Brain atrophy and white matter changes grading agreement on NCCT and MRI in ischemic stroke

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Abstract

Purpose

Evaluation of brain frailty measures like atrophy and white matter changes (WMC) are becoming increasingly relevant in stroke outcome prediction but are conventionally thought to be best seen on MRI compared to CT. We assessed agreement between baseline CT vs follow-up MRI ratings for brain atrophy and WMC; and compared their predictive validity of 90-day functional outcomes in acute ischemic stroke.

Methods

In this post-hoc, observational analysis of baseline CT and follow-up MRI data from the Alteplase compared to Tenecteplase (AcT) randomised-controlled trial, experts assessed brain atrophy as well as periventricular and deep WMC using established scales. Binary agreement (none-mild vs. moderate-severe) and agreement across the full range of scores between atrophy and WMC measures on CT and MRI were calculated using Gwet's agreement coefficient (AC1). Logistic regression and DeLong's test were used to compare prediction of 90-day modified Rankin Scale (mRS) 0–1.

Results

Among 1,577 AcT participants, 491(31.1%) had interpretable CT and MRI. Binary agreement was substantial for periventricular (AC1 = 0.70) and total WMC (AC1 = 0.68) scores, Koedam scale (AC1 = 0.76) and frontal atrophy (AC1 = 0.80). Almost perfect agreement (AC1:0.81–0.97) was found for all other measures. There was no significant difference between NCCT or MRI in predicting 90-day mRS 0–1 for any measures.

Conclusions

CT ratings of brain atrophy and WMC by experts have substantial to almost-perfect agreement compared to MRI. Both generally achieve similar prediction of 90-day functional outcomes. This implies that it is reasonable to use CT scans to evaluate these brain frailty measures in clinical practice and stroke trials.

INTRODUCTION

Brain frailty is a common feature of participants presenting with acute ischemic stroke, representing both a risk factor for the stroke itself, as well as worsened outcomes.(1–4) Two important markers of brain frailty, the white matter changes (WMC) burden and cortical atrophy severity, are identifiable on both magnetic resonance imaging (MRI) and non-contrast computed tomography (NCCT) modalities, and are of increasing interest in the stroke community due to their relevance towards brain reserve and

functional outcomes.(1–7) Brain imaging plays a crucial role in the evaluation of acute stroke participants to identify the extent of brain damage and guide treatment decisions.(8) In the acute stroke setting, NCCT remains the imaging modality of choice, as an inexpensive, readily available option for stroke physicians.(9) Although MRI (FLAIR) seems more sensitive to white matter changes compared to NCCT, there already exists an abundance of literature that show good correlations between NCCT and MRI for both WMC and atrophy. Most of those studies however included patients with neurodegenerative disease (cognitive decline, memory disorders, neuropsychiatry etc.)(10, 11) or stroke patients with rater small sample sizes, or not considering the possible sequelae of the ischemic stroke such as edema.(12)

Whereas WMC is regularly encountered in the asymptomatic elderly population(13), the presence of WMC can be also indicative of chronic ischemia - due to an interplay of several pathophysiological vascular factors that can be location dependent – and can also cause symptoms or influence stroke outcome (14–16) As with WMC, brain atrophy also has several implications with stroke outcomes. As a surrogate marker of brain reserve, brain atrophy is associated with cognitive decline, worsened brain reserve, and poorer outcomes post stroke.(17–20)

In this study, we aimed to explore the agreement between CT and MRI for identifying markers of WMC and cortical atrophy–using well-established visual rating scales–in a set of participants from a large, pragmatic, randomized controlled trial of acute stroke participants who received intravenous thrombolysis with either tenecteplase or alteplase. We then explored the agreement between the predictive value of excellent functional outcome (defined as mRS 0–1 at 90 days) for the individual markers between NCCT and MRI.

MATERIALS AND METHODS

Study Population

This observational study is a post-hoc analysis of the Alteplase Compared to Tenecteplase (AcT) Trial: a pragmatic, multicentre, open-label, registry-linked, randomized, controlled, non-inferiority trial that compared alteplase vs tenecteplase in participants with acute ischemic stroke presenting within 4.5h of symptom onset (clinicaltrials.gov: NCT03889249).(21) Additional trial details, as well as inclusion and exclusion criteria have been previously published.(22) Importantly, owing to the pragmatic nature of the trial, participants were not excluded if they were elderly or if they had pre-existing disability or dementia. AcT enrolled participants from December 2019 to January 2022. This study was approved by each site's ethics committee and was performed in accordance with the Health Canada regulations and the Declaration of Helsinki. Deferred consent procedures were used wherever approved by local research ethics boards. Participants had the ability to withdraw their study data at any time.

Image Acquisition

Patients with both baseline CT and post-treatment MR imaging within 24–72 hours of randomization were included in this study. Due to the pragmatic nature of AcT, all imaging was done as part of standard of care and imaging up to 72h from randomisation was collected for analysis. Scans were processed using the appropriate algorithms to reduce bone artifacts and a high signal-noise ratio (SNR) for gray-white differentiation. Axial scans parallel to the inferior orbitomeatal line were obtained with both CT and MRI from the skull base to vertex. As part of routine stroke imaging protocol, MRI imaging for most participants included FLAIR with susceptibility weighted imaging (SWI) or gradient echo (GRE) sequences. Atrophy and white matter disease measures were read on axial FLAIR sequence. If the 3D FLAIR source was available, images were reformed to generate axial, coronal and sagittal images on Osirix MD software.

Image Analysis

Independent core laboratory readers (Fa. Be., I.A., F.B., and N.S.) with 4–7 years of experience reviewed baseline CT and MRI data, with disagreements being resolved by a third senior reviewer with > 10 years of experience (A.G.). Readers were previously trained and shown to have excellent inter-reader agreement, as well as intra reader inter-modality agreement.(23) The readers were randomly assessed MRI or CT images, and were blinded to treatment allocation, clinical outcomes, and follow-up imaging.

Visual rating scales are described in Table 1. Cortical atrophy was assessed using Global Cortical Atrophy (GCA) scales(24), the Koedam scale for the parietal lobe(25), and the Medial Temporal Atrophy (MTA) scale for the hippocampus(26). Regional atrophy of the frontal, temporal, occipital, and parietal lobes was assessed by applying the GCA scale to the individual lobes for increased sensitivity.(23) If the atrophy was asymmetric or there was swelling on one hemisphere of the brain, the most severely atrophic side was graded. WMC were assessed using the Fazekas scale (Table 1) separately for periventricular white matter, deep white matter and a total score which was the sum of the scores for periventricular and deep.(16)

Table 1
Visual brain atrophy and white matter changes rating scales used by readers.

Brain Atrophy		**White Matter Changes**	
GCA, Koedam Scale	MTA	Periventricular	Deep
0 – No atrophy: normal volume 1 – Mild atrophy: opening of sulci 2 – Moderate atrophy: volume loss of gyri 3 – Severe (end-stage) atrophy: "knife blade" atrophy	0 – No atrophy 1 – Only widening of the choroid fissure 2 – Also widening of the temporal horn of the lateral fissure 3 – Moderate loss of hippocampal volume 4 – Severe loss of hippocampal volume	0 – Absent 1 – "Caps" or pencil thin lining 2 – Smooth "halo" 3 – Irregular periventricular signal extending into deep white matter	0 – Absent 1 – Punctate foci 2 – Beginning confluence 3 – Large confluent areas
		Total	
		= Periventricular score + Deep score	
GCA – Global Cortical Atrophy, MTA – Medial Temporal Atrophy			

Statistical Analyses

The baseline variables of participants with both CT and MR imaging, and the rest of the trial population (with only CT or only MRI) were summarized and compared. Numeric data was shown using mean (SD) or median (IQR) for numeric data and compared with the Student's T-test and Mann Whitney U test respectively; and n values and percentages (%) were shown for the categorical and dichotomous variables and compared using the Chi squared test, or if cells contained less than 10 values, using the Fisher's exact test.

To assess the inter-modality agreement between the CT and MRI scans, we first examined the distribution of data. Much of the data for both measures of cortical atrophy and WMC was rated at "0" for no atrophy or WMC, or "1" for mild atrophy or WMC. In order to avoid the kappa paradox, a result of conventionally used interrater reliability methods such as Cohen's kappa(27), we employed a linear-weighted Gwet's agreement coefficient 1 (AC1) as previously done by our group.(23, 28) In order to interpret the AC1 results, Landis and Koch's levels of agreement – 0.21–0.40 as fair agreement, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect – were employed.(29) Agreement analyses using this approach was first performed for each category of cortical atrophy and WMC, followed by a binary analysis using no-mild vs moderate-severe cortical atrophy for each lobe and no-mild vs moderate-severe WMC. This approach was chosen based on previous studies that have suggested prognostic value for stroke outcomes in individuals that have a more severe burden of these markers.(30–33)

To further compare the similarity of the white matter and atrophy measures between CT and MRI, Logistic regression analysis – adjusted for age, sex and baseline NIHSS – was used to calculate receiver operating characteristics (ROC) to predict 90-day excellent outcome (mRS 0–1) for CT and MRI imaging markers. Area under the curve (AUC) was calculated for each variable.(34) Delong's test was then used to compare AUCs.(34) A p-value less than 0.05 was considered significant, and analyses were performed using STATA/MP 16.1 (StataCorp).

RESULTS

Among 1,577 participants in the AcT trial; 1,568 had an interpretable baseline CT (99.4%) and 767 (48.6%) had a post-treatment MRI scan completed (Fig. 1). Of these, 495 (64.5%) had adequate MRI sequences for evaluating atrophy and white matter disease. 272 cases were excluded due to a lack of appropriate scan (ie. no FLAIR), severe edema, or motion artifact. 491 (31.1% of total) participants had both an interpretable CT and MRI (Fig. 1).

Participants with both MRI and CT imaging were significantly younger (median age 70, IQR:58–81) and experienced more severe strokes with a median NIHSS of 11 (IQR:6–17) when compared to participants with only MRI or only CT imaging (75 years (IQR:65–84), NIHSS 8 (IQR:5–13)). They were also more likely to have coronary artery disease (3.1% vs 1.3%, $p = 0.021$) or dyslipidemia (8.2% vs 3.9%, $p = 0.001$), but less often had large vessel occlusions (29.0% vs 35.4%, $p < 0.0001$) (Table 2).

Table 2
Baseline characteristics of the total participant population (n = 1,577) enrolled in the Intravenous Tenecteplase Compared with Alteplase for Acute Ischaemic Stroke in Canada (AcT) trial, compared to the subset of these participants that had both MRI and CT imaging (n = 491)

AcT Population	Participants with only MRI or only CT imaging (n = 1,081)	Participants with MRI and CT imaging (n = 491)	P-value
Age, years, median (IQR)	75 (65–84)	70 (58–81)	<0.0001*
Women (n (%))	521 (48.2)	232 (47.3)	0.73
Proportion in Tenecteplase group (n (%))	539 (49.9)	221 (46.4)	0.21
Onset to needle time, median (IQR)	128 (94–183)	133 (92.5–191)	0.38
Large Vessel Occlusion Presence (n (%))	377 (35.4)	142 (29.0)	0.013*
Endovascular thrombectomy utilisation (n (%))	360 (33.3)	145 (29.5)	0.14
NIHSS at baseline, median (IQR)	8 (5–13)	11 (6–17)	< 0.0001*
Risk Factors, N (%)			
Previous stroke	11/1,004 (1.1)	1/449 (0.2)	0.12
Coronary artery disease	13/1,004 (1.3)	14/449 (3.1)	0.021*
Hypertension	495/1,004 (49.3)	223/449 (49.7)	0.91
Diabetes	188/1,004 (18.7)	88/449 (19.6)	0.70
Atrial fibrillation	130/1,004 (13.0)	61/449 (13.6)	0.74
Dyslipidemia	39/1,004 (3.9)	37/449 (8.2)	0.001*
Smoking current/past	8/1,004 (0.8)	9/449 (2.0)	0.06
NIHSS – National Institutes of Health Stroke Scale			

For periventricular WMC, 329/491 (67.0%), participants had a score ≥ 1 on MRI versus 238/491 (48.5%) for CT (Table 3). For deep WMC, 345/491(70.3%) participants had a score ≥ 1 on MRI, compared to 147/491 (29.9%) on CT. For total WMC on MRI, 373/491 (76.0%) participants had a score ≥ 1, versus 253/491 (51.5%) on CT. Agreement was substantial for periventricular (AC1 = 0.68), deep (AC1 = 0.61), and overall Fazekas scores (AC1 = 0.64) for WMC when using the full range of scores. Agreement was slightly better for each of the WMC scores when using the binary AC1 compared to AC1 for the full range

of scores, with a coefficient of 0.70 ($p < 0.001$), 0.85 ($p < 0.001$) and 0.68 ($p < 0.001$) for periventricular, deep, and total respectively with binary AC1.

Table 3
Agreement between CT and MRI ratings for markers of WMC and cortical atrophy. A1C values of 0.2–0.4 = fair; 0.4–0.6 moderate; 0.6–0.8 substantial; 0.8-1 = almost perfect.(30)

Variable	Scan	Median (IQR)	% Agreement (95% CI)	Full AC1	Binary AC1
Periventricular WMC	MRI	1 (0–2)	0.85 (0.79–0.82)	0.68†	0.70†
	CT	0 (0–1)			
Deep WMC	MRI	1 (0–1)	0.81 (0.79–0.83)	0.63†	0.85‡
	CT	0 (0–1)			
Total WMC	MRI	2 (1–3)	0.84 (0.82–0.86)	0.64†	0.68†
	CT	1 (0–2)			
Temporal GCA	MRI	0 (0–1)	0.88 (0.86–0.90)	0.80‡	0.85‡
	CT	0 (0–1)			
Frontal GCA	MRI	1 (0–1)	0.85 (0.83–0.87)	0.71†	0.80‡
	CT	1 (0–1)			
Koedam Scale	MRI	1 (0–1)	0.83 (0.81–0.85)	0.68†	0.76†
	CT	1 (0–1)			
Occipital GCA	MRI	0 (0)	0.94 (0.92–0.96)	0.93‡	0.97‡
	CT	0 (0)			
MTA Scale	MRI	0 (0–1)	0.90 (0.89–0.92)	0.84‡	0.85‡
	CT	0 (0–1)			
Overall GCA	MRI	1 (0–1)	0.85 (0.83–0.87)	0.73†	0.81‡
	CT	1 (0–1)			

AC1 – Gwet's agreement coefficient 1, CT – computed tomography, GCA – global cortical atrophy, MRI – magnetic resonance imaging, MTA – medial temporal atrophy, WMC – white matter changes. † = substantial agreement. ‡ = almost perfect agreement.

For the cortical atrophy burden of participants with both CT and MRI scans, the frequency of any atrophy (score ≥ 1) depended on the lobes examined (Table 2). There was at least mild atrophy identified on the frontal lobes on MRI in 256/491 (52.1%) participants versus 297/491 (60.5%) on CT. For the temporal lobes, 204/491 (41.5%) participants had atrophy identified on MRI versus 145/491 (29.5%) on CT.

Parietal lobe atrophy per the Koedam scale saw 268/491 (54.6) with atrophy identified on MRI versus 262/491 (53.4%) on CT. Occipital lobe atrophy was rarest, with 67/491 (13.6%) participants identified as having atrophy on MRI versus 26/491 (5.3%) on CT. MTA rates were 170/491 (34.6%) on MRI compared to 154/491 (31.4%) on CT. As for overall GCA ratings, 264/491 (53.8%) participants had any atrophy identified on MRI versus 279/491 (56.8%) on CT. Binary AC1 showed almost perfect agreement for all atrophy measures but the Koedam scale, where the AC1 coefficient was substantial at a value of 0.76 ($p < 0.001$) (Table 2).

When adjusted for sex, age and baseline NIHSS, the predictive value of the individual ratings of WMC and atrophy with respect to 90-day mRS 0–1 were not significantly different between CT and MRI (Table 4).

Table 4
Comparison of MRI versus CT ratings of brain atrophy and white matter changes for the prediction of 90-day functional outcome (modified Rankin Scale 0–1) CT. Areas under the curve (AUCs) and 95% CI were estimated using 100 bootstrap replications. DeLong's test was used to compare AUCs between modalities. Models were adjusted for age, sex, and baseline NIHSS.

90d Functional Outcome Prediction (mRS 0–1), CT vs MRI ratings			
Variable	**MRI AUC (95%CI)**	**CT AUC (95%CI)**	**Delong's Test p-value**
Periventricular WMC	0.62 (0.57–0.67)	0.58 (0.53–0.63)	0.07
Deep WMC	0.60 (0.54–0.65)	0.57 (0.52–0.62)	0.45
Total WMC	0.65 (0.58–0.68)	0.60 (0.55–0.65)	0.18
Temporal GCA	0.54 (0.50–0.59)	0.54 (0.48–0.59)	0.76
Frontal GCA	0.57 (0.52–0.62)	0.58 (0.53–0.63)	0.82
Koedam Scale	0.56 (0.51–0.61)	0.53 (0.48–0.58)	0.39
Occipital GCA	0.51 (0.46–0.57)	0.51 (0.45–0.56)	0.82
MTA Scale	0.58 (0.53–0.63)	0.54 (0.49–0.59)	0.22
GCA	0.56 (0.51–0.61)	0.57 (0.52–0.62)	0.65

AUC – area under the curve, CT – computed tomography, GCA – global cortical atrophy, MRI – magnetic resonance imaging, MTA – medial temporal atrophy, WMC – white matter changes.

DISCUSSION

In this post-hoc analysis of 491 participants from the AcT trial, baseline CT and 24hr MRI scans showed substantial to almost-perfect agreement for markers of brain atrophy and WMC, when assessed by trained experts using pragmatic, visual rating scales. When comparing none to mild groups, to moderate and severe groups in a binary fashion, there was excellent agreement across the measures of deep WMC, temporal, frontal, occipital and global cortical atrophy, as well as for the MTA. Although CT

generally tended to underestimate cortical atrophy and WMC burden compared to MRI, both CT- and MRI-derived measures had similar predictive validity with respect to 90-day functional outcomes.

The non-binary, standard assessment, cortical atrophy findings from this study were similar to those found in a post-hoc analysis of the Safety and Efficacy of Nerinetide (NA-1) in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) trial.(23) This current study includes patients in the early time window – <4.5 hours since symptom onset – compared to the 12 hour time window for ESCAPE-NA1 where patients may have more exaggerate swelling or hypodensities.(21) In the 558 participants with acute ischemic stroke in this trial, who had both interpretable CT and 24hr MRI, similarly high rates of agreement between MRI and CT atrophy ratings were demonstrated. When comparing none to any atrophy, agreement dropped further for all measures in this study. Here, by combining none with mild atrophy, and moderate with severe atrophy, then comparing agreement between the two imaging modalities, the agreement was similar or better for all measures in comparison to this previous study, and improved scores compared to the standard assessment within this study. Considering the pragmatic and visual nature of the rating scales used here, approaching the rating of CT and MRI imaging for markers of brain frailty in a binary fashion of none to mild versus moderate to severe appears to facilitate better agreement between imaging modalities, while remaining clinically relevant, since more severe brain frailty burden is associated with worse stroke outcomes compared to no or mild burden.(2, 4)

These findings support the use of CT in the acute stroke setting to assess frailty and atrophy, an environment when CT may be the only imaging available. In the clinical setting, these measures can aid prognostication, especially in settings where MRI may be contraindicated, limited, or delayed. Identifying these markers of brain frailty earlier, with confidence on their similarity to MRI, would facilitate conversations of prognostication, risk profiles for interventions, post-stroke rehabilitation and advance care planning.(3, 6, 20) From a research perspective, the results of this study support the use of CT-based brain atrophy and WMD assessments as feasible and accessible alternatives to MRI-derived markers, in large, pragmatic stroke studies. This would facilitate the harmonization of brain frailty measures without the requirement for MRI standardization across sites.

There are several strengths to this study, including the large, pragmatic, and randomized-controlled study design of the parent trial, with imaging being acquired in the acute stroke setting. The ACT trial was multicentre and across Canada, including centres with variable scanners and imaging techniques. Furthermore, there were no strict exclusion criteria of older individuals, as well as those with pre-morbid cognitive impairment or disability.(21) Imaging modality was not randomized and was reflective of real-world imaging patterns. As such, the generalizability of this data is increased. The physicians in our study had similar training, years of expert experience in assessing neuroimaging, and had previously been shown to have excellent interrater agreement in assessing scans.(23) However, our findings may not apply to imaging agreement between physicians of considerably different experience levels. Of note, the participants who received both MRI and CT imaging were significantly younger and experienced more severe strokes as per the NIHSS scale when compared to those with just MRI or just CT imaging;

the younger age in particular likely meant that the burden of atrophy and WMC in our sample was milder than that in the overall population. However, as seen in our study, CT agreed better with MRI for more severe grades of atrophy and WMC, so agreement may well be higher in the general stroke population. Due to severe edema interfering with the ability to accurately assess atrophy and white matter changes, individuals with this complication, often a result of a large stroke, were excluded from comparative analyses and may not be fully represented in this dataset. Further, there is an absence of baseline mRS scores reported for participants in this trial, which limits the interpretation of the predictive nature of the markers of white matter and brain atrophy, as the change from baseline is unknown.

CONCLUSIONS

Although NCCT tended to underestimate WMC compared to MRI, ratings of brain atrophy and WMC showed substantial to almost-perfect agreements and achieve similar predictions of 90-day functional outcomes in acute stroke participants, using simple and pragmatic measures. This implies that it is reasonable to use NCCT scans to evaluate such brain frailty measures in clinical practice as well as in stroke trials.

Abbreviations

AIS, acute ischemic stroke; AUC, area under the curve; LVO, large vessel occlusion; WMC, white matter changes

Declarations

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST:

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Author Contribution

W.B. and N.S. are co-first authors on this submission. All authors reviewed, provided comments and approved the manuscript. W.B., N.S., I.A., F.Ba., F.Be., K.L., A.G., contributed to data acquisition, analysis

and interpretation. J.C., C.D. and A.T. contributed to data analysis and interpretation. N.S., F.Ba., F.Be., B.B., L.C., A.T., T.S., R.S., B.M., and A.G., contributed to study design and data acquisition.

HUMAN ETHICS AND CONSENT TO PARTICIPATE DECLARATIONS

The trial was completed in accordance with Health Canada regulations and the Declaration of Helsinki, under the approval of research ethics boards at each participating center. Deferred consent procedures were used wherever approved by local research ethics boards. The AcT study followed the Consolidated Standards of Reporting Trials guidelines.

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Figures

Figure 1

Participants with both interpretable CT and MRI scans inclusion flowchart for the alteplase compared to tenecteplase (ACT) trial.