Combining neurovascular and neurodegenerative MRI measures in stroke

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Abstract

Background and purpose: Individual markers of cerebral small vessel disease and cerebral atrophy explain a small proportion of variance in vascular risk factors and cognitive function. Combining these markers into a single measure of neurovascular and neurodegenerative disease may be more powerful. We assessed this using data contained in the Virtual International Stroke Trials Archive (VISTA) Prevention sub-archive.

Methods: We extracted white matter hyperintensities (WMH) and cerebrospinal fluid (CSF) volumes from 317 people with ischaemic stroke or transient ischaemic attack who had a baseline MRI, and assessed progression of volumes in 208 people who had two-year follow-up MRI. WMH and CSF volumes were segmented from FLAIR and T1 images. The combined neurovascular and neurodegenerative measure was the sum of WMH and CSF volume normalised by intracranial volume. We assessed: 1) the relationship between baseline vascular risk factors and imaging markers; and 2) the relationship between baseline imaging markers and mini mental state examination (MMSE) score at follow-up using multiple linear regression. We also assessed implications for sample size calculations using N=208 participants with follow-up MRI.

Results: Vascular risk factors accounted for 7%, 11%, and 12% of the variance in WMH, CSF, and combined volume, respectively (all $P<.001$). The association between baseline combined volume and six-month follow-up MMSE (β=-0.442, standard error (SE)=0.07, $P<.0001$) was 32% greater than WMH (β=-0.302, SE=0.06, $P<.0001$) and 12% greater than CSF (β=-0.391, SE=0.07, $P<.0001$) alone. The combined volume required between 207 and 3305 (20%) fewer patients per arm than WMH alone to detect reductions of 10-40% in volume progression over two years.

Conclusions: A combined neurovascular and neurodegenerative MRI measure including WMH and CSF volume was more closely related to vascular risk factors and cognitive function than either WMH or CSF volume alone. The combined volume may be a more sensitive measurement for clinical trials.

Introduction

Combined measures of neurovascular and neurodegenerative features on magnetic resonance imaging (MRI) have recently been proposed to better characterise age- and stroke-related brain tissue damage[1,2]. The "Total Small Vessel Disease (SVD) Score" was based on combinations of clinical visual scores[1] and the "Brain Health Index (BHI)" was based on automated processing of several MRI sequences[2]. The Total SVD Score has limited granularity and is prone to ceiling effects while the BHI requires high resolution T1, T2, FLAIR, and GRE sequences to be robust. These sequences may not always be available, particularly in studies using routine clinical imaging and/or in those designed to assess white matter hyperintensities (WMH) and other features of SVD using visual ratings, where thicker MRI slices may have been obtained.

WMH volumes and measures of atrophy, e.g., cerebrospinal fluid (CSF) volume, may still be acquired from thicker slice images and only require FLAIR and T1 MRI. Individually these volumes are related to vascular risk factor burden, however vascular risk factors have been shown to explain very little of their variance[3,4]. Further, these volumes are related to cognitive impairment but the relationship is often weak[2,5]. It is unknown whether these individual volumes can be combined to better predict cognitive impairment.

This study assessed whether a combined measure of WMH and CSF volume could: 1) increase variance accounted for by vascular risk factors in stroke-related brain MRI features; 2) improve predictions of cognitive impairment; and 3) reduce sample sizes required to detect potential treatment effects in clinical trials.

Methods

Participant and data extraction

Data were obtained from the Virtual International Stroke Trials Archive (VISTA) Prevention sub-archive (http://virtualtrialsarchives.org/vista). VISTA holds fully anonymised data from completed clinical trials, negating the need for local ethical approval. The project was approved by the VISTA steering committee. We extracted baseline and two-year follow-up MRI, Mini-Mental State Examination (MMSE) scores at six months (to limit confounding effects of stroke on cognition at baseline) and two-year follow-up, and vascular risk factors at baseline, where available. Vascular risk factors included reported diagnosis of hypertension, hypercholesterolemia, diabetes, smoking, atrial fibrillation and measured systolic and diastolic blood pressure. All data that we generated in this study will be made publicly available in VISTA and requests for access can be made at http://virtualtrialsarchives.org/vista.

Brain MRI acquisition and processing

Brain MRI was acquired at baseline and two-year follow-up; acquisition parameters are fully described in supplementary material Table I (please see http://stroke.ahajournals.org). The methods for WMH, CSF, and intracranial (ICV) volume processing using T1 and FLAIR images have been described previously[7]. All volumes were visually verified and WMH were checked and edited according to STRIVE guidelines[8]. WMH and CSF volumes were normalised (divided) by ICV. The combined neurovascular and neurodegenerative MRI measure was simply the sum of normalised WMH and normalised CSF volume.

Statistical analysis

All statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4 (© 2002-2012 SAS Institute Inc.). PROC REG was used to perform linear regression analyses between brain volumes, vascular risk factors, and MMSE using N=317 baseline participants. All regression beta (β) coefficients were standardised and compared with percent differences calculated as: $((\beta_1-\beta_2)/\beta_1)*100$. PROC POWER was used for sample size calculations with brain volume progression data from N=208 participants. Sample size

calculations were based on detecting reductions of 10-40% in the change from baseline to two-year follow-up in each brain volume with power=0.8 and alpha=0.05.

Results

Participant Characteristics

Characteristics of all 317 participants at baseline, divided by those that had a useable follow-up MRI and those that did not, are in supplementary material Table II (please see http://stroke.ahajournals.org); N=208 participants had a useable follow-up MRI. Reasons for lack of a useable follow-up MRI included image artefact/motion and participant loss to follow-up. There were limited differences between participants that had a useable follow-up MRI and those that did not: death during study (a main reason for loss to follow-up) was higher in those without a follow-up MRI, and incidence of diabetes and diastolic blood pressure were higher in those with a follow-up MRI, as shown in supplementary material Table II (please see http://stroke.ahajournals.org).

Variance in individual and combined brain MRI volumes accounted for by vascular risk factors

Vascular risk factors accounted for 7% of the variance in WMH volume (F=4.03, *P*=0.0003), 11% of the variance in CSF volume (F=5.64, *P*<.0001), and 12% of the variance in combined WMH and CSF volume (F=6.28, *P*<.0001) in N=317 participants. Full regression tables for vascular risk factors are in supplementary material, Tables III-V (please see http://stroke.ahajournals.org).

Associations between individual and combined brain MRI volumes at baseline and cognition at six months

Standard beta for the association between combined WMH and CSF volume and MMSE at six months (β=-0.442, standard error (SE)=0.07, *P*<.0001) was 32% greater than WMH alone (β=-0.302, SE=0.06, *P*<.0001) and 12% greater than CSF alone (β=-0.391, SE=0.07, *P*<.0001), when adjusting for vascular risk factors, age, and sex in N=317 participants. Full regression tables for MMSE are in supplementary material, Tables VI-VIII (please see http://stroke.ahajournals.org).

Prediction of two-year follow-up cognition via baseline brain MRI volumes

The association between two-year follow-up MMSE, adjusted by MMSE at six months, and combined WMH and CSF volume (β=-0.219, *P*<.0001) was 31% greater than WMH (β=-0.151, *P*=0.0005) and 11% greater than CSF (β=-0.194, *P*<.0001) alone.

Changes in individual and combined brain MRI volumes and sample size calculations

Changes in individual and combined brain MRI volumes in N=208 participants over two-year follow-up are in Table 1. Sample size calculations based on these changes and hypothesised reductions (treatments effects) of between 10 and 40 percent are in Table 2. Combined WMH and CSF volume had the greatest two-year change effect size (Cohen's *d*=0.35) and required between 207 and 3305 participants (20%) less per arm than WMH volume alone, depending on hypothesised treatment effect (Table 2).

Discussion

We have shown that vascular risk factors explain over one-third more of the variance in a combined WMH and CSF volume measure than WMH alone. Further, this combined measure better predicted post-stroke cognition than individual volumes. Furthermore, smaller sample sizes would be required to detect treatment effects in the combined measure compared to WMH and CSF alone. These results add to growing support for the use of combined brain damage metrics in stroke[1,2].

WMH are often referred to as "of presumed vascular origin" however, as with others[3,4], we found that multiple vascular risk factors explained a very small proportion of variance in WMH. Although atrophy is often implicated in neurodegenerative rather than neurovascular conditions[9], vascular risk factors explained approximately one-third more of the variance in CSF compared with WMH. Variance accounted for by vascular risk factors in the combined volume and CSF were very similar.

WMH volume had the weakest association with MMSE (compared with CSF volume and the combined WMH and CSF volume) and this is consistent with previous work finding that WMH are more closely associated with individual cognitive domains rather than global cognitive function[10]. We will assess associations between individual and combined (WMH and CSF volumes) and individual cognitive domains in the XILO-FIST trial[7].

WMH volume has previously been shown to reduce required sample sizes for clinical trials over cognitive scores[11]. Our estimates for sample sizes required in a WMH trial are consistent with recent results from the Mild Stroke Study in Edinburgh that based sample size calculations on a hypothetical treatment stabilising and preventing progression of WMH[6]. The combined WMH and CSF measure developed here further reduced sample sizes required to detect hypothetical treatment effects by the low hundreds to several thousands, depending on effect size. However, even with a moderate treatment effect of 20%, the combined measure still required over three thousand participants per arm. Adding more tissue volumes and/or diffusion metrics to the combined brain damage measure may further reduce required sample sizes and this will be assessed in future. Additionally, individual measures may be given different weights in a future combined metric rather than simply computing their sum.

Potential treatments for WMH and brain atrophy are currently being trialled[7,12] and the totality of our results (greater variance accounted for by vascular risk factors, stronger associations with cognition, reduced sample size requirements), provides support for the use

of a combined WMH and atrophy measure in early phase studies designed to limit post-stroke brain degradation and tackle vascular cognitive impairment.

Our work has limitations. As we used data from clinical trials there is the risk of confounding from relevant variables that were not assessed, and limited generalisability to patients not well enough or motivated to take part in a trial. We obtained a limited battery of vascular risk factors that did not include, for example, physical activity, diet and waist-hip ratio. However, we did acquire vascular risk factors that contribute to most of the population attributable risk of stroke[13]. One third of participants did not have a useable follow-up MRI and this limits the generalisability of our work to participants not well enough to return for a scan or lie still in the scanner at follow-up. However, these concerns are mediated by the limited differences between participants with and without useable follow-up MRI. WMH and CSF volumes required manual checking and editing, and this may limit application of our method to much larger samples. Several different scanners were used to acquire MRI however this replicates the reality of many clinical trials that are multisite. Further, inter-participant differences have long been shown to far outweigh inter-scanner differences and our results are similar to single scanner studies[3,14]. MMSE is a crude measure of global cognitive function and this may not be sensitive to vascular cognitive impairment which in turn may be more closely related to WMH. Additionally, we did not have assessments of cognition prior to stroke therefore could not adjust for premorbid cognitive ability. Finally, further work is required to understand WMH regression and brain volume reduction due to a decrease in interstitial fluid which may not have adverse clinical consequences.

Notwithstanding these limitations, we have provided a new combined neurovascular and neurodegenerative MRI measure in stroke that strengthened associations with clinical and cognitive parameters and reduced sample size requirements for prospective clinical trials. These results provide support for the use of a combined WMH and atrophy measure in early phase studies designed to assess the efficacy of treatments for brain degradation and cognitive impairment in stroke.

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Table 1. Mean changes in WMH, CSF, and combined volumes over two-year follow-up

Volume*	Baseline (Mean±SD)	Two-years (Mean±SD)	Mean difference (Mean±SD)	Cohen's *d*
WMH	0.0091±0.0095	0.0102±0.0101	0.0012±0.0037 (t=4.50, *P*<.0001)	0.32
CSF	0.2087±0.0367	0.2139±0.0333	0.0053±0.0181 (t=4.19, *P*<.0001)	0.29
Combined (WMH+CSF)	0.2177±0.0417	0.2241±0.0392	0.0064±0.0183 (t=5.04, *P*<.0001)	0.35

Note: *volumes are normalised (divided by intracranial volume); SD=standard deviation; WMH=white matter hyperintensities, CSF=cerebrospinal fluid.

Table 2. N per group required to detect reductions in WMH, CSF, and combined volume progression over two-year follow-up

Treatment effect*	40%	30%	20%	10%
Volume				
WMH	1011	1796	4040	16154
CSF	1166	2073	4661	18641
Combined (WMH+CSF)	804	1429	3213	12849

Note: *Treatment effects are hypothesised percent reductions in change from baseline to two-year follow-up between active treatment and control in each volume. WMH=white matter hyperintensities, CSF=cerebrospinal fluid.