Introduction

There are more than 100,000 strokes in the UK each year,[1,2] with stroke being the second biggest killer in the world.[3] Stroke is broadly classified into two groups: Ischaemic stroke (IS) or intracranial haemorrhage (ICH).[4] The National Institute for Health and Care Excellence (NICE) emphasise the importance of distinguishing between these two forms of stroke for treatment and patient management purposes.[5]

Treatment options for stroke are time and case sensitive. Ischaemic stroke may require thrombolysis drug therapy or mechanical thrombectomy.[6-8] Intracranial haemorrhage treatment may include neurosurgery to relieve intracranial pressure and drug therapy to reverse the effects of blood-thinning medication being taken.[9] Transient ischaemic attack (TIA) (minor stroke) comes under the umbrella term of IS, and also needs to be diagnosed for management proposes to prevent a future full stroke.[10,11] Risk factors for stroke include arterial hypertension, atrial fibrillation and previous history of stroke/TIA. Individuals at high risk of IS or TIA are often given anticoagulation medication.[12] One of the risks regarding anticoagulation is its unpredictable nature and its ability to cause a secondary ICH.[13]

In recent years, the advantages of diagnosing cerebral microbleeds (CMBs) in acute stroke patients have become apparent. CMBs are small focal areas (<5mm) of chronic blood products (mainly hemosiderin) found in otherwise normal brain tissue.[14] There are many terms used to describe CMBs, including: microhaemorrhages, cerebral amyloid angiopathy (CAA),[15] superficial siderosis,[16] hemosiderin deposits,[14] or hypertensive arteriopathy.[15] The detection of CMBs in acute stroke patients can affect two main areas: the stroke prognosis (and future stroke risk) and the consideration of drug therapies prescribed in stroke. Anticoagulant drugs used to prevent secondary strokes, and thrombolysis treatment used in acute IS could result in an even higher risk of secondary ICH in those with CMBs.[17,18] Also, great care should be taken to control blood pressures in those with CMBs having had an ICH. The likelihood of ICH can be reduced by 77% in patients with established CMBs, who are actively treated with antihypertensive drugs than those not treated.[19,20]

 CMBs can optimally be detected using magnetic resonance imaging (MRI) T2* gradient echo sequences (T2*GRE) or MRI susceptibility weighted imaging (SWI).[21,22] Using T2*GRE MRI at magnetic field strengths of 1.0T & 1.5T, CMBs have been demonstrated to naturally occur in 3-6% of the healthy elderly population,[23,24] but this can increase up to 74% in those with stroke.[24,25] CMBs are more prevalent among recurrent strokes than first time strokes.[24]

CAA: cerebral amyloid angiopathy, CMBs: cerebral microbleeds, GRASE: gradient and spin echo, ICH: intracranial haemorrhage, IS: ischaemic stroke, SWI: susceptibility weighted imaging, T2*GRE: T2* gradient echo, TIA: transient ischaemic attack

Clinical relevance

Computed Tomography (CT) and MRI are routinely used to determine stroke type in those suspected of an acute stroke. A typical acute stroke MRI protocol may include: 1) an anatomical T2/FLAIR sequence, 2) a blood sensitive sequence for the detection of haemorrhage and blood products as well as of CMBs (this can often be a T2* or SWI sequence), a diffusion sequence for the early detection of ischemic and salvageable brain tissue (35). Perfusion imaging and MR angiography can sometimes also be used. This 30-minute protocol can provide reliable information about the type of stroke, laterality of vessel occlusion, the extent of potentially salvageable brain tissue, and the exclusion of differential diagnoses of ischemic stroke (36).

Ideally, imaging protocols can detect CMBs at the same time as investigating stroke. Different national guidelines clearly state patient imaging pathways for suspected stroke (table 1), however the combination of MRI sequences to be used can be less specific or standardised and is summarised in table 2. MRI sequences differ between clinical sites as every site uses protocols available to them in an optimal way for early diagnosis.

Not all suspected stroke patients are scanned routinely with either a T2*GRE sequence or SWI. if these protocols are omitted, then CMB depiction might be compromised on MRI scans and its incidence may be considerably lower than that suggested in the literature.

Table 1. UK guidelines for acute stroke imaging. All TIA MRI imaging is within 24 hours of symptom onset for those at high risk of developing a full stroke, and within 7 days for those at low risk. For acute stroke, CT & MRI can be used interchangeably depending on individual stroke unit resources. DoH= Department of health, SoR= Society of Radiographers, DWI= Diffusion weighted imaging.

	Acute Stroke		TIA	
Guidelines	**CT**	**MRI**	**CT**	**MRI**
NICE (National Institute for Health and Care Excellence) (2019)[6]	• Immediately if time-sensitive treatment a possibility. • Non-enhanced CT brain.	• Within 24 hours of symptoms onset if no indication for immediate brain imaging. • CT also a possibility.	• No (unless clinical suspicion of alternative diagnosis detectable by CT)	• DWI and blood sensitive sequence.
DoH (2008)[26]	• First-line imaging.	• First-line imaging if available and not contraindicated.	• No (unless MRI is contraindicated)	• DWI and T2*GRE sequence.

| SoR (2015)[27] | • When CT diagnosis unclear.
• 'Brain imaging' immediately for time-sensitive treatment.
• 'Brain imaging' as soon as possible when time-sensitive treatment is not a possibility. | • No (unless MRI is contraindicated) | • DWI and blood sensitive sequence. |

Table 2. A list of suggested MRI sequences to be used in acute stroke imaging according to UK based literature. Y= Yes/suggested, N= No/not suggested. The need for diffusion weighted imaging (DWI) and T2*GRE/SWI imaging is common in all literature. T2SE= T2 spin echo, FLAIR= fluid attenuated inversion recovery.

Authors	DWI	T2SE	T2*GRE/SWI	FLAIR
Mair & Wardlaw (2014)[28]	Y	Y	Y	Y
Wintermark et al (2008)[35]	Y	Y	Y	Y
Leiva Salinas and wintermark (2010)[36]	Y	Y	Y	Y
Muir & Santosh (2005)[29]	Y	N	Y	N
Wardlaw (2001)[30]	Y	Y	Y	N

Rationale

The purpose of the study was to explore the use and application of blood sensitive MR sequences for the detection of CMBs, with the intention of improving local practice. This study will particularly explore the importance of T2*GRE imaging in the detection of CMBs in suspected stroke cases and offer recommendations for practice in the absence of other specialised sequences.

Methods

Design, setting and ethical approval

This retrospective research quality improvement study was conducted in an acute specialist stroke unit within the UK. Ethical approval was obtained from the unit's clinical effectiveness unit (3 May 2019) prior to the study commencing.

Equipment used and imaging sequences in retrospective analysis

A sample of anonymised MRI brain scans performed over a consecutive 6 month period (January 2018-June 2018) at a single UK acute stroke centre was used. All cases were scanned using a 1.5 tesla scanner (Phillips, Achieva, Eindhoven, The Netherlands) and patients were all imaged for suspected stroke. Only those scanned with the SENSE NeuroVascular (NV) coil and SENSE head coil were included for parity of image quality. Equipment and imaging protocol details were identified and recorded through the picture archiving and communication system (PACS).

The routine protocol for suspected stroke imaging at the study site includes diffusion weighted imaging (DWI) and gradient-and-spin echo (GRASE) sequences.

DWI is essential for infarct detection.[28-30] GRASE is a blood-sensitive sequence for haemorrhage detection[31] and T2*GRE is for CMB detection (and confirms ICH).[21]

Additionally, T1, T2 spin echo (T2SE) and fluid attenuated inversion recovery (T2 FLAIR) are acquired when other pathology mimicking stroke is suspected.[28-30] In our site a T2*GRE is performed upon request by the stroke physician on call (SPOC) or when there is suspicion of ICH on previous imaging sequences.

Cases only having had DWI, had insufficient data to be included in the analysis, so were automatically excluded.

Data review methods, inclusion and exclusion criteria

The local radiology computer system (Soliton Radiology+, Felden, UK) was employed to review and identify all acute stroke cases of brain MRI within the six-month period. The imaging report for each of the cases was retrieved and qualitatively reviewed to determine if an acute stroke

diagnosis had been made. Table 3a lists the full inclusion and exclusion criteria for the MRI data review. Table 3b includes the key scan parameters of the used MRI protocols at our clinical site.

Table 3a. Full inclusion and exclusion criteria for MRI brain scans used for data review. MRI coils and sequences were established using the picture archiving communication system (PACS). NA= not applicable.

	Inclusion	**Exclusion**
Date of MRI	01.01.2018 to 30.06.2018	Any other date
Demographics	All ages, genders, races	NA
Clinical Indications	Suspected stroke at time of MRI	Known stroke at time of MRI
Diagnosis	Acute stroke	Chronic stroke, no stroke, other pathology
Patient Pathway	Resus, TIA clinic, stroke ward	Any other pathway
MRI	First MRI since symptom onset	Previous MRI for same symptoms/follow up MRI scan
MRI coils used	SENSE NV coil, SENSE head coil	SENSE Flex-L coil
MRI sequences	DWI with GRASE and/or T2*GRE, T1, T2SE and/or T2 FLAIR	DWI only
Image quality	Diagnostic, no artefacts	Artefacts (motion, metal, etc).

Table 3b : key scan parameters of the used MRI protocols at this clinical site.

Protocol	Sequence	Scan Parameters					Detects:
		TE (ms)	TR (ms)	Slice Thickness (mm)	FOV (mm)	Scan Time (Mins)	
Routine stroke	DWI	100	3666	5	240	0:44	Infarct
	GRASE	120	6117	5	230	3:03	ICH
When requested	T2*GRE (T2 FFE)	23	703	5	240	3:37	ICH, CMBs
Routine brain	T1	15	672	4	240	2:32	'other pathology'
	T2	120	5850	5	230	1:56	ICH, 'other pathology'.
	T2 FLAIR	90	8000	5	230	2:56	ICH, 'other pathology'

Data analysis methods

Having established the cases suitable for analysis, the radiology reports were also qualitatively reviewed for a CMB diagnosis, looking also for alternative CMB terminologies as described earlier.. The terminology used for CMB diagnosis in each positive case was recorded. Microsoft excel was used to record, review and analyse data. For quantitative analysis descriptive statistics was used. In addition, the qualitative relationship between CMB detection on the radiology report, and the use of a T2*GRE sequence in the imaging protocol was also examined. CMB detection rates were reported for each stroke category.
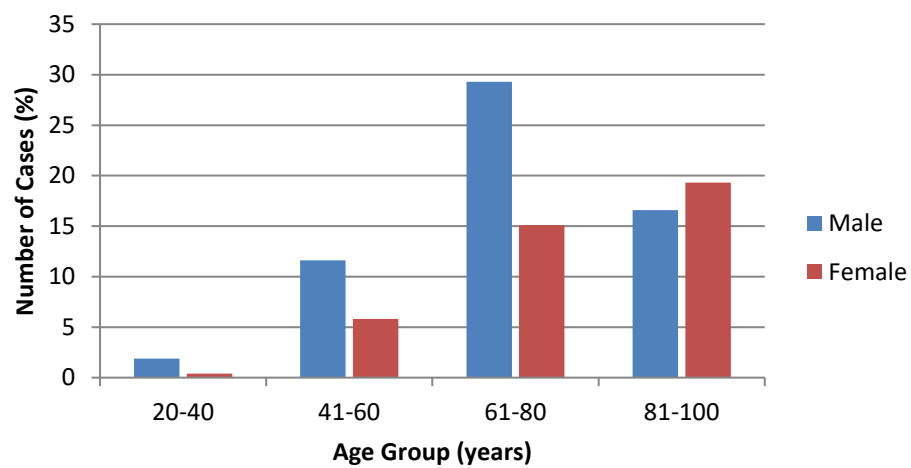
Results

In the 6-month period, 281 acute stroke patients meeting the inclusion criteria (table 3), attended for MRI brain imaging. Of those 113 (40.21%) were female and 168 (59.79%) were male (median age range 72 years, age range of 27-97 years). Of the initial sample size 259 (92.17%) had an ischaemic stroke, 16 (5.69%) had an ICH and 6 (2.14%) had both ischaemic stroke and ICH (haemorrhagic transformation). Thirteen (4.63%) of the total 281 patients, had a diagnosis of CMBs (table 4). Table 4 summarises the total number of cases for each diagnosis. Figure 1 (A,B,C and D) shows the percentage of total number of stroke (and CMB) cases in relation to age group and gender.

Table 4. Summary of acute stroke cases, and the number of cerebral microbleed cases within this acute stroke population (N= 281).

Diagnosis	Total Number of Cases	Number of Cases (%)
Intracranial Haemorrhage	16	5.69
Ischaemic Stroke	259	92.17
Both IS with ICH	6	2.14
TOTAL	**281**	**100%**
Cerebral Microbleeds	13	4.63

A. Ischaemic Stroke (N=259)

B. Intracranial Haemorrhage (N=16)

C. Both Ischaemic Stroke with Haemorrhagic Stroke (N=6)

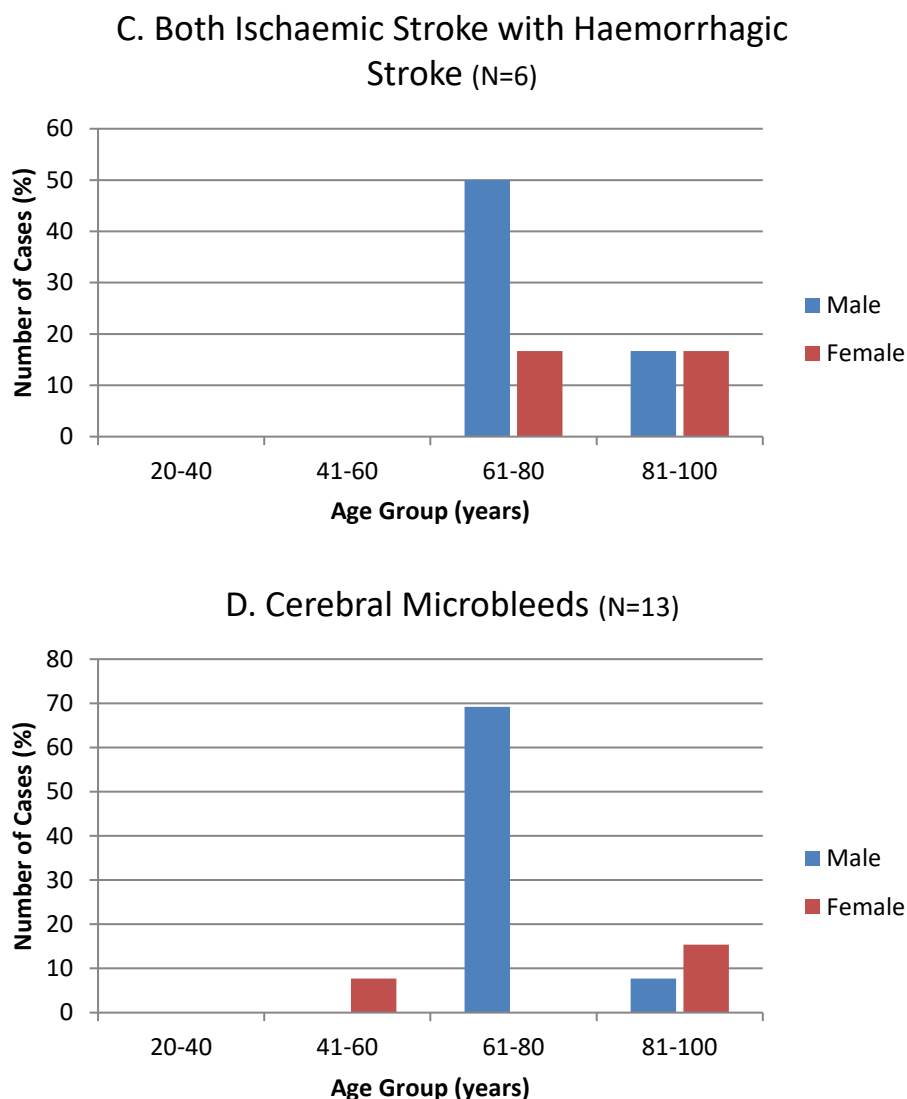

D. Cerebral Microbleeds (N=13)

Figure 1. Percentage number of cases for stroke and CMB diagnosis in each age group and gender. A= ischaemic stroke cases, B= intracranial haemorrhage cases, C= both (IS & ICH), D= CMB cases. The majority of stroke cases and CMB cases occurred in the 61-80 year old age group.

The terminology used in diagnosing these 13 CMBs cases, as present in the radiologists' report, is summarised in table 5. Of these 13 patients, 100% had a T2*GRE sequence. None of the other 268 patients (without T2*GRE) had a diagnosis of CMBs (figure 2). Eight of 259 acute IS cases had CMBs (3.09%) whereas 3 of 16 acute ICH cases (18.75%) had CMBs. Two of the 6 cases with both IS and ICH had CMBs (33.33%). Of the13 CMB cases, 2 were from the TIA clinic (15%), one was from resus (8%) and 10 were from the stroke ward (77%) (figure 3).

Table 5. Terminology used to diagnose CMBs, and the number of cases in each group.

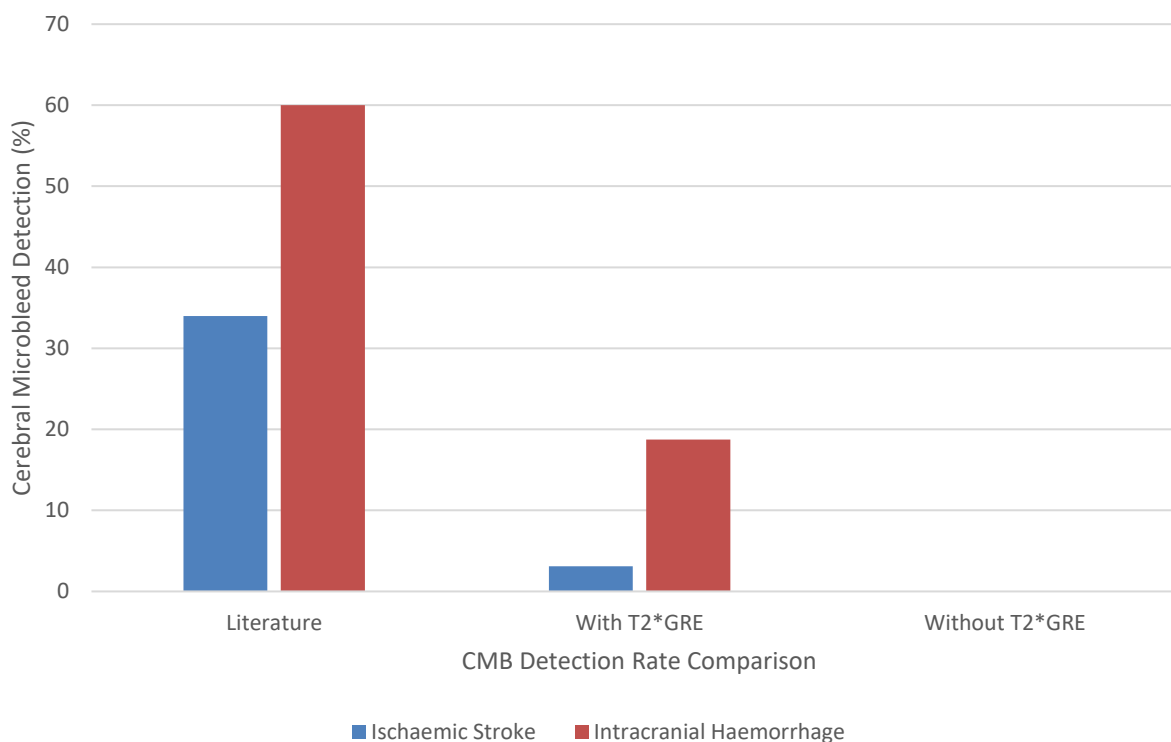| Terminology	Number of Cases (N= 13)
CMBs	6
CAA	1
CMBs & CAA	2
Superficial Siderosis	1
Superficial Siderosis & CAA	1
Hemosiderin Deposits	2

Figure 2. Cases of CMBs detected in those with an acute IS (3.09%) or acute ICH (18.75%), with a T2*GRE sequence (middle of this graph) and without a T2*GRE sequence (far right of this graph). Total number of cases: IS= 259, ICH= 16. These have been compared to literature based CMB detection rates for stroke; those with IS= 34%, ICH= 60%.[24]
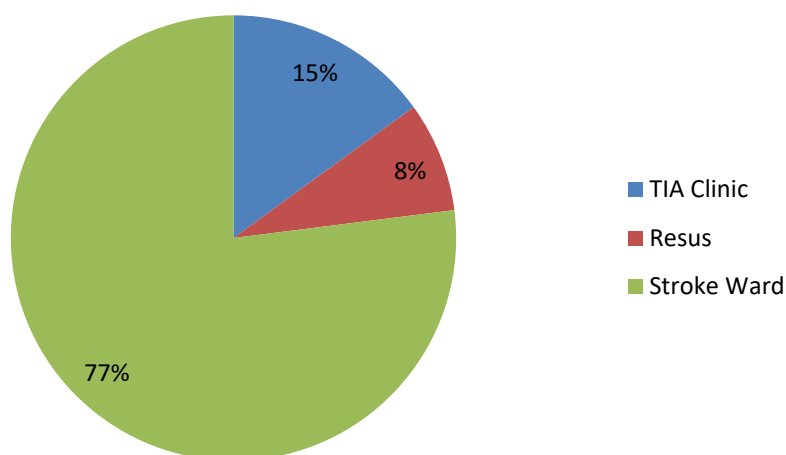
Figure 3. Percentage of CMB cases from each patient pathway. The majority of CMB cases (and T2*GRE imaging) occurred in those referred from the stroke ward. N= 13.

Also, to note, of the 22 patients with an identified ICH, 3 (13.64%) did not have a T2*GRE sequence incorporated by the radiographer. There were also 5 cases where the SPOC had requested a T2*GRE but it had not been completed. One of these returned at a later date to have T2*GRE imaging.

Discussion

MRI protocols/sequences for suspected acute stroke

Acute stroke imaging pathways/protocols at the study site are in accordance with UK imaging guidelines (table 1). The MRI sequences completed at the study site, are in accordance with NICE (2019)[6] guidelines, as DWI and a blood sensitive sequence are routinely completed. Although GRASE, a hybrid gradient echo and spin echo sequence, is not widely used as a blood sensitive brain sequence, and there is sparse literature supporting its use in stroke imaging, research has shown it can be as sensitive as T2SE for ICH lesions in stroke imaging.[31] This is the preferred sequence for stroke imaging at the study site because of its time efficiency compared to separately scanning both T2SE and T2*GRE sequences, which has certain advantages for agitated stroke patients. GRASE also has reduced motion artefacts, less

susceptibility and chemical shift artefacts and lower specific absorption rate (SAR) than other T2 sequences, as it brings together the benefits of gradient echo and spin echo imaging.[32]

However, due to the closely spaced 180˚ refocussing pulses and blurring in the phase-encoding direction, GRASE is not as good at detecting small haemorrhagic lesions (CMBs) as T2*GRE or SWI sequences.[33] This has been demonstrated by the results of the data analysis that found CMBs were only detected with T2*GRE sequences and never with GRASE imaging alone (figures 2 and 4).
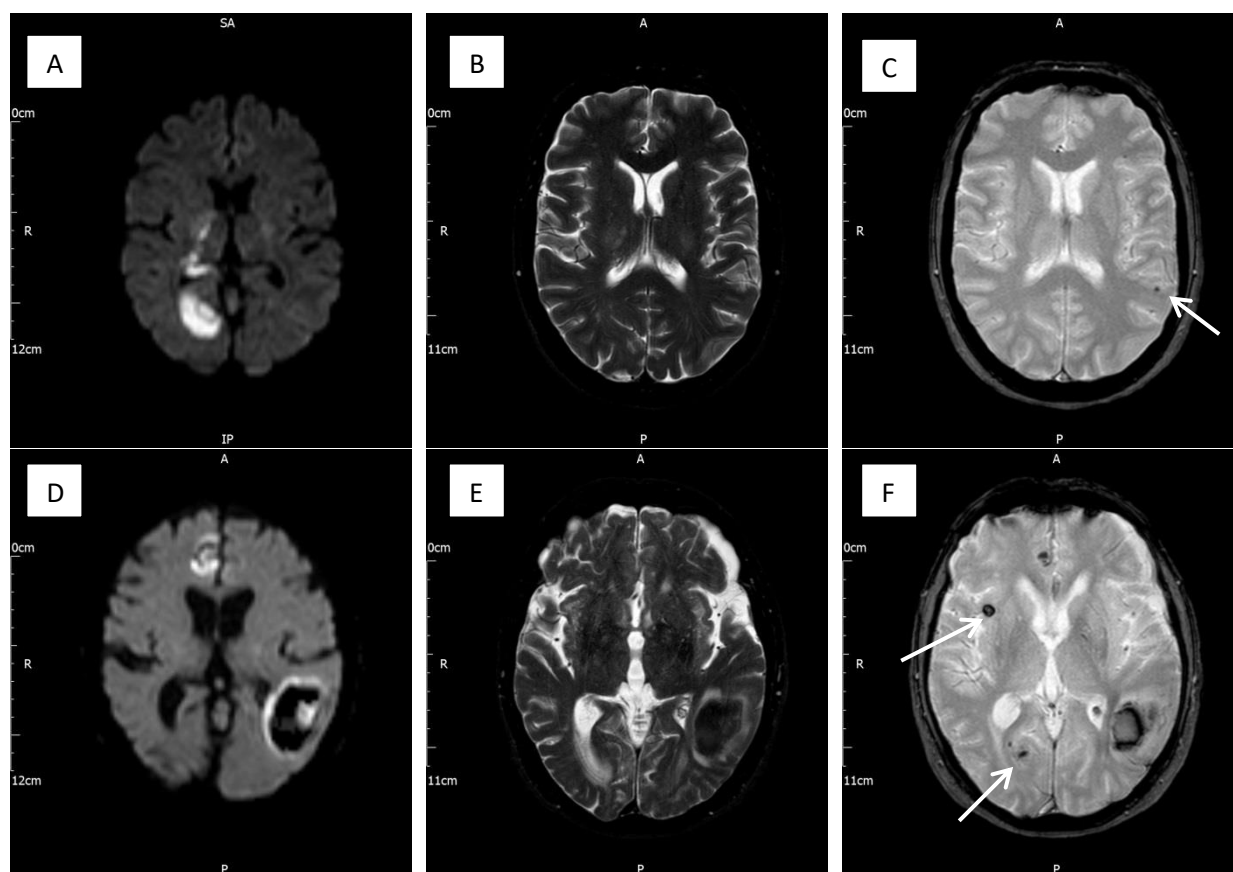

Figure 4. Example images from the stroke protocol performed at the study site. Images A & D- DWI, B & E, GRASE, C & F- T2*GRE. Images A to C- on a 46 year old female patient with a large area of restricted diffusion on the left side of the brain. CMBs present (arrow). Images D to F- 76 year old male patient with multiple haematomas seen throughout both cerebral hemispheres. Several CMBs seen (arrows). CMBs only deliniated on T2*GRE sequences.

The retrospective data analysis has demonstrated the need for true T2*GRE imaging for CMB detection. No cases of CMBs were detected in patients without a T2*GRE sequence (figure 2). The incidence rates for CMBs in both IS and ICH are substantially lower than those found in the

literature[24] (figure 2),where CMBs are present in 34% of IS patients and 60% in ICH[24]. This would suggest cases of CMBs are being missed due to the lack of T2*GRE imaging for all acute stroke patients. CMBs cannot be considered in important clinical decision making and patient management if they are undetected.

As a true T2*GRE (or SWI) sequence is not currently routinely completed for all suspected acute stroke patients, the data analysis found that of the 22 patients with an identified ICH (16 ICH cases, plus 6 cases of ICH with IS), 3 (13.64%) did not have a true T2*GRE sequence added by the radiographer, as described above in results, including five cases requested by the SPOC. When a T2*GRE referral is missed, patients can attend at a later date for this imaging protocol, however this may be unsettling for patients and their families but is also ineffective for imaging department workflows. Furthermore, stroke patient management is time-sensitive so important treatments might be inadvertently delayed. It is important that local policies explicitly state that all suspected acute stroke patients should have T2*GRE included for stroke imaging, to prevent a looser interpretation of formal stroke guidelines.

The majority of CMB cases were detected in stroke ward patients rather than those from resus or the TIA clinic (figure 3). This may be attributed to length of time spent in clinical care. Clinicians have more time to discuss medical history and access patients' notes once a patient is admitted to a ward. The requesting clinician may have longer to consider the likelihood of CMBs (ie cardiac history) and request a T2*GRE sequence. However if T2*GRE was a routine protocol, CMBs would be detected irrespective of patient pathway.

Study limitations

One limitation of doing a retrospective data analysis is there is no guarantee reporting radiologists reported on all CMB cases seen. A prospective study requiring radiologists to specifically report on CMBs (using specific terminology) would better guarantee CMB incidence rates. CMBs may not have been considered of clinical significance in an acute setting.

There are also several medical terms for characterising CMBs (table 5). If Table 5 is not a full and extensive list of terms used, some CMB diagnoses may have been missed during data review.

Sample size was representative and inclusive of a period of 6 months; however a larger sample size of 12 months might have allowed for more variability in the data and could have supported more conclusive results.

Finally the SWI sequence is not readily available at all clinical sites due to scanner compatibilities and resource rationalisation. Therefore more focus was drawn in this paper on the T2*GRE sequence, as it is a frequently available blood sensitive sequence at different clinical sites.

Recommendations for practice

Cerebral microbleed detection in acute stroke can play an important role in clinical decision making with regards to the medical management of stroke. Therefore T2*GRE (or SWI) imaging should be completed on all suspected stroke patients that undergo MRI. Even though the NHS must consider time and cost as well as diagnostic accuracy, this suggest indicates that including a T2*GRE acquisition rather than a GRASE or T2SE alone, can increase the detection of CMBs. A routine T2*GRE sequence means irrespective of patient pathway, SPOC request or radiographer initiative in the presence of ICH on previous imaging protocols, each patient has equal chance of getting a CMB diagnosis, that can be considered for clinical decision making.

If available, SWI should be the sequence of choice with regards to CMB detection. Its sensitivity and acquisition speed (2-4mins) make it the ideal sequence.[34] If SWI is not available, as in this study, T2*GRE should be considered as the most appropriate sequence for CMB detection.

Whether SWI or T2*GRE imaging is used to detect CMBs, both must be used in conjunction with a T2SE sequence. This is to confirm ICH diagnoses and to differentiate from stroke-mimicking pathology.

Suggested sequence acquisition order for stroke imaging could be; 1) DWI (for infarct & ICH), 2) T2*GRE (for ICH & CMBs), 3) T2SE (for ICH & stroke-mimics) and finally 4) T2 FLAIR (for ICH & stroke-mimics, if locally deemed necessary). This ensures the most clinically useful sequences for stroke detection are performed first incase the patient becomes agitated and un-cooperative during MR imaging.

All stroke unit reporting radiologists must be made aware of the importance of a CMB diagnosis in acute stroke. Radiologists, and stroke clinicians, should be provided with a universal list of CMB terms to be used in reporting. Currently there are several terms being used (table 5). This would ensure all cases of CMBs would be officially diagnosed.

Conclusion

For patients undergoing MRI for suspected acute ischaemic stroke certain sequences may be beneficial for the timely and accurate detection of CMBs. If a SWI sequence is unavailable, T2*GRE imaging must be included. The detection of CMBs should be used as it may inform clinical decision making with regards to patient management.

Conflict of Interests

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