Frailty and Cerebral Small Vessel Disease: a cross-sectional analysis of the Tasmanian Study of Cognition and Gait (TASCOG)

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Abstract

Background: Frailty is a prevalent geriatric condition associated with poor health outcomes. The pathogenesis of frailty is incompletely understood. We aimed to evaluate the relationship between cerebral small vessel disease (SVD) and frailty.

Methods: People aged between 60 and 85 were randomly selected from the electoral roll into the Tasmanian Study of Cognition and Gait. Participants completed standardised questionnaires regarding medical history and underwent objective sensorimotor, gait and cognitive testing. These data were used to calculate a frailty index score. Magnetic resonance imaging was performed on all participants to measure SVD. Automated quantification was used to measure white matter hyperintensities (WMH), with manual consensus for sub-cortical infarction (SI) and cerebral microbleeds (CMB). Multivariable linear regression was used to determine the association between SVD and frailty.

Results: The mean age of the sample (n=388) was 72.0 years (SD 7.0), 44% (172/388) were female and the median Frailty Index was 0.20 (inter-quartile range 0.12, 0.27). WMH, SI and CMB in unadjusted models were positively associated with higher frailty scores ($p<0.05$). In final models including all brain variables, higher burden of WMH (β 2.16, 95% CI 0.75, 3.57; p=0.003), but not SI (β 2.96, 95% CI -0.44, 6.35; p =0.09) or CMB (β -0.46 95%CI –4.88, 3.96; p=0.84), was independently associated with a higher frailty score.

Conclusions: We provide cross-sectional evidence for a positive association between larger burden of WMH and frailty. Longitudinal design is required to determine the temporality of this relationship.

Key words: Brain, MRI, cognition, gait, motor

Introduction

Frailty is a prevalent condition in older people, conceptualised as a reduction in reserve across multiple physiological systems resulting in a diminished capacity to respond to stressors (1, 2). Frailty has been shown to be an adverse marker for poor health outcomes in the elderly including falls, disability, and mortality (3-5). The prevalence in community-dwelling older population is approximately 10% and increases with age (6). Therefore, mitigation of frailty is an important part of geriatric care.

Cerebral Small Vessel Disease (SVD) is also a common finding in the older community-dwelling population. Included under the umbrella of SVD are white matter hyperintensities of presumed vascular origin (WMH) (7), cerebral microbleeds (CMB) (7) and subcortical infarcts (SI) (8). Typically, features shown on Magnetic Resonance Imaging (MRI) are used as a surrogate marker for SVD. WMH can be visualised as a signal abnormality, of variable size that is hyperintense on T2-weighted MRI (7, 9). WMH are found in varying degrees in nearly all persons aged 60 and older (10). SI are defined as hypointense lesions on T1-weighted MRI and fluid attenuated inversion recovery (FLAIR) between 3 and 20mm, often with a hyperintense rim (8). The estimated prevalence of SI shows considerable variability, with the majority of published literature concluding figures between 10-20% and showing a clear increase in prevalence in those over 70 years (11). CMB are seen as 2-10mm hypointense, homogenous lesions on T2-weighted gradient enhanced echo sequences that are round or oval in shape (7).

Past research has elucidated links between SVD and certain components of frailty and its adverse outcomes (e.g. gait speed, falls and disability) (12-15). However, the relationship between SVD and frailty is not well understood, with conflicting data

arising from the few studies that have examined the relationship. Infarcts appear to be associated with frailty (16, 17), but this may only be for 'macroinfarcts', not 'microinfarcts' using autopsy methodology (18). For WMH, some studies show a positive relationship (16, 19), while others found no relationship (17, 20), and only one study to our knowledge has found a positive relationship between CMB and frailty (17). Potential reasons for these conflicting findings may be the time of assessment (e.g. at death on autopsy) or the semi-quantitative measurement of WMH. No studies have examined multiple markers of SVD, their interactions or used the cumulative deficit frailty model, which provides a continuous rather than a categorical measure of frailty. A better understanding of the biological underpinnings of frailty may assist in preventing functional decline and adverse health outcomes in older people. This research aims to examine the association and interactions of WMH, SI and CMB and frailty in a population-based study of older people.

Methods:

Sample

The Tasmanian Study of Cognition and Gait (TASCOG) is a population-based study conducted in Hobart, Tasmania, Australia. Sample recruitment methodology has been described previously (12). Briefly, people 60 to 85 years, inclusive, were randomly selected from the Southern Tasmanian electoral roll. Exclusion criteria were inability to walk unaided, any contraindication to MRI, a diagnosis of dementia or residing in an aged care facility. Measurements were conducted between January 2005 and December 2008. Written consent was obtained from all study participants. The Southern Tasmanian Health and Medical human research ethics committee approved this study.

MRI brain measures

MRI was obtained using a 1.5-Tesla machine (LX Horizon, General Electric, Milwaukee, WI) with the following sequences: high-resolution T1-weighted spoiled gradient echo (repetition time (TR) 35 ms, echo time (TE) 7 ms, flip angle 35°, field of view 24 mm; voxel size 1 mm^3) comprising 120 contiguous slices, T2-weighted fast spin echo (TR 4,300 ms, TE 120 ms, one excitation, turbo factor 48; voxel size 0.90 x 0.90 x 3 mm); fluid-attenuated inversion recovery (FLAIR) (TR 8,802 ms, TE 130 ms, time interval 2,200 ms; voxel size 0.50 x 0.50 x 3 mm), gradient echo (GRE) (TR 800 ms, TE 15 ms, flip angle 30°; voxel size 0.93 x 0.93 x 7 mm). WMH were identified using fully automated morphological segmentation with adaptive boosting classification applied to FLAIR and T1- and T2-weighted scans. SI were determined by two experts in the field using a definition of 3–20 mm with a surrounding hyperintense rim, with care taken not to misclassify perivascular spaces as infarcts (21). CMB were also identified by consensus as small, rounded hypointense lesions with clear margins and size ranging from 2 to 10 mm on gradient echo images.

Frailty index measures

Comorbidities: Self-reported medical history (hypertension, angina, myocardial infarction, hyperlipidemia, diabetes, stroke, migraine, arthritis and falls history) was obtained using a standardised questionnaire.

Cognitive function: Five domains of cognitive function were assessed by a trained neuropsychologist utilising the following standardised tests: *Executive function* - using the Controlled Word Association test (COWAT; letters F, A and S) (22), and the Victoria Stroop test (two subtests: 1) congruent colored words, 2) incongruent color names) (23); *Processing speed and attention* – the Symbol Search, Digit Span

and Digit Symbol Coding subtests of the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) (24); *Visuospatial Ability* – The Rey Complex Figure copy task (22); *Memory* – using the Hopkins Verbal Learning Test – Revised (22) (total immediate recall, delayed recall and recognition memory) and a delayed reproduction after 20 minutes of the Rey Complex Figure (22); *Language* was assessed with Category Fluency Test (animals).

Physical and sensorimotor function: The short version of the Physiological Profile Assessment (PPA) (25) was used to measure sensorimotor function (postural sway standing on a foam mat with the eyes open; knee extension strength; simple hand reaction time; lower limb proprioception using a matching test; visual contrast with the Melbourne edge test); grip strength was measured with a bulb dynamometer; walking speed as the mean of 6 walks on a 4.6m GaitRite computerized walkway; steps per day using the mean of 7 days recorded with a Yamax Digi-Walker SW-200 pedometer.

Other measures: Quality of life with the 15 item Assessment of Quality of Life (AQol) questionnaire (26); Mood using the 15-point Geriatric Depression Scale (GDS); Disability with the Lawton Instrumental Activities of Daily Living questionnaire (27); and Body Mass Index (BMI) was calculated using measures of weight and height.

Frailty Index:

We used the cumulative deficit model of frailty which allows frailty to be progressively graded rather than present or not (28), whereby higher scores indicate more frail subjects. Binary variables were coded with 1 point when deemed present or impaired, and 0 when absent or intact. Continuous variables were dichotomised, with a full list of numerical cut points provided in Supplementary Table 1. Cognitive

function was classified as impaired in each domain if a test in that domain was ≥1.5 standard deviations (SD) below the age-, sex- and education level-appropriate norms as described previously (29). For steps per day, grip strength and the PPA variables the lowest quintile of the sample (sex specific for grip and knee strength) as per previous definitions (30, 31) was used as the cut point. For visual contrast sensitivity 19dB units was chosen as the nearest cut point to the lowest quintile. The following cut points were used for other variables as previously reported in the literature: gait speed of 80cm/s (32); BMI of <18.5kg/m^2 or >35 kg/m^2 (33); for each AQoL question - answers were assigned 0, 0.5, 1 or 1 (31); GDS-15 scores of ≥6 (34) and ADL scores <21 were deemed as having significant disability. The Frailty Index score (FI) was calculated for each individual by summing the number of deficit points and then dividing by the total number of variables (maximum of 41) for each individual, giving a theoretical range of 0-1.0.

To compare results with the FI, we constructed a physical frailty score similar to that of the Fried criteria using the lowest quintile for low grip strength, steps per day, gait speed and BMI and a negative response to item 13 of the GDS – "Do you feel full of energy". These variables were then summed for a total score out of 5, categorising those with none of the criteria as robust, 1-2 criteria as pre-frail, and 3-5 criteria as frail (16, 19).

Statistical analysis:

For ease of interpretation the FI was multiplied by 100 before analyses, thus giving a range of 0-100. A two-sided T-test was used to compare participant characteristics between those with and without each SVD measure. Spearman correlations were used to examine correlations between each brain measure. In regression analysis WMH was log transformed. Univariable linear regression was used to assess the

association between SI, WMH and CMB (independent variables) with the FI (dependent variable). Multivariable linear regression was then conducted for each marker of SVD in separate models adjusting for age, sex, years of formal education, and total intracranial volume (TIV; only in the case of WMH). In secondary analysis, WMH were divided into fifths to explore threshold effects (12). In the final model all brain structural variables (SVD markers, gray and white volumes) were included to determine which SVD markers were independently associated with the FI. Two-way interactions were assessed between SVD markers using the following product terms: SI×WMH, WMH×CMB and SI×CMB. Shapley value regression was performed to assess the relative contribution of each brain measure to frailty. Finally, two sensitivity analyses were performed. To determine the contribution of motor and cognitive measures to the model we constructed a cognitive index (the five cognitive variables) and a motor index (low grip, low knee strength and slow gait), using the same variables as the original FI. We then performed multivariate regression with these indices as the outcomes adjusting for age, sex, education, TIV and an index made of the remaining frailty measures. Secondly, we examined the associations of brain variables with the Fried criteria score using multinomial regression. Analyses were performed using STATA version 12.1 (Stata Corp., College Station, TX).

Results:

Initial response rate for the TASCOG study was n=431/804 (53.6%). Three participants were excluded as they had a diagnosis of dementia. Thirty-nine participants did not have an MRI scan. Two further participants were excluded because of poor quality scans, leaving 388 participants for analysis. Comparison of those without, to those with scans showed no significant differences in age (p=0.55), sex (p=0.82) or years of formal education (p=0.61), but those without MRI data had a

higher FI (median=0.25, IQR: 0.17, 0.42; p=0.002). Of the participants included in the study, 84% (n=327) had complete variables for the FI, 12% (n=47) had one missing variable, 3% (n=11) had <5 missing, and one individual had 15 missing variables. Exclusion of this participant in the analyses did not alter results, and as such this participant was maintained in analyses.

Table 1 presents the sample characteristics. The mean age of the sample was 72.0 (7.0 SD) years and 44% (172/388) were female. The median WMH volume was 5.7ml (IQR 3.55-10.65), 18.3% (n=71) had SI and 7.7% (n=30) had CMB. Those with SVD tended to be older ($p<0.05$), and have a higher FI ($p<0.01$). Participants with low WMH volume had more years of education (p=0.03).

Associations between SVD and the FI

Supplementary Table 2 shows the correlations between brain variables. The strongest correlations between markers of SVD were between SI and CMB (r=0.59), WMH and SI (r=0.31). A Box-cox power transformation (0.56) in Stata was used prior to regression analyses to remove skewness of the FI (see Supplementary Figure 1). Transformation was then reversed to present beta-coefficients and 95% CI in original units. Table 2 shows the results of the linear regression analyses of each SVD measure with the FI in separate models, and a model including all brain measures. All SVD measures were significantly associated with a higher FI in unadjusted analyses ($p<0.05$). After adjusting for age, sex and years of education (and TIV for WMH), CMB were no longer associated with frailty (β 3.26 95% CI -0.80, 7.33; p=0.12). The presence of SI (β 4.49 95% CI 1.67, 7.31; p=0.002) and WMH (β 3.32 95%CI 1.92, 4.72; $p<0.001$) remained associated with a higher FI. A WMH squared term was not significant (p=0.33). In the final model including all brain variables, WMH volume remained independently associated with the FI (β 2.16 95% CI 0.75, 3.57; p=0.003),

while SI (β 2.96 95%CI -0.44, 6.35; p=0.09) and CMB (β -0.46 95% CI-4.88, 3.96; p=0.84) were no longer significant. If CMB were removed from model, the association between SI and the FI was not statistically significant (β 2.76 95%CI -0.02, 5.53; p=0.05). There were no interactions between the product terms WMH×SI (p=0.98), WMH×CMB (p=0.99) and SI×CMB (p=0.53). The final model explained 26.6% (partial R squared) of the variance in the FI. Of this variance WMH contributed22.5%, SI 7.9%, CMB 1.6%, to the R squared value, with gray and white matter contributing a further 18.2% and 10.7%. respectively. Supplementary Table 3 shows the results of adjusted secondary analyses where WMH were divided into fifths, finding a quadratic trend across categories (p=0.02) and a threshold identified for WMH volume ≥ 6.87mL. When other brain variables were added to the model this weakened (p=0.17), but a linear term was significant (p=0.005).

Association between SVD and motor and cognitive indices

In fully adjusted models, none of the SVD variables were associated with the cognitive index: WMH (β 0.94 95%CI -1.19, 3.07); SI (β 0.95 95%CI -4.17, 6.08); CMB (β -2.54, 95%CI -9.61, 4.53). CMB (β 12.08, 95%CI 0.44, 23.71), but not WMH (β -1.46 95%CI -4.97, 2.05) or SI (β -6.15 95%CI -14.58, 2.28), were associated with the motor index.

Associations between SVD and the Fried criteria

Using the Fried criteria 31.7% (n=123) of participants were classified as healthy, 59.3% (n=230) as pre-frail and 9.02% (n=35) as frail. Supplementary Table 4 shows the estimated relative risk ratio for each SVD marker with the pre-frail and frail groups relative to the robust group. There were no significant associations (p>0.05) between any of the markers of SVD and frailty categories.

Discussion

In a population-based study of older people we found that WMH was independently associated with greater frailty, measured using a continuous frailty index. No prior studies to our knowledge have examined the independence or interactions of multiple SVD markers using the cumulative deficit measure of frailty.

This study has several strengths. The random selection of participants from the general population allows for greater generalisation than those from studies of volunteers. Sensitive and quantitative methods were used for measuring SVD increasing internal validity. The use of automated segmentation for analysing WMH also reduced the potential for inter-rater error. In addition, we carefully adjusted for confounders and examined the interactions between SVD measures. In sensitivity analysis, we created a motor and cognitive index to explore whether these measures were responsible for driving our findings. We found that only CMB was associated with a motor index, suggesting that accumulation of cognitive and motor impairments alone did not underlie our findings. Secondly, we presented associations between SVD and the Fried criteria in order to contrast results with the FI.

To our knowledge this study was the first to use a cumulative deficit model of frailty rather than a variant of the phenotypical definition to examine any potential relationship to SVD. The derived FI was continuous and potentially allowed for more sensitive analysis when compared to the categorical nature of the phenotypic definition. Supporting this, we did not find any associations between brain variables and categories of the Fried criteria, although this may have also reflected the variables selected. Inclusion of variables in the FI, totalling 41, followed protocols previously proposed: biologically sensible; showing accumulation with age: not saturating too early; and being associated with adverse outcomes (31). It has previously been shown

that 30-40 variables maintains accuracy of the index (2, 3). The use of this definition is a strength, but may also be a limitation as it is possible that some variables included in the index (such as hypertension) may contribute to development of SVD. Nevertheless, the definition emphasises the accumulation of deficits rather than the effect of any one individual deficit. Other related limitations of this study are its cross-sectional nature that does not allow for directionality to be concluded; with the potential that SVD may be a marker or a result of an accumulation of deficits. It is possible that WMH were due to other factors such as multiple sclerosis (although none were diagnosed) or leukodystrophies rather than SVD (7). In addition, we were unable to consider other brain pathologies, such as atherosclerosis, arteriolosclerosis, amyloid burden or Lewy Body Disease, that have been examined in prior autopsy studies (18, 35). Participants without scans had greater frailty and this may have caused an underestimation of the association between variables. The exclusion of potentially more frail participants (i.e. nursing home residents), may have contributed to attenuated strength of associations. Finally, although the frailty index represents the overall cumulative burden of aging and disease, it does not by itself allow identification of different organ systems that may be useful in identifying new targets for interventions.

Those with a higher burden of WMH were independently associated with a continuous measure of frailty in our study. Prior studies yield conflicting evidence, with some showing no association (both from the I-Lan Longitudinal Aging Study) (17, 20) and others a positive association (both from the Cardiovascular Health Study) (16, 19). Those showing no association (17, 20) may have been due to a younger sample, and thus less WMH (10), or the potentially less sensitive categorical classification of frailty (17, 20). Interestingly, WMH greater than a moderate burden

(≥6.87mL) (corresponding to a score of approximately 2 on the Fazekas visual score (36)), appeared to show the strongest association with frailty. This is consistent with prior work that has found a threshold effect of WMH with falls (12). However, our sensitivity analysis (motor and cognitive indices) was not consistent with prior findings that WMH are associated with components of frailty such as poorer gait speed and disability (12-15). This may be due to the low numbers of participants with deficits in our indices.

Subcortical infarcts alone were associated with frailty, but when CMB and WMH were added to the model they were no longer significant. This may have been due to the high correlation between the two variables (r=0.59). However, when CMB were removed from the model, and WMH maintained, they remained non-significant. Potentially due to a lack of power. Prior evidence is less clear. Associations have been found cross-sectionally between all infarcts > 3mm on MRI and frailty (16). In contrast, infarcts visible to the naked eye on autopsy were not associated with frailty measured proximate to death (37). Further study on autopsy in a larger sample found infarcts visible to the naked eye, but not microscopic infarcts, were associated with the rate of change in frailty before death (18). Differences between studies may be due to the varying definitions of infarcts (all infarcts, subcortical or microscopic), methods of assessment (autopsy versus MRI) or time of assessment at death. Interestingly a recent MRI study (17) did find associations with infarcts using a slightly smaller definition to ours (less than 15 mm in diameter). Taken together, results of MRI studies suggest a positive association between infarcts and frailty, however evidence from autopsy suggests that only macro-infarcts at time of death are associated with frailty (18). CMB, in fully adjusted models, were not associated with frailty in our study. This is in keeping with a recent analysis that also found no

association between CMB and frailty using the Fried criteria when adjusted for other markers of SVD (17).

It is uncertain whether it is possible to slow or prevent the development of SVD, which may result in less frailty. In post-hoc analysis of the PROGRESS trial, blood pressure lowering reduced incident WMH volume in stroke survivors, and in post-hoc analysis of the ROCAS trial (participants with middle cerebral artery stenosis), statins delayed the progression of cerebral WMH among those who already had severe WMH at baseline (38, 39). In the SPS3 study lowering systolic blood pressure to a target of less than 130 mmHg versus 130-149 mmHg resulted in no reduction (0.81 95%CI 0.64-1.03) in all incident strokes or recurrent subcortical strokes (0.87 95%CI 0.62-1.22 in people with recent symptomatic small subcortical strokes (40). Future trials in this field may wish to consider the outcome of frailty in their design.

In conclusion, this work provides evidence of a cross-sectional relationship between WMH and higher levels of frailty in older people. Further research with a longitudinal design would strengthen the evidence for a relationship between SVD and frailty, and assist in ascertaining the direction of these associations.

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Table 1 Sample Characteristics by Brain Variable

	Total sample (n=388)	No SI (n=317)	SI (n=71)	p	Low WMH (n=194)	High WMH (n=194)	p	No CMB (n=358)	CMB (n=30)	p
Age, y	72.0 (7.0)	71.4 (7.0)	74.9 (6.6)	<0.01	70.0 (6.2)	74.1 (7.2)	<0.01	71.8 (7.0)	74.8 (7.4)	0.02
Female, n (%)	172 (44.0)	145 (45.7)	27 (38.0)	0.24	88 (45.3)	84 (43.3)	0.68	162 (45.3)	10 (33.3)	0.21
Education, y	10.9 (3.6)	11.0 (3.7)	10.4 (3.3)	0.24	11.3 (3.7)	10.5 (3.5)	0.03	10.9 (3.6)	10.5 (3.7)	0.52
Frailty, (IQR)	19.51 (12.20, 26,83)	17.07 (12.20,25.00)	24.39 (18.29,32.93)	<0.01	17.06 (10.98,21.95)	22.50 (15.00, 30.9)	<0.01	18.29 (12.20,25.61)	25.61 (17.07,30.49)	<0.01

SI indicates sub-cortical infarct; WMH, Median White Matter Hyperintensity volume (≥ 5.71 mL); CMB, Cerebral Microbleed; IQR, inter-quartile range

Table 2. Univariable and multivariable regression of brain variables with the frailty index score

	Unadjusted (separate models)		Adjusted for age, sex, years of education (separate models)*		Adjusted model with all brain variables in the same model	
	β	95% CI	β	95%CI	β	95%CI
Sub-Cortical Infarct	6.77	3.60, 9.88	4.49	1.67, 7.31	2.96	-0.44, 6.35
Cerebral Microbleeds	5.26	0.66, 9.86	3.26	-0.80, 7.33	-0.46	-4.88, 3.96
WMH*, *mL*	4.97	3.58, 6.36	3.32	1.92, 4.72	2.16	0.75, 3.57
Gray matter volume, *mL*					-0.07	-0.11, -0.03
White matter volume, *mL*					-0.06	-0.09, -0.02

CI, confidence interval; WMH, White Matter Hyperintensities of presumed vascular origin
*Additionally, adjusted for Total Intracranial Volume (mL)