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Disappearance of the hyperdense MCA sign after stroke thrombolysis: implications for prognosis and early patient selection for clot retrieval

[1]P Elofuke,[2]JM Reid, [4]A Rana, [3]M-J Macleod
[1]ST6 Acute and Stroke Medicine, [2]Consultant Neurologist, [3]Senior Clinical Lecturer, Acute Stroke Unit, Aberdeen Royal Infirmary, Aberdeen, UK; [4]Consultant Neuroradiologist, Department of Neuroradiology, Aberdeen Royal Infirmary, Aberdeen, UK

ABSTRACT Disappearance of the hyperdense middle cerebral artery sign (HMCAS) following intravenous thrombolysis for ischaemic stroke is associated with improved outcome. Debate exists over which radiological thrombus characteristics can predict disappearance of the HMCAS after thrombolysis such as vessel attenuation or extent of thrombus length.
Methods Ischaemic stroke patients treated with intravenous thrombolysis from our hospital were entered into a European registry. Patient demographics, stroke severity pre- and 24 hours post-thrombolysis were recorded. Patients with HMCAS were identified from the registry using records from 2010–2013. Images from the pre and post-thrombolysis computed tomography scan were measured. Thrombus characteristics (length and attenuation), extent of ischaemic change and clinical outcome (stroke severity and 3 month survival) were compared between patients with and without HMCAS disappearance. Logistic regression analysis was performed to identify predictors of HMCAS disappearance.
Results HMCAS was present in 88/315 (28%) of thrombolysed ischaemic stroke patients. 36/88 (41%) of patients had thrombus disappearance 24 hours after thrombolysis. HMCAS disappearance was associated with reduced stroke severity, less radiological ischaemic change, and higher 3 month survival (87% vs 56%). Median thrombus length was shorter in the HMCAS disappearance group (11 vs 17 mm, p = 0.0004), but no significant difference in vessel attenuation was observed (48 vs 51 Hounsfield Units, p = 0.25). HMCAS disappearance occurred in 73% of cases where HMCAS length was < 10 mm, 38% when length was 10–20 mm, and 21% if > 20 mm. Thrombus length was the only independent predictor of HMCAS disappearance (odds ratio 0.90 per mm; 95% CI 0.84-0.96, p = 0.01).
Conclusion Disappearance of HMCAS is associated with better clinical and radiological outcomes. A shorter thrombus is more likely to disappear post-thrombolysis. The data highlight the limitation of intravenous thrombolysis in patients with longer hyperattenuated vessels, and the potential role for clot retrieval in such patients.

Correspondence to JM Reid
Acute Stroke Unit
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN
UK

e-mail johnreid1@nhs.net

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INTRODUCTION

The hyperdense middle cerebral artery sign (HMCAS) seen on non-contrast computed tomography of the brain is a highly specific marker of thrombotic vascular occlusion and therefore middle cerebral artery (MCA) territory stroke.[1] In one large multicentre study (IST-3)[2] hyperdense arteries were seen in about a quarter of ischaemic strokes, predominantly in the anterior circulation. The presence of HMCAS was associated with worse outcomes but no increased risk of symptomatic haemorrhage following intravenous thrombolysis (IVT). Disappearance of the HMCAS is more likely following intravenous thrombolysis[3] and is associated with improved outcome.[4] Recent studies suggest that occlusion site,[5] clot length,[6,7] and thrombus Hounsfield Unit (HU) quantification[1,8,9] are all candidates to predict vessel recanalisation after intravenous thrombolysis. It has also been suggested that HMCAS due to cardio-embolism has higher vessel attenuation and is more likely to recanalise post-thrombolysis.[1]

Previous angiographic studies show that HMCAS disappearance post-thrombolysis indicates recanalisation of occluded vessels.[10,11] Using HMCAS disappearance as a surrogate for MCA recanalisation, this study aimed to assess predictors of HMCAS disappearance in a real-world group of thrombolysed stroke patients. This could potentially inform selection of clot retrieval therapies for patients likely to have persistence of HMCAS.

METHODS

Participants

We identified patients who received intravenous thrombolysis for acute ischaemic stroke at Aberdeen Royal Infirmary between January 2010 and May 2013, using the Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). This acute stroke unit serves a population of 523,000 in the north-east of Scotland and 42,000 in Orkney and the Shetland Isles, and admits approximately 700 patients per annum. This study had local Caldicott approval as an audit for the purposes of quality assurance and monitoring of practice. We adhered to the NHS Code of Practice on Protecting Patient Confidentiality.[12] Data recorded included blood pressure, serum glucose, atrial fibrillation and stroke severity (National Institute of Health Stroke Scale [NIHSS])[13] at 0, 2, 24 hours and 7 days after thrombolysis, which was performed using tissue plasminogen activator. Early neurological improvement or deterioration was defined as an increase or decrease of 4 points on the NIHSS scale 24 hours post-thrombolysis. Survival at 3 months is recorded in the registry; this information was derived from the patient's electronic record.

Imaging

Non-contrast computed tomography of the brain was performed using a Siemens 128 slice CT scanner. Images in continuous axial sections parallel to the orbitomeatal line from the skull base to the vertex were acquired in 1 mm section thickness. The extent of ischaemic change (Alberta Stroke Program Early CT score – ASPECTS)[14] on images at baseline and 24 hours post-thrombolysis was recorded. This score evaluates ten anatomical sites within the MCA territory for signs of ischaemic change and produces a normal maximum score of 10 (no ischaemic changes), minus one point for each area with ischaemic changes. In all non-enhanced images, thrombus in the MCA was defined by the following criteria: spontaneous visibility of the whole horizontal part of the MCA, attenuation of the MCA higher than that of the surrounding brain, disappearance on bone windows and unilaterality.[1] The M2 dot sign was defined as hyperattenuation of an arterial structure in the Sylvian fissure relative to the contralateral side. Patients found to have HMCAS by the stroke physician had this recorded in the registry. This was reassessed and confirmed on reviewing the images by two stroke physicians (JMR and PE). The neuroradiologist (AR) then confirmed the presence of HMCAS in all cases. Angiography was not routinely performed. The MCA vessel hyperattenuation, vessel length and estimated occlusion site were obtained by two independent assessors (a consultant neuroradiologist and neurologist). All radiological variables were measured blinded to outcome and clinical data.

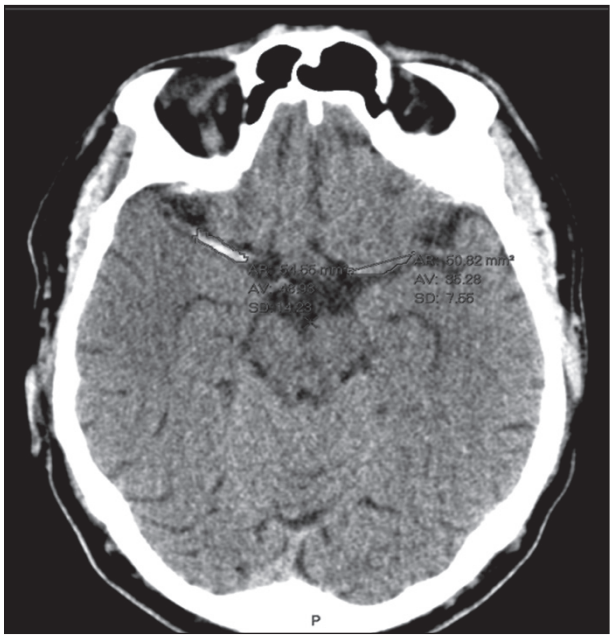

FIGURE 1A Estimation of hyperdense and contralateral middle cerebral artery vessel attenuation (ipsilateral Hounsfield unit [HU]-49.0, contralateral HU-35.3, ratio of ipsilateral/contralateral HU-1.39)

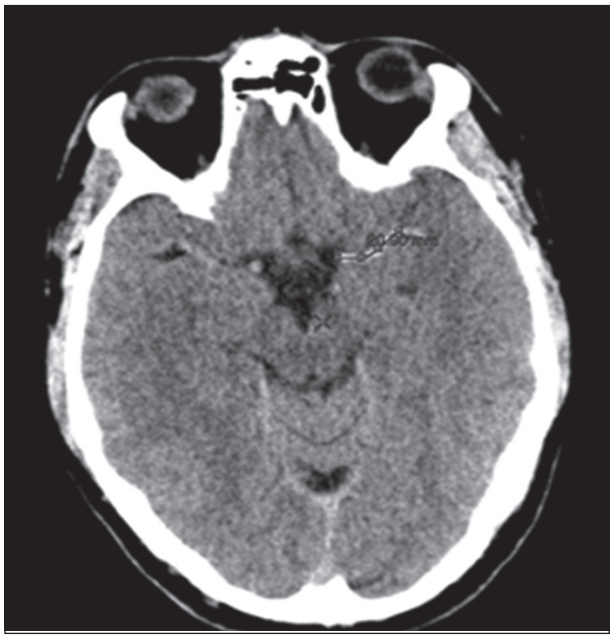

FIGURE 1B Estimation of hyperdense middle cerebral artery vessel thrombus length (= 20.9 mm)

The HU measurements were obtained on the basis of 3 mm computed tomography slices as previously described.[1] Regions of interest were manually placed on the thrombus (HMCAS) and on the contralateral MCA. The ratio of the ipsilateral to contralateral HU defined as rHU was calculated to correct for haematocrit; rHU = [iHU] MCA symptomatic side/[cHU] MCA asymptomatic side. Thrombus length was measured as previously described[7] using the HMCAS detected in images with slice thicknesses of 1.25 mm. Examples of

TABLE 1 Clinical characteristics of patients with or without a hyperdense middle cerebral artery sign (HMCAS). The new denominator is specified where the data are incomplete

Characteristics	No HMCAS	HMCAS	p value
n (%)	227 (72)	88 (28)	-
Mean age (years) (SD)	69 (12)	71 (11)	0.19
Female sex (%)	97 (43)	35 (40)	0.63
Atrial fibrillation (%)	48/213 (23)	46/86 (53)	<0.001
Independent pre-stroke (%)	196/208 (94)	70/75 (93)	0.78
Mean glucose (mmol/l) (SD)	6.7 (0.3)	6.5 (1.0)	0.74
Baseline mean systolic BP (mmHg) (SD)	151 (25)	149 (20)	0.62
Baseline mean diastolic BP (mmHg) (SD)	80 (15)	83 (12)	0.34
Mean NIHSS pre-IVT (SD)	9.8 (7.8)	15.7 (7.2)	<0.001
Mean NIHSS 24 hrs post-IVT (SD)	7.7 (8.3)	12.5 (9.3)	0.001
3 month survival (%)	179/211 (85)	60 (68)	0.01
Mean ASPECTS pre-IVT (SD)	9.5 (0.9)	8.4 (1.7)	<0.001
Mean ASPECTS 24 hrs post-IVT (SD)	8.3 (2.4)	5.4 (2.9)	<0.001
Any intracerebral haemorrhage (%)	24/222 (11)	21 (24)	0.003
Parenchymal haemorrhage (Type 1 or 2) (%)	12/222 (5)	11 (13)	0.03
Symptomatic intracerebral haemorrhage (%)	13/222 (6)	5 (6)	0.95

NIHSS: National Institutes of Health Scale; BP: blood pressure; IVT: intravenous thrombolysis; ASPECTS: Alberta Stroke Program Early CT score.

calculations of the regions of interest of contralateral and ipsilateral MCA HU, and clot length are shown in Figure 1.

Statistical analysis

Baseline data were analysed using the Student's t-test for continuous variables and the Chi-squared test to compare proportions between groups. Significance was taken as $p < 0.05$ for all analyses. Mean values are shown with standard deviations. For analysis, vessel length and HU estimation were taken as the mean value between the two assessors. Four variables were selected a priori to perform stepwise logistic regression analysis to predict HMCAS-D to avoid an event to variable ratio < 10.[15] Based on prior published studies and biological plausibility;[1] age, baseline NIHSS, HU ratio and HMCAS length were chosen. Regression analysis was also tested using all clinical and radiological variables in case any other variables could have been significant independent predictors. Analyses were performed using SPSS version 22 (IBM, NY, USA).

RESULTS

Eighty-eight (28%) of 315 patients receiving intravenous thrombolysis for ischaemic stroke between January 2010 and April 2013 were identified as having HMCAS. Patients with HMCAS had worse stroke severity, higher rates of atrial fibrillation, a greater degree of ischaemic change on the pre and post-thrombolysis CT scans, higher rates of intracerebral haemorrhage after thrombolysis, and lower survival at 3 months (Table 1).

Thirty-six (41%) patients had disappearance of HMCAS (HMCAS-D) on the 24 hour post thrombolysis CT scan. The mean attenuation measured was 3.6 HU higher (95% confidence intervals -16.1 to +9.3) when measured by the neurologist (average 44 HU, range 19–134 HU), compared to the radiologist (41 HU, range 17–141 HU, $p = 0.004$). The mean radiologist measured HMCAS length was 1.6 mm shorter (mean 16.7 mm, range 5–74 mm) compared to the neurologist (mean 18.3 mm, range 5–55 mm, $p = 0.32$).

Details of baseline characteristics of those patients with disappearance and persistence of HMCAS are given in Table 2. There were no significant differences in baseline clinical variables between patients with and without disappearance of HMCAS. The only significantly different radiological variables at baseline were HMCAS vessel length, which was shorter in the HMCAS-D group (median 11 [interquartile range, IQR 8-16] vs 17 [IQR, 11-24] mm, $p = 0.004$), and the fact that no patient with involvement of the terminal internal carotid artery achieved HMCAS disappearance.

The probability of HMCAS disappearance was 73% (16/22) if HMCAS length was < 10 mm, 38% (14/37) if 10–20 mm, and 21% (6/29) > 20 mm. Analysis of patients with and without atrial fibrillation did not demonstrate any difference in rates of HMCAS disappearance (36 vs 44%, respectively, $p = 0.45$), vessel length or HU quantification. In stepwise logistic regression analysis limited to four a priori selected variables, only HMCAS vessel length was an independent predictor of HMCAS disappearance (odds ratio 0.90 per mm, 95% confidence interval 0.84–0.96, $p = 0.01$).

TABLE 2 Characteristics of patients with disappearance (HMCAS-D) and persistence (HMCSA-P) of hyperdense MCA sign

Characteristic	HMCAS disappearance	HMCAS persistence	p value
n (%)	36 (41)	52 (59)	–
Mean age (years)	75 (10)	72 (11)	0.11
Female sex (%)	16 (42)	19 (37)	0.46
Atrial fibrillation (%)	22 (61)	24/51 (47)	0.20
Independent pre-stroke (%)	30/32 (94)	40/43 (93)	0.90
Mean glucose (mmol/l) (SD)	6.3 (1.4)	6.7 (2.0)	0.34
Baseline mean systolic BP (mmHg) (SD)	152 (22)	147 (19)	0.26
Baseline mean diastolic BP (mmHg) (SD)	83 (11)	82 (12)	0.29
Mean symptom onset to treatment (min) (SD)	148 (63)	158 (72)	0.53
Mean NIHSS pre-IVT (SD)	14.8 (5.7)	16.9 (6.3)	0.11
Mean NIHSS 2 hrs post-IVT (SD)	13.3 (7.5)	16.1 (6.7)	0.08
Mean NIHSS 24 hrs post-IVT (SD)	10.0 (8.0)	17.5 (8.1)	<0.001
Mean NIHSS 7 days post-IVT (SD)	9.3 (7.7)	13.8 (7.0)	0.03
24 hr NIHSS improved ≥ 4 points (%)	20 (56)	12 (23)	0.002
24 hr NIHSS worsened ≥ 4 points (%)	3 (8)	12 (23)	0.013
3 month survival (%)	31 (87)	29 (56)	0.009
Radiological characteristics			
Mean ipsilateral HU (SD)	48.3 (5.4)	51.0 (13.9)	0.25
Mean contralateral HU (SD)	34.2 (5.7)	35.5 (5.1)	0.23
Mean HU ratio (SD)	1.44 (0.28)	1.45 (0.38)	0.91
Left MCA involved (%)	18 (50)	21 (40)	0.16
M1 involved (%)	24 (75)	43 (83)	0.39
M2 or more distal only (%)	16 (44)	19 (37)	0.46
Terminal internal carotid involved (%)	0 (0)	7 (13)	0.02
Mean ASPECTS pre-IVT (SD)	8.9 (1.4)	8.4 (1.3)	0.16
Mean ASPECTS 24 hrs post-IVT (SD)	6.4 (2.3)	3.8 (2.6)	<0.001
Median HMCAS length (mm) (IQR)	11 (8–16)	17 (11–24)	0.004
Any intracerebral haemorrhage (%)	8 (22)	13 (25)	0.77
Parenchymal haemorrhage (Type 1 or 2) (%)	3 (8)	8 (15)	0.02
Symptomatic intracerebral haemorrhage (%)	1 (3)	4 (8)	0.32

NIHSS: National Institutes of Health Scale; BP: blood pressure; IVT: intravenous thrombolysis; HU: Hounsfield Unit; HU ratio (ratio of ipsilateral to contralateral HU); ASPECTS: Alberta Stroke Program Early CT score; IQR: interquartile range. Symptomatic ICH is any ICH with worse NIHSS score at 24 hrs post thrombolysis.

DISCUSSION

This study demonstrates that HMCAS disappearance is associated with improvement in the stroke severity score, lower parenchymal haemorrhage rates and better survival after intravenous thrombolysis. HMCAS disappearance may not guarantee neurological improvement as only HMCAS features at 24 hours are measured, which may be because only vessel recanalisation within the first few hours may allow salvage of ischaemic tissue at risk of infarction.

There was a clear relationship between HMCAS length and HMCAS disappearance. One study suggested that HMCAS disappearance post-thrombolysis occurs only in hyperdense arteries with a thrombus length of 8 mm or less,[7] whereas 83% of those we observed in whom HMCAS disappeared had a HMCAS length greater than 8 mm. Another study of 41 thrombolysed patients with HMCAS also suggested that HMCAS disappearance is length dependent, occurring in 86% with lengths < 10mm, 38% if 10–20 mm, and in no cases > 20 mm.[6] Our results, obtained in a larger patient group, broadly concur. Determination of thrombus length and estimated occlusion site is not cumbersome and shows promise as a predictor of HMCAS disappearance post-thrombolysis.

No patient with terminal internal carotid artery involvement showed disappearance of the HMCAS. Some studies excluded patients with internal carotid artery involvement on angiography,[1] but as we did not routinely perform angiography we included this group so as to be representative of our whole population of treated patients. The International Stroke Trial-3 randomised trial has recently reported that intravenous thrombolysis improves the odds that the hyperdense artery regresses or disappears with odds ratios between 0.51–0.66 if limited to single segment, proximal or distal arteries.[3] However this study did not report vessel length or attenuation. Of the non-thrombolysed

patients with distal or proximal HMCAS, 51% had no regression/disappearance compared to 32% in the thrombolysis arm.[3] The low level of HMCAS disappearance we observed, particularly for lengths > 10 mm, highlights the need for additional treatments such as clot retrieval for patients with large vessel occlusive stroke. Early recognition of the HMCAS may help to identify patients eligible for clot retrieval in a timely fashion, although the absence of the HMCAS does not exclude a large vessel occlusion.[1,3]

We could not replicate the findings of Puig et al.[1] who found that the ratio of contralateral to ipsilateral HU ratio <1.382 (i.e. ratio of ipsilateral to contralateral vessel attenuation) predicted persistent occlusion after intravenous tissue plasminogen activator with high sensitivity and specificity.[1] A further study found that for intravenous thrombolysis, intra-arterial thrombolysis and mechanical revascularisation, patients with vessel recanalisation had on average higher hyperdense vessel attenuation.[8] It may be that methodological differences explain the variability of these findings; one study[1] used transcranial Doppler monitoring which is known to be associated with higher rates of recanalisation.[16] The aforementioned study also included a minority of patients with vessel occlusion identified by CT angiography without HMCAS, and vessel recanalisation was confirmed by angiographic or ultrasonic methods.[1] One study[8] found no relationship between clot volume and recanalisation, whether using thrombolysis or mechanical approaches.

HMCAS clot length is dependent on the site of the occlusion, with more proximal clots being longer.[17] Patients with more proximal HMCAS are less likely to improve clinically, and HMCAS disappearance is less likely than those with a distally located HMCAS.[1,18] Furthermore, our population age is older than those included in previous studies.[1,8] Some studies suggest patients with cardioembolic stroke or atrial fibrillation are more likely to recanalise with intravenous thrombolysis.[1,5] However we found no evidence for this, in keeping with larger studies demonstrating no differential effect of thrombolysis on cardioembolic compared to non-cardioembolic strokes.[19,20] Similar to our findings, a recent study found no difference in HU ratio or early recovery depending on whether the aetiology of thrombus was thought to be cardioembolic or atherothrombotic.[9]

The significant trend towards reduced parenchymal haemorrhage we observed in patients with HMCAS disappearance is likely due to the smaller ischaemic volume, represented by higher ASPECTS scores and reduced stroke severity. Indeed HMCAS disappearance is associated with striatocapsular infarcts, in keeping with ASPECTS scores of 6 or higher seen in the HMCAS disappearance group.[21]

There are limitations to our study that mandate cautious interpretation of the results. The sample size is small and the data were collected retrospectively, though blinded to clinical outcome. Disappearance of HMCAS may not necessarily equate to vessel recanalisation as we had not confirmed this with transcranial Doppler or angiography. Ernst et al.[22] described slightly better inter-rater evaluation of HU (mean difference of 2.1), perhaps because we included assessment by a neurologist, whereas the aforementioned study used two neuro-radiologists. Since the overall number of patients with HMCAS is small, this study may be underpowered to detect other variables to predict HMCAS disappearance. In view of the challenge of attempting to implement clot retrieval services in the UK with limited provision of neuro-interventional services our findings are a justification for more prospective studies to develop a model for predicting HMCAS disappearance as a surrogate for vessel recanalisation. This could influence patient selection for clot retrieval, particularly in a resource-limited health system, although ideally all patients with large vessel occlusive stroke should be considered for clot retrieval.

CONCLUSION

The presence of a HMCAS is associated with higher stroke severity and worse outcome; however disappearance of the HMCAS is associated with improved clinical and radiological outcomes. Only HMCAS vessel length predicted HMCAS disappearance. The persistence of HMCAS particularly with longer thrombus length highlights a potential role for clot retrieval in these patients.

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