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Maintaining vascular health is likely to be very important because healthy blood vessels support these clearance and exchange processes

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Q1 Earlier in your career, small vessel disease was often regarded as an unavoidable consequence of ageing. What evidence first made you question that assumption?

There were several things, but a main one was that the visible features that we see on brain imaging were so variable. You could have people in their 50s who had quite a lot of small vessel disease features, and people in their 70s, 80s, 90s who had hardly any. And if it was so inevitable and primarily due to ageing, then you would have expected a slightly more consistent pattern. I would say it is still the case that many people just dismiss it as: "Oh, it's your age." So, I am not sure that things have changed that much.

Q2 Small vessel disease and lacunar stroke were historically interpreted through atherosclerosis models, whereas your work has emphasised endothelial dysfunction and diffuse microvascular injury. How settled is that shift now, and what evidence most strongly displaced the traditional view?

This is partly because a large proportion of ischaemic strokes are indeed due to atheroma or an embolus, and by association it was assumed that lacunar ischaemic stroke must be the same. There have been many studies showing that patients with lacunar stroke do have atheroma, but that does not necessarily mean that the two are directly connected.

I first started questioning this some time ago, when we looked at people who had had a lacunar ischaemic stroke or who had white matter disease, which is a feature of small vessel disease, we could find no relationship between the location of the atheromatous stenosis (of any degree) in the underlying arteries, and the side of the brain affected by the lacunar stroke or that the white matter disease was worse on the side with the atheroma. Recently, we found that the patients who had atheroma were much less likely to have a lacunar ischaemic stroke and much more likely to have cortical ischaemic stroke. There were patients with lacunar stroke who did have some atheroma, but there was no relationship between the side of the atheroma and the side of the lacunar stroke. Interestingly, we did find a relationship between widening of the large arteries that supply the brain and lacunar stroke and small vessel disease.

What tends to happen at the moment is that lacunar ischaemic strokes get treated just like any other type of ischaemic stroke in terms of secondary prevention. But actually, having done some large-scale meta-analyses, for the European Stroke Guidelines for example, we really struggled to find good evidence that antiplatelet drugs really help prevent recurrent lacunar ischaemic stroke. We certainly found no evidence that they were helpful for people who had white matter disease but had not yet had a stroke. We actually found quite a lot of evidence to suggest that antiplatelet drugs could be hazardous in these people because they cause bleeding without any benefit of reducing ischaemic strokes, so it is slightly complicated.

Q3 Before STRIVE, definitions of small vessel disease varied widely across centres. How did standardising MRI descriptors change not just comparability, but the way we interpret what these lesions actually represent biologically?

Before STRIVE, there were a lot of assumptions about the various different types of lesions seen on brain scans. People assumed that these were all different, and that they all had a different aetiology or causative mechanism. I think what STRIVE helped to do was, first of all, simplify the language used to describe the lesions so that people were on the same page. We did an update in 2019 and identified some more features that can reasonably be considered part of the small vessel disease spectrum, and I think that would not have been so straightforward without STRIVE initially pulling the main features together.

It has also helped to translate high-end imaging research into clinical practice, and improve standardisation of radiological reporting, and the way that information gets translated into clinic letters to GPs or to patients. So, I think it has had knock-on effects on clinical practice. But while it has helped on a number of fronts, I think there is still a long way to go. Recognising that small vessel disease is not just a consequence of ageing, and not just about vascular risk factors or atheroma, is still something we are working through.

Q4 Perivascular spaces were long dismissed as incidental MRI findings, yet they are increasingly linked to brain fluid clearance pathways. How central is impaired clearance to small vessel disease, and how close are we to measuring it clinically?

We have shown that enlargement or increased visibility of perivascular spaces is likely an early stage in small vessel disease. And like some other small vessel disease features, perivascular spaces can also reverse, at least early on. In terms of brain fluid clearance, there has been rising interest, particularly in Alzheimer's disease research, because the damaging protein accumulation may be linked with failure of clearance mechanisms. It then became apparent that perivascular spaces are probably part of that overall fluid clearance pathway. In the last 10 years, other groups and we have developed methods to try and track fluid movement through the brain in people using brain MRI techniques. The brain sits in a fluid environment inside the skull, and it was always assumed this was mainly for buoyancy and protection, but actually, that fluid circulation system is now recognised to play an important role in continuously clearing waste. We are now seeing emerging patterns in some brain diseases that are consistent with slowed clearance, where debris and proteins may not be clearing as efficiently as they should.

This is a very complex process, and we are only just beginning to unpick it, but there appear to be relationships with small vessel disease progression, as well as inflammation and other processes. Small vessels are likely important also because their pulsation with each heartbeat and other vascular dynamics help drive fluid movement through the brain. So, the brain fluid and waste clearance system is an engineering challenge in a sense:

maintaining high blood flow, exchange of oxygen and glucose, and clearance of waste to support healthy brain cell activity, all within a closed box (the skull).

Q5 Do you think there could one day be therapies targeting clearance?

Potentially. For example, some general anaesthetic agents may be less disruptive to clearance processes. Many Alzheimer's therapies are already aimed at increasing clearance of amyloid and tau proteins. Maintaining vascular health is likely to be very important because healthy blood vessels support these clearance and exchange processes. Drugs that improve the function of the lining of small vessels, the endothelium, may therefore also help maintain or improve clearance, and potentially slow or reverse progression of small vessel disease and other neurodegenerative pathologies.

Q6 Much of small vessel disease is clinically silent until a stroke, or cognitive or physical decline emerges. When abnormalities are found incidentally, what should guide clinical communication and management?

This is a common problem, and we are trying to increase the information about current management, for example through the European Stroke Organisation Guidelines. There is a range of things that can be triggering, but currently it is mostly about controlling vascular risk factors

such as blood pressure, diabetes, not smoking, cholesterol, adopting a healthy lifestyle including diet, exercise and good sleep habits, and maintaining a reasonable body weight.

Diet, in particular not adding salt to your diet, as well as the usual dietary advice encouraging a Mediterranean-orientated diet, with not too much saturated fat or meat, is essential. Everything should be eaten in moderation, but certainly with plenty of green leafy vegetables. Vegetables like beetroot, spinach, kale, chard, and celery all contain compounds which actually actively help blood vessels maintain their function by supporting the formation of nitric oxide (NO), which is a really key molecule that helps control blood vessel function so as to maintain optimum blood flow.

One of the reasons why some of the newer diabetic drugs may help reduce the risk of heart attacks and strokes in addition to controlling diabetes is because they help reduce BMI (hence are now also popular for weight loss) and help improve blood vessel health.

If someone has a scan and it does show evidence of small vessel disease, then it is worth asking whether the amount is 'appropriate for age'. Small vessel disease does increase with age; however, there is a lot of inherent variation with no absolute rights and wrongs. It is an opportunity to check for vascular risk factors that could be treated (especially blood pressure) or lifestyle elements that could be modified (especially smoking cessation and more exercise). If someone has a particularly striking degree of small vessel disease, particularly at a youngish age, then there are a number of rare genetic causes which are being recognised that can run in families and which are worth considering if this might be the case.

Q7 LACI-2 (LACunar Intervention Trial 2) tested repurposed agents such as isosorbide mononitrate and cilostazol as the first potential specific treatments for lacunar stroke, with LACI-3 scaling this approach. What makes repurposing attractive in small vessel disease specifically, and what would a positive result change in routine practice?

The advantage of repurposing established drugs from their existing use to a new area is that their safety is usually already well understood, unexpected adverse effects are unlikely, and the drugs are generic, so they are less expensive and potentially very affordable for most healthcare systems. It happens that there are a number of repurposed drugs, or drugs already in use for other conditions including cardiovascular disease, which have modes of action that theoretically might help improve the health of the small blood vessels in the brain, and this might help prevent the long-term effects of small vessel disease.

Isosorbide mononitrate has been widely used for many decades to help control angina and ischaemic heart disease. It is a bit like glyceryl trinitrate (GTN) that people take as an oral spray or tablet under the tongue if they are having an angina attack, except that isosorbide mononitrate is given as a regular dose. It increases the amount of NO that helps restore small blood vessel function and tone, and a number of other things, such as reducing blood vessel inflammation.

Cilostazol is considered an antiplatelet drug, but actually it has a number of other effects. It helps improve endothelial function, it helps stop the breakdown of NO so that the NO lasts longer, and it has secondary effects which help the small blood vessels to interact better with other cells in the brain to maintain their health too.

We could not decide which one of these two drugs to test, so we thought we would test both in the LACI-2 trial. The LACI-2 results suggested that one or both drugs, particularly when used together, may reduce recurrent lacunar ischaemic stroke, reduce dependency, reduce cognitive decline, and improve quality of life. So now, we are testing if this is true in the LACunar Intervention Trial 3 (LACI-3), which is Phase III, larger, and including more centres, aiming for about 1,300 patients. If either or both drugs show the benefit seen in LACI-2, we have already discussed this with the UK drug regulator, who gave us advice on the conduct of LACI-3 to ensure that if the results are positive, then the licence for the drugs could be extended so the drugs can be prescribed to patients with lacunar ischaemic stroke.

Q8 Dementia research has been heavily weighted toward amyloid biology. How well does current research investment reflect disease burden and modifiability in ageing brains?

There have been surveys looking at numbers of trials in different types of dementia, and the vast majority of funding is going into Alzheimer's disease, with a very small number of trials looking at vascular causes. Nonetheless, there is a large amount of evidence showing that good lifestyle and blood pressure

management, etc are associated with a lower risk of cognitive decline or dementia. There is also some evidence from clinical trials supporting better lifestyle, blood pressure, and vascular risk factor control, which may not necessarily prevent cognitive decline entirely, but they help slow it. If you are at risk of cognitive decline or in early stages, you should have your blood pressure managed anyway, regardless of dementia risk. Dementia clinics are in an ideal position to implement vascular risk reduction according to standard vascular disease prevention principles. But everybody is so focused on amyloid and tau that vascular contributions often get ignored. Vascular disease is not the only one; Lewy body dementia and other types of dementia are also somewhat under-recognised, but vascular is particularly important because we know so much about how to manage it already from stroke medicine.

The brain is nothing without its blood supply. But even in the Alzheimer's field, many people still do not really appreciate the relevance of small vessel disease such as white matter lesions or visible perivascular spaces. They may accept that perivascular spaces are involved in waste clearance, but still see these features as epiphenomena.

Meanwhile, there is optimism around antibody therapies for Alzheimer's disease, which is understandable. But in the end, I think we will have a combination approach to prevention and treatment of cognitive decline and dementia, a bit like stroke prevention where there is treatment to reduce blood lipids, treatment to reduce blood pressure, and treatment to stop platelets sticking together and clots forming. Given the multifactorial components of dementia, it is unlikely there will be a single magic bullet.

Q9 If you had to choose one unresolved question that would most change diagnosis or treatment, what would it be?

I think we have important signals of benefit around the drugs we are testing in the LACI trials. I would like to see those drugs tested in vascular cognitive impairment, or even cognitive impairment more broadly. We have a small single-centre trial starting imminently in people attending memory clinics with a mainly vascular cause of cognitive decline. There could be mixed vascular and some Alzheimer's pathology since this scenario is very common; we are not excluding Alzheimer's pathology, just ensuring there is a main vascular component.

It is a small start, but ideally, we need a larger trial.

One of the things that holds everything up is that obtaining the approvals, the regulatory environment, even for repurposed drugs, is very complex and time-consuming. The whole process from writing the protocol to finally getting the green light to recruit and treat participants can take many, many months, and that is after the years that it can take to get the funding to pay for the trial.

And if I had one additional suggestion, it would be for people to look more closely at brain lesion patterns on imaging, because different patterns of disease and types of lesion can reflect different underlying causes, and this will inform prevention and treatment in the long run. We are moving from 'this is small vessel disease' to more specific inferences: e.g., vascular risk factor- or lifetime vulnerability -related disease, cerebral amyloid angiopathy, apolipoprotein E-related patterns, or rarer genetic forms. That next level of stratification would be very helpful.