Acute Stroke Imaging: Current Trends

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Abstract

The management of acute ischemic stroke has witnessed a paradigm change in the last few years with the advent of mechanical thrombectomy. Imaging plays a key role in evaluation and patient selection. Computed tomography (CT) forms the workhorse in most centers due to its widespread availability and quick performance, though magnetic resonance imaging (MRI) can also be adopted as a reasonable alternative. The key role of imaging is to rule out hemorrhage and other stroke mimics while at the same time establish early signs of ischemia and provide detailed information of cervicocranial vasculature and salvageable brain parenchyma; all in the shortest timeframe. Key imaging predictors of good clinical outcomes are good Alberta stroke protocol early CT score (ASPECTS) (greater than 6) and collateral scores. Selection of patients beyond the standard window period of 6 to 8 hours has become possible by tissue perfusion imaging with some recent trials demonstrating the utility of thrombectomy even up to 24 hours. Quick MRI-based protocols are being devised to achieve similar information as on CT with no adverse effects related to radiation and contrast effects. Research is underway to decipher the intricacies of blood flow in the brain through more sophisticated imaging methods in attempt to increase the base for mechanical thrombectomy, which will benefit more number of patients.

Keywords
- ischemic stroke
- mechanical thrombectomy
- computed tomography
- MRI
- cervicocranial vasculature
- salvage brain parenchyma

Introduction

The realization in the last couple of decades that manifestations of stroke can be reversed has completely transformed the management strategies from palliative care to immediate and prompt institution of treatment. From intravenous tissue plasminogen activator (tPA) therapy[1] to clot retrieval by endovascular mechanical means,[2] the last two decades have witnessed a paradigm shift in stroke treatment. The only hurdle that still remains is time following stroke onset at which the patient arrives and receives treatment,[3] which still proves to be a dealmaker or a deal-breaker. As in many other pathologies of the human body, so also in acute stroke, imaging and treatment strategies are closely intertwined. Imaging results often govern the choice of treatment options and many a times the reverse is also true whereby, a particular treatment modality may determine what imaging needs to be performed. Thus, imaging has an immense role to play in choosing which patients will best respond to stroke treatment. The various nitty-gritties of acute stroke imaging form the core of the following article.

Pathophysiology

The optimal functioning of neurons and synapses is heavily dependent on the availability and supply of oxygen and nutrients. Any interruption in these can lead to progressive irreversible damage of the functional neural systems over a course of few hours. This is unlike other cells of the body, which have the capacity of healing and regenerating. Time, indeed, is brain. For a better perspective, approximately 1.9 million neurons die each minute of nutrient deprivation, which extrapolates to aging by approximately 3.6 years each hour without treatment.[4] In terms of clinical interpretation,

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analysis of SWIFT PRIME and STAR trial data[5] showed that treatment initiated within 2.5 hours of symptom onset resulted in independent function in 91% of patients; 1 hour delay in treatment decreasing a positive clinical outcome by 38%.[6] Beyond 3.5 hours after symptom onset, every 60-minute delay results in a 20% lower chance of regaining function independence.

The pathological connotation of acute stroke can be understood based on a three-compartment model of brain parenchyma following arterial occlusion. The central area of "infarct core" is the first to be involved and represents nonviable brain that cannot be salvaged even with very prompt treatment. The immediately surrounding "ischemic penumbra" represents brain with reduced blood flow that has potential for survival if blood flow is rapidly restored. The outermost affected zone represents brain tissue that is likely to survive even without such treatment. Biochemically, tissue damage occurs by the influx of Ca^{2+} into cells, the release of excitatory amino acids, and the activation of receptors and receptor-operated ion channels.[7] Protein synthesis reduction is the earliest and most sensitive metabolic response to ischemia that may be reversible in the penumbra but not in the core.[8] The penumbra thus forms the target volume of brain reperfusion therapy.[9]

Aim of Imaging

Intravenous tPA was the only Food and Drug Administration-approved treatment of acute ischemic stroke within 4.5 hours, for a long time. After the success of various thrombectomy trials, stentrievers were subsequently approved in suitably selected patients, the main determinant of which is brain imaging. The aim of imaging is multifold, beginning from choosing the most appropriate patients for treatment, to excluding those who are unlikely to benefit, to the extreme subset of the ones who will potentially deteriorate following reperfusion. In the current scenario, imaging modalities essentially involve cross-sectional imaging by either computed tomography (CT) or magnetic resonance imaging (MRI). The target of assessment is the brain parenchyma and the vessels supplying the corresponding parenchyma as well as same/distant perfusion status (►**Fig. 1**).

Broadly, the objectives of imaging are as follows:

1. Identifying infarct/hemorrhage.
2. Ruling out other potential stroke mimickers, for example, gliomas, infections, etc.
3. Detecting early signs of ischemia/infarct (parenchymal evaluation).
4. Identifying the site and extent of vascular occlusion (evaluation of pipe).
5. Attempt to prognosticate the patient's response to treatment and evaluating the ischemic penumbra (perfusion and penumbra).
6. Formulating a treatment decision based on the assessment of all the above-mentioned parameters.

The entire exercise of providing all these answers should not take more than 10 to 15 minutes.

Imaging Modalities

Computed Tomography

CT currently forms the workhorse of acute stroke imaging due to its easy availability, quick data acquisition capability, and reasonably good demonstration of findings. The first and the foremost consideration is to rule out hemorrhage so that intravenous therapy can be immediately instituted if the patient is in window of being treated. This is followed by exclusion of other pathologies (clinical mimics) and identification of signs of ischemia. The CT correlate of ischemia is hypodensity, which develops owing to cytotoxic edema and increased water content followed imminent or actual cell lysis. This hypodensity may be manifested in the form of sulcal effacement and/or loss of gray–white distinction in the ischemic or oligemic zones.[10] The various signs described are loss of insular ribbon sign (►**Fig. 2A**), obscure lentiform

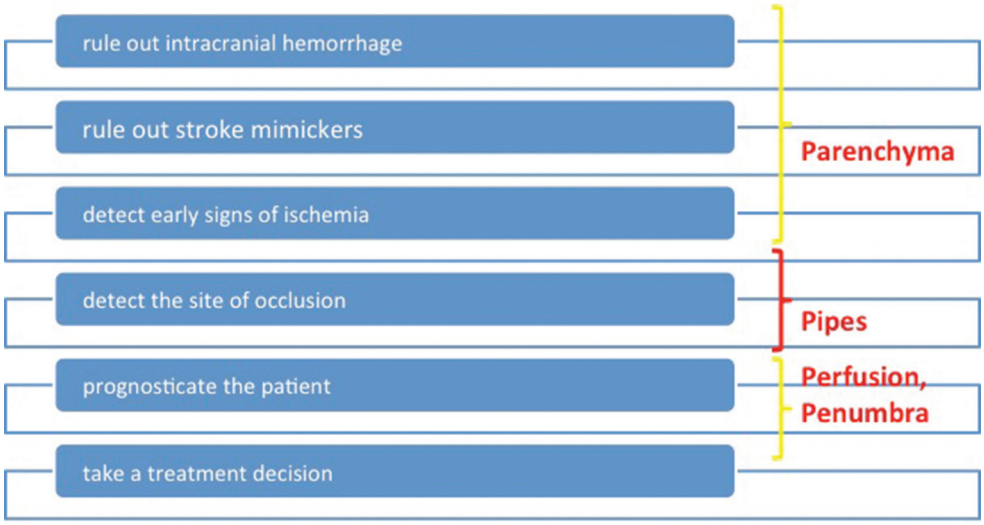

Fig. 1 Algorithmic approach to imaging in acute stroke with reference to the 4 P's (parenchyma, pipes, perfusion, and penumbra).

nucleus sign (►**Fig. 2B**), hyperdense artery sign (hyperdense middle cerebral artery [MCA]/basilar dot sign) (►**Fig. 3**), etc. Standard 5-mm thick sections are often enough, though thin (0.5–1 mm) slices are helpful for increased spatial resolution for detection of small infarcts and to resolve partial volume averaging effects. It may also help in reconstruction of the image in other planes to delineate the infarcts and arterial thrombi better.[11] Sometimes, subtle hypodensities are not discernible. It has been suggested to view all such scans on the console after changing the window settings to "stroke window," which is nothing but reducing the window width to reach a level and width to between 30 and 40 HU (►**Fig. 4**).[12]

It has been seen that the degree of early ischemic changes on CT correlates with stroke severity scores, which is a predictor of clinical outcome.[13] This can be objectively assessed using the Alberta Stroke program early CT score (ASPECTS), which can help in appropriate patient selection for endovascular therapy as well as provide a prognostic marker for treatment response.[14] ASPECTS is a 10-point score which is derived from CT images at ganglionic and supraganglionic sections (►**Fig. 5**). Each structure in the MCA territory is given a 1-point score, with maximum possible being 10. One point is deducted when hypodensity is detected in a particular area. A score of 6 or greater signifies a better response to reperfusion than score of below 6.[15]

There are limitations associated with plain CT scan. It does not accurately indicate the core and the penumbra. However,

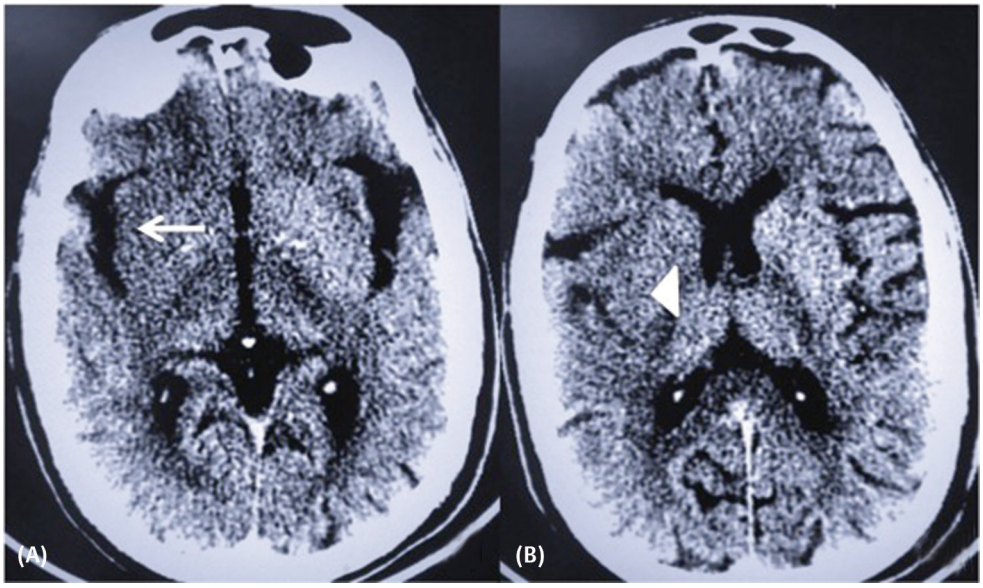

Fig. 2 Axial noncontrast computed tomography (CT) brain sections demonstrating the two early signs of stroke corresponding to loss of gray–white matter definition, namely loss of "insular ribbon" sign (arrow, **A**) and "obscure lentiform nucleus" sign (arrowhead, **B**). Note the normal attenuation of similar structures of the contralateral side.

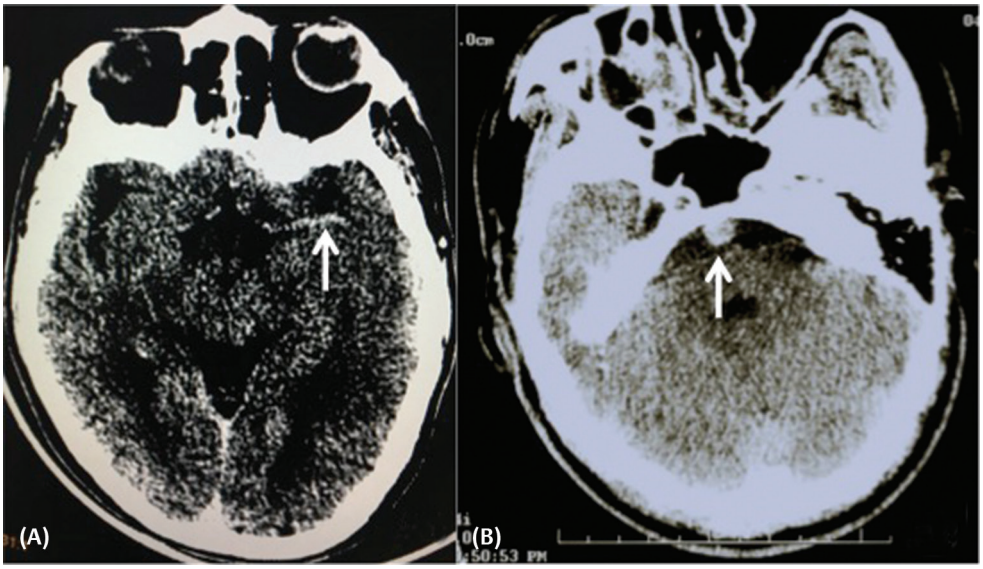

Fig. 3 Axial noncontrast computed tomography (CT) brain sections showing hyperdense arteries (arrows) in two different patients of left middle cerebral artery (MCA) thrombus (**A**) and basilar thrombus (**B**). Note the expanded hyperdense artery.

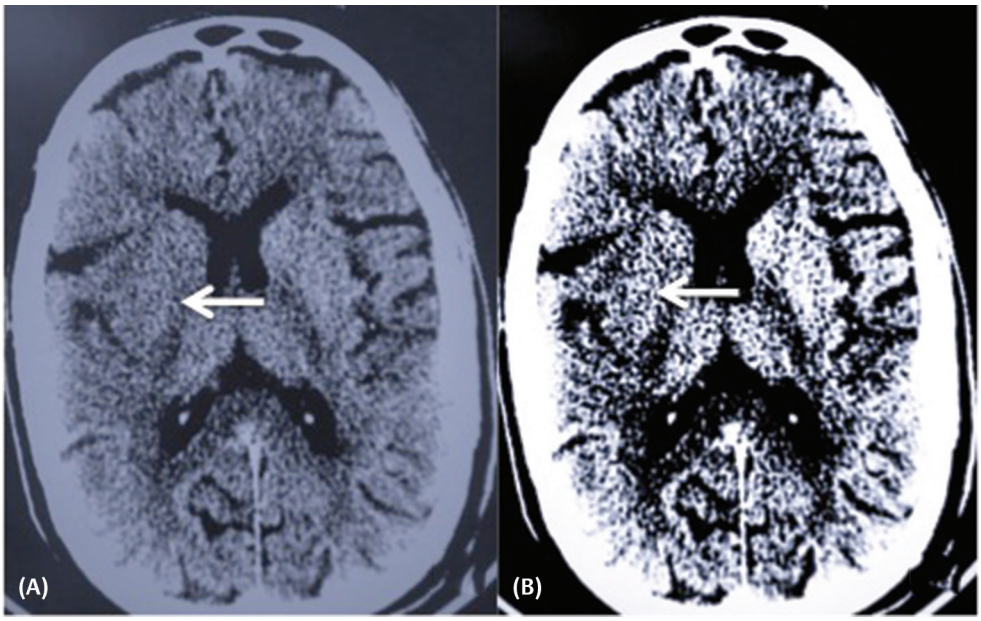

Fig. 4 Axial noncontrast computed tomography (CT) brain section at standard brain window (**A**) and narrow window width setting (**B**) with arrow indicating increased resolution of lentiform hypodensity in the latter settings.

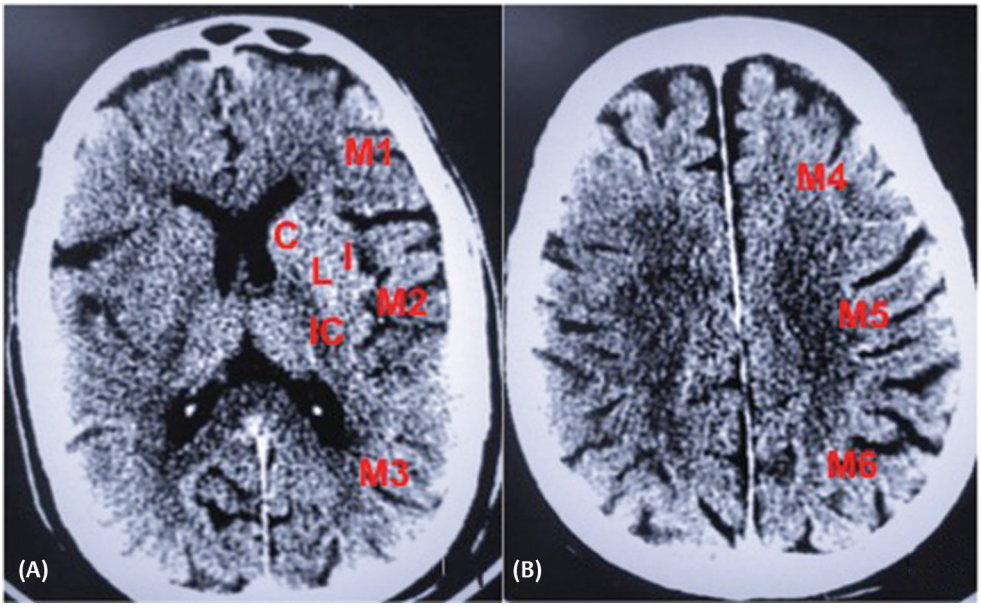

Fig. 5 Demonstration of Alberta stroke protocol early CT score (ASPECTS) at basal ganglionic (**A**) and supraganglionic (**B**) levels. C, caudate; I, insular cortex; IC, internal capsule; L, lentiform; M^{1-6} respective territorial supply of middle cerebral artery (MCA) territory.

whatever information it provides is currently reasonable for taking treatment decisions. Other pitfalls include artifacts in thin slice imaging, artifacts due to calcification especially in evaluation of the vessels, and radiation hazards.

CT Angiography

CT angiography (CTA) forms an essential part of stroke evaluation providing information regarding the presence, site, and size of the thrombotic occlusion. Volumetric acquisition of the arterial tree from the aortic arch to the vertex is performed when the iodine-based contrast is within the arterial system following "bolus chase" technique. It is quick and provides images with excellent spatial resolution, which can be viewed and reconstructed (►**Fig. 6**) in any plane.[16] Proximal large vessel occlusions (LVOs) respond poorly to intravenous tPA and are indications for endovascular methods. Distal occlusions with low clinical scores respond better to intravenous tPA showing early and better response with fewer number of hemorrhagic complications. CTA may also provide information on possible source of embolism, if any, and identifies tandem lesions. It provides a roadmap to intracranial access prior to thromobectomy.[17] Another potential advantage is the capability of assessing the collateral status distal to the vascular occlusion (►**Fig. 7**). Maintained good distal perfusion has been noted to be a marker for positive

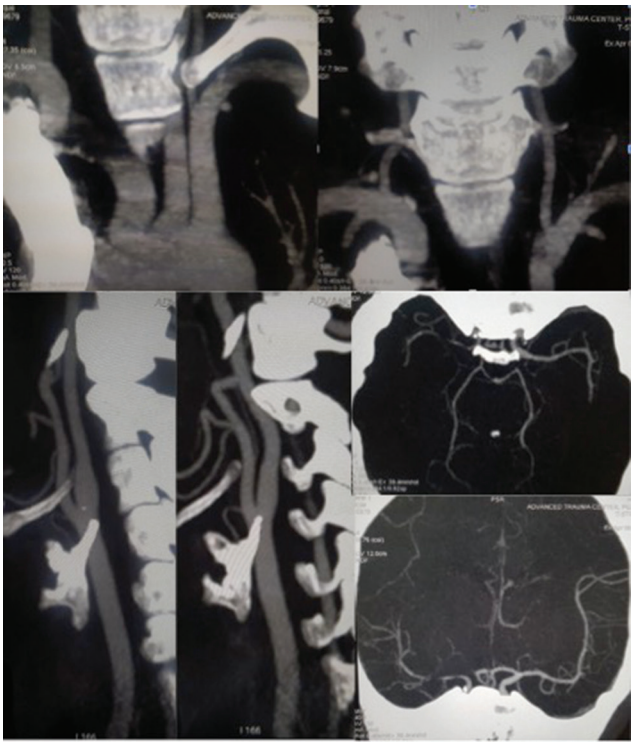

Fig. 6 Computed tomography (CT) angiography depiction of the entire cervicocranial arterial system during stroke evaluation. Note thrombus in the right middle cerebral artery (MCA).

clinical outcome.[18] Several collateral scoring systems are described, most of which classify the collaterals into poor, intermediate, and good grades. The overall essence is that the system should be easily classifiable and replicable having good interobserver agreement with accurate predictive outcomes. Single arterial phase imaging may not always be informative. Some workers have described multiphasic CTA acquisition (typically triphasic), which better brings out the distal vascular details due to opacification of the cortical branches in the delayed phase.[19] The first phase is acquired from the aortic arch to the skull vertex, whereas the subsequent two phases are acquired from the base skull to the vertex at an interval of 4 to 5 seconds each. We, at our institute, have modified the protocol to obtain first and third phase in a quest to reduce radiation dose, achieving reasonably good results. Another advantage of a multiphasic acquisition is the better delineation of intravascular thrombus and accurate measurement of its length and volume. A pseudothrombus can be distinguished from slow/static blood which tends to fill in the delayed phase (►**Fig. 8**). These parameters have been seen to correlate with reperfusion rates with intravenous tPA. Clot length of 8 mm has been described by a group of authors as the cut-off for successful recanalization of MCA occlusion with intravenous tPA.[20]

It has been seen in certain instances of internal carotid artery (ICA) terminus occlusion that slow blood flow in the cervical ICA gives the false impression of a long segment ICA "pseudo" occlusion as the contrast bolus in such cases is so much delayed that it does not reach the proximal cervical ICA in the arterial phase. Delayed phase CTA in such cases is beneficial.

CT Perfusion

CT perfusion (CTP), which initially formed an essential part of stroke imaging CT protocol, fell into disrepute due to its no significant proven role in stroke management, if the patient is in window period. Of late, however, CTP has again bounced back as a modality for demonstrating the salvageable brain tissue in select group of patients beyond the window period as highlighted in DAWN and DEFUSE 3 trials.[21,22] Data acquisition involves scanning the volume of interest (with the availability of multidetector CT scanners currently, the entire brain can be scanned) in either "helical shuttle mode" or "toggle mode" following injection of 40 to 50 mL intravenous iodine-based contrast agent at 5 mL/sec using 18 G intravenous access. CTP samples the first pass wash-in and wash-out of contrast bolus.[23] The data set is processed on the respective workstations to obtain the following maps: cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak. These parameters help one in

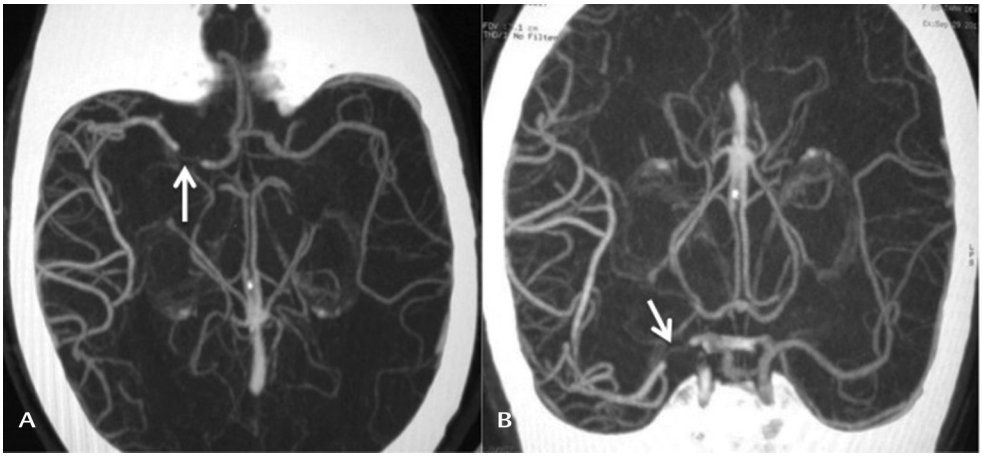

Fig. 7 Axial (**A**) and coronal (**B**) maximum intensity projection formats of computed tomography (CT) angiography demonstrating very good collateral score, depicted by complete opacification of middle cerebral artery (MCA) territory distal to the thrombus (arrow).

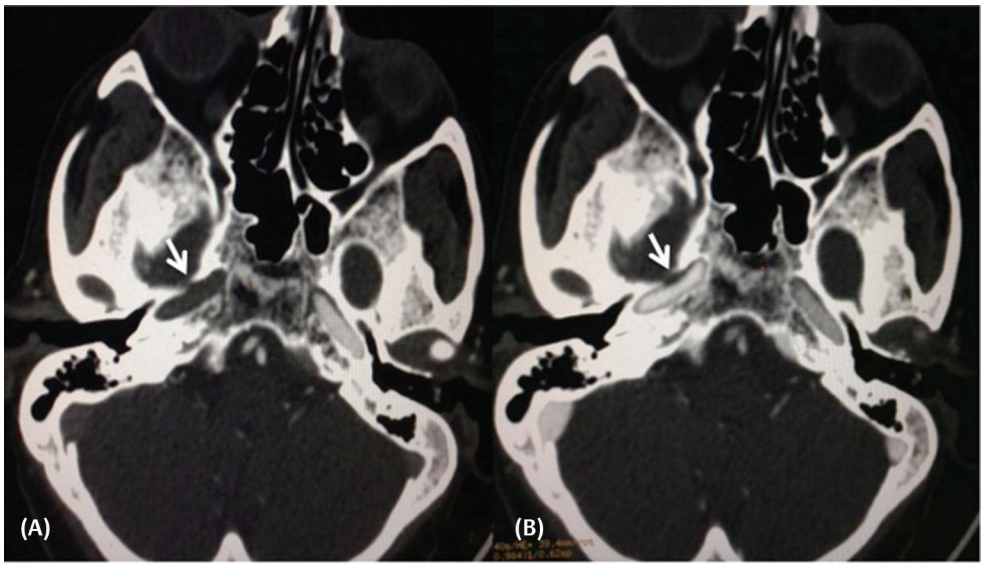

Fig. 8 Arterial (**A**) and venous (**B**) phase of biphasic computed tomography (CT) angiography demonstrating progressive opacification of the right petrous internal carotid artery (ICA) in the venous phase which was nonopacified in the arterial phase (arrow) signifying "pseudothrombus" and highlighting another use of multiphasic computed tomography (CT) angiography acquisition.

deciphering the extent of infarct core and the amount of salvageable tissue. Infarcted area (►**Fig. 9**) shows reduced CBF (< 40–50% of contralateral reference) and CBV with increased MTT (> 145% contralateral reference), while the salvageable penumbra has increased MTT, slightly reduced CBF but maintained or raised CBV. The penumbral hypothesis proposes that the higher is the mismatch between the volume of irreversible ischemia and the volume of hypoperfused but functional brain tissue, the more beneficial the revascularization would be.[24] CTP has also been used for predicting the incidence of hemorrhagic transformation in ischemic stroke and recognize stroke mimics.[17,25] The processing of CTP data sets is time consuming, potentially delaying the treatment. However, to reduce estimation times and increase objectivity for the estimation of volumes of infarcted and penumbral brain tissue, computer software are available which can automatically generate the various tissue volumes. One of these (RAPID) has been shown to significantly improve the patient care by giving accurate values.[26]

The other concerns with CTP are increased radiation dose to the patient, inaccuracies due to carotid stenosis, atrial fibrillation, or reduced cardiac output. Seizures and vasospasm may also give false positive results. Inspite of these, the benefits CTP offers far outscores its deficiencies in stroke patients presenting beyond the window period or in other scenarios where the onset is not clear, for example, wake-up strokes, etc.

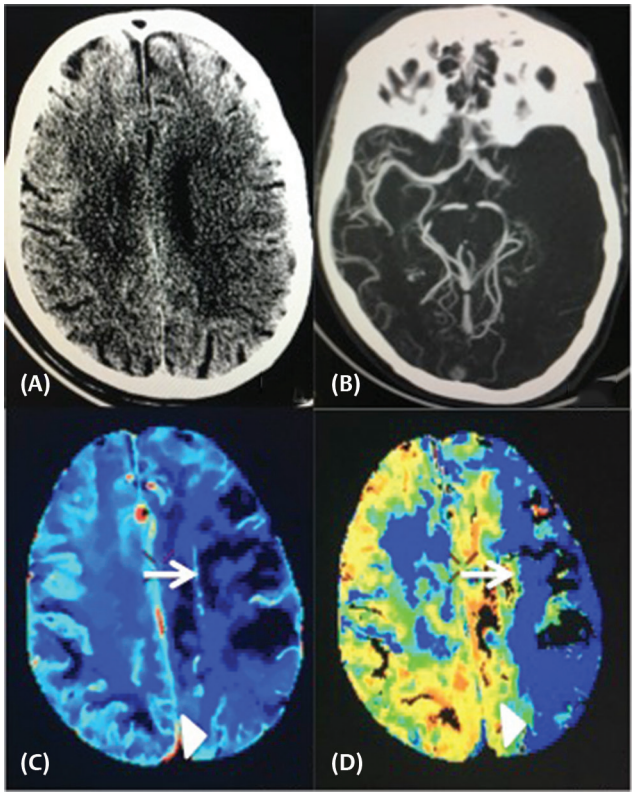

Fig. 9 Noncontrast computed tomography (CT) (**A**), axial maximum intensity projection (MIP) (**B**) CT angiography and subsequent CT perfusion-based cerebral blood volume (CBV, **A**) and mean transit time (MTT, **B**) maps demonstrating left middle cerebral artery (MCA) thrombus with a large infarct core (reduced CBV and prolonged MTT, arrow) and a small ischemic penumbra (maintained CBV but prolonged MTT) posterior to it (arrowhead).

Magnetic Resonance Imaging

MRI provides better soft tissue details than CT. However, its use is limited by scarce availability, long acquisition times, patient motion issues, and problems with metallic hardware that sometimes needs to accompanied with the patient especially in cases of acute stroke. The goals of imaging in acute stroke and the information to be sought, however, stay the same, irrespective of the modality being used, namely CT or MRI. The MR sequences employed for the purpose are T2-weighted, fluid-attenuated inversion recovery (FLAIR)-weighted, diffusion-weighted (DW), and

susceptibility-weighted (SW), perfusion-weighted images along with MR angiography (MRA). However, the entire protocol may take close to 20 to 25 minutes, which is contradictory to basic fundamental of stroke treatment—brevity and promptness. For addressing this issue, short protocols have been devised to reduce the acquisition times and to avoid delay in initiating treatments.[27] MR protocol with FLAIR, diffusion-weighted imaging (DWI), gradient recalled echo (GRE)/SW sequence, and MRA, which can be acquired in 6 to 7 minutes, is seen to provide reasonable information, on which the decision to intervene may be taken. Contrast perfusion may be added depending on the information required.

T2/FLAIR

T2/FLAIR sequences help in identification of early edema. FLAIR may detect subtle subarachnoid hemorrhage that may have been precluded on CT.

GRE/Susceptibility-Weighted Imaging

These sequences have a high sensitivity for identifying hemorrhages. Sometimes clinically silent bleeds and microhemorrhages are detected. In such cases, a dilemma arises whether to reperfuse or not. It has been seen that few bleeds do not negate reperfusion therapy. However, large bleeds may make the patient prone for large hematomas.[12]

DWI

DWI signal changes are determined based on the molecular motion of water. It should be interpreted in the context of apparent diffusion coefficient maps to rule out T2 "shine through" effect. It is the most reliable sequence for detecting cerebral ischemia and delineation of the infarct core. It can detect ischemia as early as 11 minutes after symptom onset.[28] Reversal of DW positive infarcts has been documented following reperfusion in few studies.[29] Large DW lesions have poor clinical outcomes. Some studies have identified 70 mL as the cut-off,[30] while others have found 25 mL as the threshold.[31] Contradictory reports are also available for increased incidence of hemorrhagic transformation following therapy in large sized DW lesions.[32,33]

MRA

MRA is useful for evaluating occlusions, stenosis, intraluminal clots, etc. Noncontrast time of flight method is often useful, though at times, it may falsely overestimate occlusions due to slow flow states.[34] Yet, it has proven to be of clinical benefit when MR is being used for stroke evaluation.[35]

MR Perfusion

MR perfusion (similar to CTP) is very useful for demonstrating potentially salvageable tissue. It can either be performed without contrast (arterial spin labeling [ASL]) or following gadolinium-based contrast (dynamic susceptibility contrast imaging [DSCI]). ASL, being based on water which is an endogenous contrast, may not provide accurate information on CBF.[36] DSCI is the technique of choice where MR protocol is being followed. The information, which it provides is akin to CTP. The DSCI parameters are used in conjunction with DWI to obtain a mismatch, which signifies salvageable penumbra.

Concept of DWI–FLAIR Mismatch

T2 signal on MRI progressively increases with passage of time following acute arterial occlusion on T2 FLAIR images in areas of DWI positive stroke. Immediately following acute stroke, the DW hyperintense ischemic lesion does not show any changes on FLAIR sequence. It was shown that this phenomenon best identifies the patients to be within 3-hour window in whom intravenous tPA should be recommended, who would favorably respond to perfusion.[37] This was labeled as DWI–FLAIR mismatch (►**Fig. 10**) and was initially interpreted as a sign of salvageable penumbra. It needs to be understood that it would be more appropriate to believe this parenchymal area to be a stable core based on the unstable core model.[38] In short, FLAIR negative stroke appears to be a reasonable indication for stroke therapy with reasonable results.

It is beyond doubt that the MR provides a wealth of information about acute ischemic stroke. The issue however is the appropriate utilization of the data and making it relevant to patient care immediately, which at this point is lacking. An example is the increased detection of hemorrhages not evident on CT, but inability of the investigators to

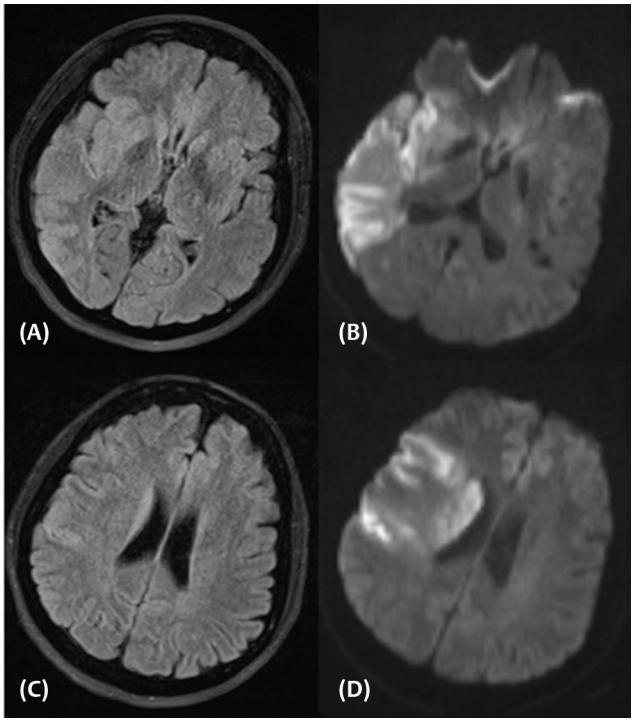

Fig. 10 Axial fluid-attenuated inversion recovery (FLAIR) weighted (**A**, **C**) and diffusion weighted (DW) (**B**, **D**) magnetic resonance imaging (MRI) images showing mismatch in the FLAIR and DW hyperintensities suggesting that the ischemic insult is within 3 to 4 hours and the patient can potentially benefit from reperfusion therapy. (FLAIR signal changes are not clearly seen while the diffusion changes are well appreciated.)

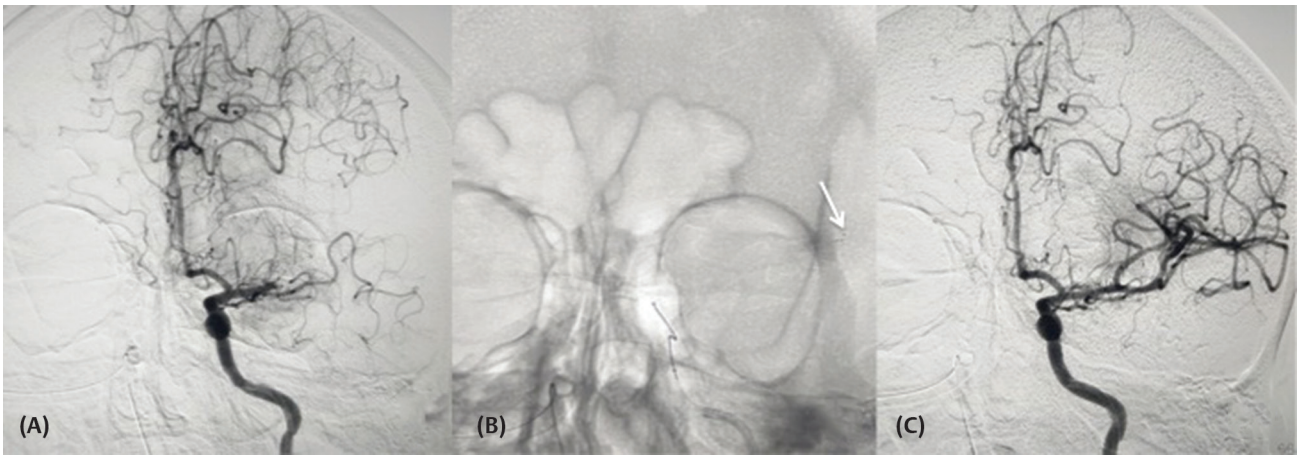

Fig. 11 Frontal digital subtraction angiography (DSA) (**A**, **C**) and radiography (**B**) image showing complete recanalization of middle cerebral artery (MCA) branches following mechanical thrombectomy using stentriever (arrow pointing to its distal aspect) in acute ischemic stroke due to MCA occlusion.

utilize this additional information.[39] It is therefore difficult to prove that increased sensitivity of MR to certain findings will translate to better clinical outcomes. The areas that MRI definitely scores, time constraints let aside, are in excluding stroke mimics, accurately identifying hemorrhages, and recognizing patients who, though rapidly improving, are likely to decline due to early recurrence, for example, in vascular stenosis. These patients may initially skip treatment, feigning improvement, on the contrary, my go down clinically in the ensuing few hours or days.[40]

CT versus MRI

This question has many perspectives to it. The main consideration in stroke imaging is to provide quick, prompt, accurate, and meaningful information with least adverse effects to the patient. One modality scores over the other in some aspects while it is versa on other fronts. CT is quick, easily available providing both qualitative and quantitative results. The two disadvantages are radiation exposure and use of iodinated contrast, which can be potentially renotoxic. MR can provide all these details with increased accuracies without radiation issues. It, however, tends to be a longer investigation (inviting motion artifacts), less easily available, expensive, and is contraindicated in patients with cardiac pacemakers, metallic prosthesis, and who are medically unstable. Practically, the choice is usually based on institutional preference, availability, and clinical information required.

Role of Catheter Digital Subtraction Angiography

Catheter digital subtraction angiography (DSA) still remains the gold standard; however, has practically fallen into disrepute due to the excellent information provided by noninvasive modalities of CT and MR. DSA, however, shows the vascular anatomy, vessel patency, and collateral supply exquisitely. The biggest benefit remains that of dynamic evaluation of blood flow in a particular arterial territory. Cerebral DSA is anyway done prior to attempting thrombectomy (►**Fig. 11**) for LVOs which can help one in confirming the vascular findings obtained previously by CT or MRI.

Conclusion

Last 5-year period has seen a paradigm shift in the management of acute ischemic stroke with literature showing tremendous results with mechanical thrombectomy in acute ischemic stroke-related LVOs. The primary aim of imaging is selection of potential candidates who are most likely to be benefitted with treatment. In resource poor setting, a plain CT is often enough in clinically appropriate patients prior to starting intravenous tPA. CT provides information regarding the presence and quantum of infarcts (ASPECTS). LVO needs to be established with CT/MRA for considering endovascular therapy. Patients presenting beyond the window period having low/borderline ASPECTS should undergo CT/MR perfusion to identify and quantify the salvageable penumbra. More studies are underway to decipher the intricacies of blood flow in the brain in attempt to increase the base for mechanical thrombectomy, which will benefit more number of patients.

Conflict of Interest
None declared.

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