria for ***pre-clinical models*** relevant to VCID. This would include improving reproducibility, ensure replication of the disease or condition in humans and involve pharmaceutical companies that have data and expertise to support this work.

iv) Identify and validate a range of relevant biomarkers for VaD, including MRI and combinations of MRI and other biomarkers, such as biomarkers present in the blood, spinal fluid or immune system. Existing datasets should be maximised and biomarkers that are best at detecting changes in the brain over time should be identified and validated.

v) Studies are needed to identify pathways to target for the development of new drugs. There is a need for pre-clinical or experimental medicine approaches to understand how VaD develops, which will help to discover ways to treat it.

vi) We must develop ways to stratify patients to identify those most at risk of developing VaD and to improve these methods for clinical trials.

Having discussed the above topics at our roundtable event on 29 January 2015, the following research priorities were agreed:

i) Basic science is needed to understand how VaD develops and the pathways involved. We also need research to identify ways that new drugs could be developed.

ii) Classification of vascular disease is necessary to help identify people most at risk of developing VaD.

iii) Clinical trials could be used to look at existing drugs or testing new *lipid lowering agents*.

iv) Identify and validate biomarkers for VaD: make use of existing data on inflammatory and cardiovascular markers; perform MRI and biomarker comparison studies.

v) Validate pre-clinical models of VaD.

vi) Large-scale validation of the previously developed classification systems for VaD.

At the roundtable event, it was agreed that any research we fund should consider the following:

- Use a big data approach: make use of brain banks and existing datasets, including *high throughput data* from the pharmaceutical industry, and in particular, incorporate use of Dementia Platform UK (DPUK) and/or UKBiobank.

- Bring expertise in *proteomics*, *metabolomics* and new technologies into the field.

- Capacity building in this field is essential – we should aim to bring in fresh talent with new skills, technologies and fresh perspective (from other fields, for example).

- Multi-disciplinary research teams are essential to bring expertise and understanding of both stroke and dementia, as well as multiple and fresh perspectives into the field.

6. Next steps

We will use this report to inform further discussions with stroke survivors, people who have VaD and researchers, to find out what they think the priorities are in this field.

To do this, we will host a workshop for people affected by stroke and dementia and their family members and carers to discuss what they think the priorities should be. We will also invite research experts and other funders to participate in this discussion. This research priority setting workshop will be held on 4 September 2015.

Following this, we will meet with other funders of dementia research to see if there are areas where we may have mutual interests and can work together. We'll arrange this meeting for autumn 2015, and if we find funders to work with, we plan to go ahead with a call for research proposals in early 2016. Our intention is to fund new research in this area at the end of 2016.

The following table outlines when we think these activities will happen:

Timeframe	Activity
January 2015	Round table with research experts on vascular dementia to discuss current research and future research priorities
May – July 2015	Writing a State of Play review
August 2015	Publish State of Play Review and a State of Play Lay Summary on Stroke Association website
4 September 2015	Priority setting workshop with people affected by stroke and dementia
October 2015	Funders meeting to discuss priorities and areas of mutual interest
October – December 2015	Develop a call for proposals
January/ February 2016	Launch a call for proposals

July 2016	Deadline for applications
November 2016	Awards panel meeting
December 2016	Council of Trustees approve funding awards Research awards made

Appendix 1: Agenda from roundtable on vascular dementia, 29 January 2015

Meeting	Research Round table on Vascular Dementia
Date	29 January 2015
Time	10.45 – 16.15hrs (followed by reception until 18:00)
Venue	Council Chambers, Stroke Association House

Chair: Professor Seth Love, University of Bristol

10.45-11.00 Arrival and Refreshments

11.00-11.10 Welcome and Introductions

11.10-11.20 Stroke Association Research Strategy and Introduction to the Vascular Dementia Priority Programme – Dr Kate Holmes (Stroke Association)

Session 1: Overview

11.20-11.40 "Vascular dementia: where are we now?" An overview by Professor John O'Brien University of Cambridge)

11.40-12.00 "The pathophysiology of vascular dementia" by Professor Raj Kalaria (Newcastle University)

12.00-12.45 Questions and discussion of morning

12.45-13.15 Lunch

Session 2: Clinical Trials Update

13:15-13:30 "MRI imaging in VCI and its potential use in clinical trials" by Professor Hugh Markus (University of Cambridge)

13.30-13.45 AFFECT study: Professor Peter Passmore (Queens University Belfast)

13:45-14:00 PODCAST study: Professor Philip Bath (University of Nottingham)

14.00-14.45   Questions and discussion about current/recent research and the next priorities in vascular dementia/cognitive vascular impairment

14.45-15.00   Refreshment break

15.00-15.45   Feedback from discussions, what are the research priorities in this field?

15.45-16.15   Next steps agreed

16.15-18.00   Reception and networking

Appendix 2: Attendance at roundtable on 29 January 2015

Professor Philip Bath	University of Nottingham
Dr Giovanna Zamboni	University of Oxford
Professor Stuart Allan	University of Manchester
Professor Seth Love	University of Bristol
Dr Atticus Hainsworth	St George's University of London
Professor Peter Passmore	Queen's University, Belfast
Professor Martin Rossor	University College London
Professor Rob Stewart	King's College London
Professor Paul Ince	University of Sheffield
Professor Hugh Markus	University of Cambridge
Professor Joanna Wardlaw	University of Edinburgh
Professor John O'Brien	University of Cambridge
Professor Raj Kalaria	University of Newcastle
Dr Roxana Carare	University of Southampton
Dr Dale Webb	Stroke Association
Dr Kate Holmes	Stroke Association
Dr Madina Kara	Stroke Association
Dr Shamim Quadir	Stroke Association
Miss Rachael Sherrington	Stroke Association
Dr Shannon Amoils	British Heart Foundation
Professor Jeremy Pearson	British Heart Foundation
Dr Clare Walton	Alzheimer's Society
Dr Simon Ridley	Alzheimer's Research UK
Dr Catherine Moody	Medical Research Council

Appendix 3 – Glossary

Biomarker – A biomarker is a measurable indicator of the presence, or severity, of a particular disease or condition.

CADASIL – This stands for "Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy" and is the most common form of hereditary stroke disorder. It is thought to be caused by genetic mutations of the Notch 3 gene.

Cerebrovascular – The term cerebrovascular refers to the blood supply to the brain, so for example, cerebrovascular disorder refers to a disorder or problem in the blood supply to the brain.

Executive function – This is an umbrella term for the regulation and control of cognitive processes in the brain, including working memory, reasoning, task flexibility, problem-solving and planning. Executive functions are skills everyone uses to organize and act on information.

Haemorrhage – A haemorrhage in the brain refers to bleeding in the brain.

High throughput data – This is data generated by taking thousands of measurements per sample, to provide a more robust analysis.

Imaging features – This refers to specific findings that can be seen when looking at an MRI scan, such as unusual brain cell structure or presence of a haemorrhage in a specific part of the brain. When looking at one finding in one part of the brain, this is called a single imaging feature.

Lipid lowering agents – These are drugs used to lower the lipid (fatty acid) levels in the blood, similar to the cholesterol-lowering drugs known as statins.

Metabolomics – This is the study of the chemical and metabolic processes of human cells. This can be used to identify the cellular processes that are involved in, or can be used as indicators of, the development of a particular disease.

Multi-Infarct – An infarct is small area of dead brain cells caused by a lack of blood supply. Multi-infarct refers to multiple numbers of these small areas of dead cells in the brain.

Neuroimaging –The use of various techniques to visualise the structure and function of the nervous system.

Neuropathological – Neuropathology is the study of disease in the nervous system tissue, usually in the form of either small surgical biopsies or whole autopsies. Neuropathological examination refers to examination of disease in the nervous system.

Pre-clinical models – The term pre-clinical refers the stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility and safety data is collected. The term 'models' usually refers to the use of animals in experiments in order to replicate the disease being studied in other mammals before starting to test in humans. The animals that are used this can vary from mice and rats to larger animals such as dogs and primates.

Proteomics – This is the large-scale study of proteins, with the particular aim of identifying their structures and functions. This helps to establish which specific proteins may be involved, or can be used as indicators, in the development of a particular disease.

Small vessel disease – This is a condition where the small arteries in the brain become narrow. This condition may also affect the heart and other small arteries in the body, but in this instance it is referring to the brain.

White matter – This is a part of the central nervous system in the brain, which contains nerve fibres. It has a distinct appearance on MRI scans. White matter accumulates or changes when disease develops in the brain.