

Imaging Modalities in Acute Ischemic Stroke

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As “time is brain”, acute ischemic stroke is considered a medical emergency. With the introduction of thrombolytic therapy and availability of modern neuroimaging modalities, timely diagnosis of an ischemic lesion, exclusion of intracerebral hemorrhage, assessing the degree of brain injury, and evaluation of cerebral vasculature is necessary in acute stroke management. Various neuroimaging techniques have been used in selecting patients and guiding reperfusion therapies in patients with acute ischemic stroke during the initial hours of symptom onset. In this review we will highlight the importance of available imaging modalities used to assess patients with acute ischemic stroke.

Keywords: acute ischemic stroke, magnetic resonance imaging (MRI), computed tomography (CT)

Background

Stroke is the fifth leading cause of death accounting for approximately one in every 20 deaths in the United States (1). It is also a major cause of severe long-term disability (2). Stroke is classically characterized as an acute neurological deficit attributed to a vascular cause (3). Up to 87% are ischemic with 10% being intracerebral hemorrhage (ICH) and 3% being subarachnoid hemorrhage (SAH) strokes (2). The aim of neuroimaging in acute stroke is to obtain rapid information on tissue and vessel status to aid acute stroke intervention.

With the introduction of intravenous thrombolytic therapy and availability of modern neuroimaging modalities, timely diagnosis of an ischemic lesion and determining its vascular location and extent has led to efficient management of acute ischemic stroke and improved stroke outcomes (4-8).

The standard imaging modality used in the initial diagnosis of stroke is a non-contrast computed tomography (CT) scan of the head. This modality helps determine a hemorrhagic versus ischemic stroke (9). Magnetic resonance imaging (MRI) may eventually be substituted for CT as these become more readily available. MRIs can rapidly detect early ischemic lesions and the “ischemic penumbra” (10). One of the diagnostic advances with MRI is the diffusion-weighted image (DWI) acquisition and apparent diffusion co-efficient (ADC) which allows early detection of an infarcted lesion (i.e., ischemic core) within minutes of a stroke (9).

In this review, we will highlight the various neuroimaging modalities currently available for diagnosing acute ischemic stroke and their utility in selecting patients for early reperfusion therapies, which has become a cornerstone of acute ischemic stroke intervention.

Ischemic Penumbra

Acute ischemic stroke is caused by an abrupt cessation of blood supply to the brain causing a decrease in cerebral blood flow (CBF). There exists a compensatory auto-regulatory mechanism in the brain parenchyma that maintains a constant cerebral blood flow during the initial periods of hypoperfusion (11). This autoregulation is via recruitment of collaterals and dilatation of smaller arterioles (11). This allows for maximal oxygen extraction by the hypoperfused tissues to maintain tissue oxygenation and cellular viability (11). However, when the CBF falls below a threshold of 20 to 23 mL/100 g tissue/min, neuronal function becomes impaired (11-14). Further drop in the CBF beyond this threshold leads to decrease in the cerebral perfusion pressure as the collaterals fail to provide tissue oxygenation, resulting in metabolic injury and tissue death (11-14). The membrane channels ultimately fail causing a net shift of water into the cells resulting in cytotoxic edema and irreversible damage to the neuronal cells (11-14). This zone of irreversible cell injury is referred to as the “ischemic core”. It is surrounded by a zone of tissue at risk of infarction referred to as the “ischemic penumbra” (14-16). The penumbra is potentially salvageable and is the target of various reperfusion strategies in the management of acute ischemic stroke.

With the development of functional imaging modalities, such as CT perfusion (CTP) and DWI/perfusion weighted MRI, salvageable tissue can be identified for timely reperfusion therapy (17).

Computed Tomography (CT)

Due to its widespread immediate availability, CT remains the most common and the first line imaging modality used in acute ischemic stroke (18). It is used to rule out hemorrhagic strokes (e.g., intracerebral hemorrhage (ICH)). By excluding ICH, patients presenting within the therapeutic window (3 to 4.5 hours from symptom onset) may be eligible for intravenous tissue plasminogen activator (tPA) (19).

CT may demonstrate subtle early signs of ischemia. An early finding on CT indicating cerebral ischemia is loss of gray-white matter differentiation (Figure 1), which occurs from the increasing water concentration from ion pump failure (i.e., cytotoxic edema) (20, 21). It may be detected in the region of basal ganglia (i.e., lenticular obscuration) or insular cortex (i.e., insular ribbon sign) (22, 23). However, the inter-rater agreement in recognizing these CT findings is variable (24-29). These findings are also time dependent. They appear in $\leq 67\%$ in patients imaged within 3 hours but increase to 82% at 6 hours (24-29). To improve the detection rates and inter-rater reliability, the Alberta stroke program early CT score (ASPECTS) was developed to assess early ischemic changes (3 hours from stroke onset) in patients with acute ischemic stroke of the anterior circulation (30, 31). It is a simple rating scale which divides the affected middle cerebral artery into ten segments: internal capsule, caudate nucleus, lentiform nucleus, insula, and six segments for cortical areas. One point is deducted for each area showing early ischemic changes. A score of 10 reflects a normal CT scan. A score of 0 indicates diffuse ischemic involvement throughout the complete middle cerebral artery (MCA) territory (30).

CT head may also show evidence of a thrombus within an artery, seen as an increased density in the transverse M1 segment (i.e., hyperdense MCA sign) (Figure 2) or in cross-section within the Sylvian fissure or basilar artery (i.e., dot sign) (32). This indicates vessel occlusion with a high specificity but moderate sensitivity of 30-40% (33). The appearance of this early sign of

acute ischemic stroke may be associated with worse prognosis and an increased risk of thrombolysis-associated hemorrhage (34). It is a predictor of early neurological deterioration with a positive predictive value of 91% (35, 36).

Ischemic strokes with hemorrhagic transformation are classified as either hemorrhagic infarction (HI) or parenchymal hematoma (PH). The hemorrhagic transformed strokes are then classified as HI1 (small petechiae), HI2 (more confluent petechiae), PH1 (<30% of infarcted area with some mild space-occupying effect), and PH2 (> 30% of the infarcted area with significant space-occupying effect) (37).

Disadvantages:

Although CT helps in excluding ICH, it cannot reliably differentiate between irreversibly damaged brain tissue (i.e., infarct core) and viable brain tissue (i.e., ischemic penumbra). Thus, it may be limited in selecting patients for various reperfusion therapies with an indeterminate time of symptom onset. It is also relatively insensitive in detecting acute and/or small cortical or subcortical infarctions, especially in the posterior fossa (38).

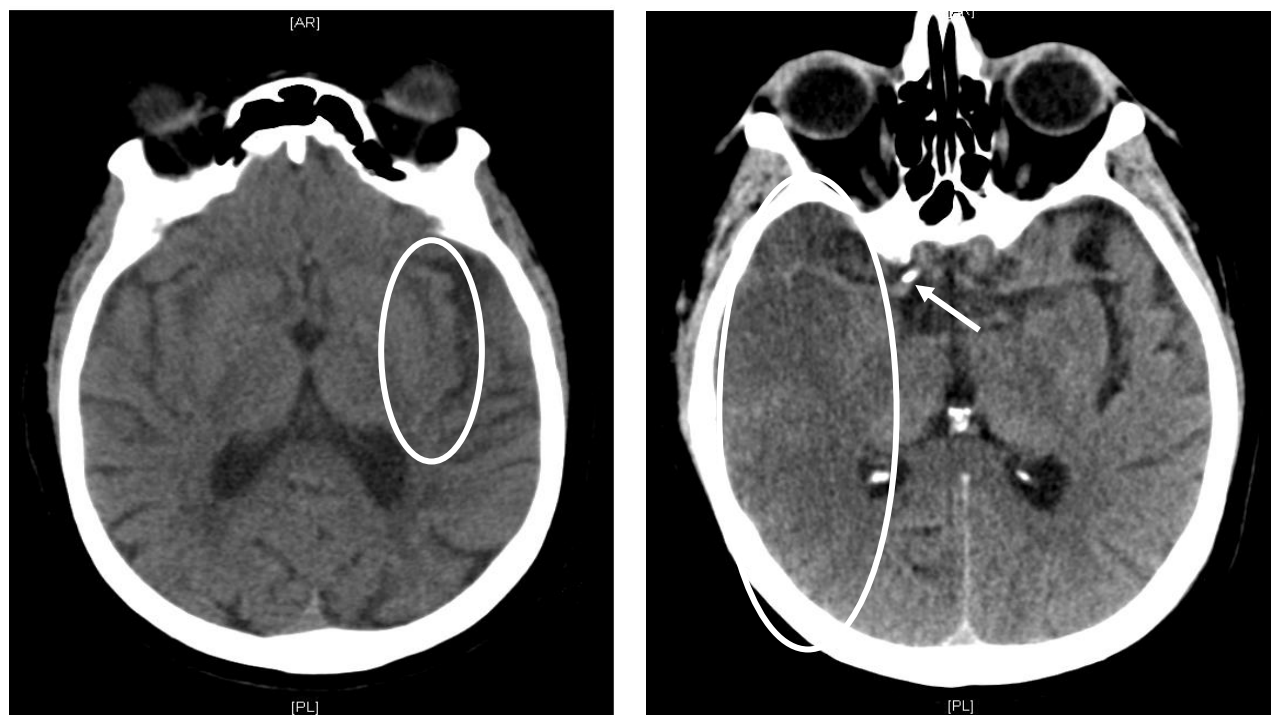


Figure 1 (left). Axial computed tomography. Loss of gray-white matter differentiation in the left insular region is seen on the left (circle). **Figure 2 (right).** Axial computed tomography. Evolving stroke is seen in the right middle cerebral artery (MCA) territory (circle). Hyperdense MCA sign is seen on the right MCA (arrow).

CT Angiography (CTA) and CT Perfusion (CTP) Imaging

An important component of CT imaging protocol in the treatment of acute ischemic stroke is CT angiography (CTA), and at some centers CT perfusion (CTP) techniques. By allowing imaging of the intracranial vasculature, it can help identify the exact location and extent of vascular occlusion.

CT Angiography (CTA)

CTA is a relatively rapid technique making it ideal in acute stroke management. It is a thin-section volumetric spiral (i.e., helical) technique following a time-optimized bolus of iodinated contrast medium to enhance visualization of the extra- and intra-cerebral circulations (39). The availability of new multidetector row CT technology and fast speed of acquisition of reformatted angiographic images has allowed visualization with high spatial resolution (39). It is useful in visualization of vessels from the aortic arch through the Circle of Willis within seconds (40). The sensitivity and specificity of CTA for the detection of intracranial occlusions is high ranging 92-100% and 82-100%, respectively (41-44) (Figure 3). CTA is also sensitive and specific for imaging the extra-cranial vasculature as compared to carotid ultrasound in differentiating carotid occlusion from a very high grade stenosis (i.e., string sign) (45).

Disadvantages:

CTA requires the use of intravenous iodinated contrast medium, thus limiting its use in patients with contrast allergies and abnormal renal function.



Figure 3. Axial computed tomography angiography (CTA). Occlusion of the right terminal internal carotid artery/proximal middle cerebral artery (MCA) is shown (arrow). Note the relative paucity of contrast filling vessels in the right MCA territory (circle) compared the left. This may indicate poor collateral circulation.

CT Perfusion (CTP)

CTP is a functional brain imaging modality which requires the administration of an intravenous bolus of an iodinated contrast agent. This technique allows perfusion imaging of the brain parenchyma and is useful in differentiating infarct from ischemic penumbra (46). CTP can reliably predict and identify ischemic penumbra and the irreversible ischemic core in patients with acute ischemic stroke within a few minutes on admission with a sensitivity and specificity of > 90% (47). This is achieved by measuring the following parameters: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) (Table 1).

Table 1. CT/MRI Perfusion Imaging Parameters in Acute Ischemic Infarct

	Ischemic penumbra	Infarct core
MTT and TTP	Increased	Increased (threshold of 145%)
CBV	Normal to increased	Decreased
CBF	Decreased (< 50% reduction)	Decreased (> 60% reduction)

MTT = mean transit time; TTP = time to peak. Cerebral blood volume (CBV) is the total volume of blood in a given unit of brain volume (normal = 4-5 mL/100 g). Cerebral blood flow (CBF) is the volume of blood moving through a given unit of brain volume per unit time (normal range in grey matter = 50-60 mL/100 g/min). Mean transit time (MTT) is the time difference between the arterial inflow and venous outflow (normal = 4 secs in grey matter). Time to Peak Enhancement (TTP) is the time from the beginning of contrast material injection to the maximum concentration of contrast material within a region of interest (ROI). The relationship between CBF and CBV is expressed by the equation $CBF=CBV/MTT$.

CBF is defined as the volume of blood flowing per 100g of brain mass per minute (48, 49). It is expressed as $CBF=CBV/MTT$ (48, 49). Prolonged MTT together with CBF-CBV mismatch is the most sensitive measure in detecting the tissue at risk of infarction. A decrease in total CBV is the most specific indicator of the ischemic core (50, 51). Typically, in patients with acute ischemic stroke, CBF and CBV are low in the infarct core; whereas a decrease in CBF with a normal or increased CBV along with a prolonged MTT is seen in the ischemic penumbra (52, 53) (Figure 4).

The ability of CTP to identify the penumbra makes it useful in treatment decisions in patients with indeterminate times of stroke onset or in cases of wake-up strokes (54). These patients may benefit from various reperfusion strategies. Figure 5 is an example of a right MCA occlusion seen on digital subtraction angiography (A) with recanalization of the superior division of the MCA (B). Any patient with a stroke (i.e., an acute neurological change within the past 24 hours) should be evaluated at a stroke center. At most stroke centers, a multimodal CT stroke protocol including CT head, CTP, and CTA is used. CTP imaging has the advantage of being performed during the same setting as CTA.

Disadvantages:

CTP requires repeated scanning of the same portion of the brain parenchyma until the contrast agent passes through the entire cerebral vasculature and produces a greater amount of radiation

exposure. It also requires a multi-detector CT and a trained technician to set up the special software package and equipment. This limits its widespread availability. Use of a 2nd bolus of iodinated contrast agent (after CTA) can predispose patients with renal insufficiency to contrast-induced nephropathy.

CT, CTA, and CTP all have the disadvantage of radiation exposure.

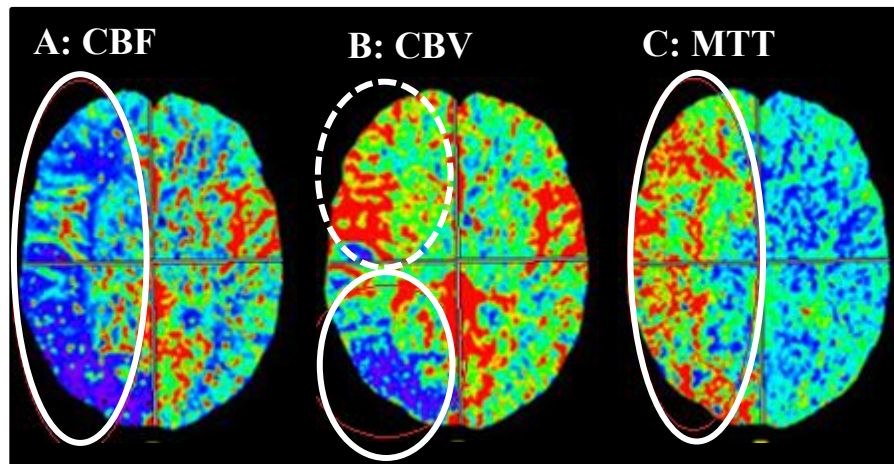


Figure 4. Computed tomography perfusion. A) Cerebral blood flow (CBF) showing decreased (circle) area of flow. B) Cerebral blood volume (CBV) showing area of decreased volume (solid circle) indicating core infarct with surrounding area of normal/increased CBV consistent with area of penumbra (dotted circle). C) Mean transit time (MTT) showing area of increased transit.

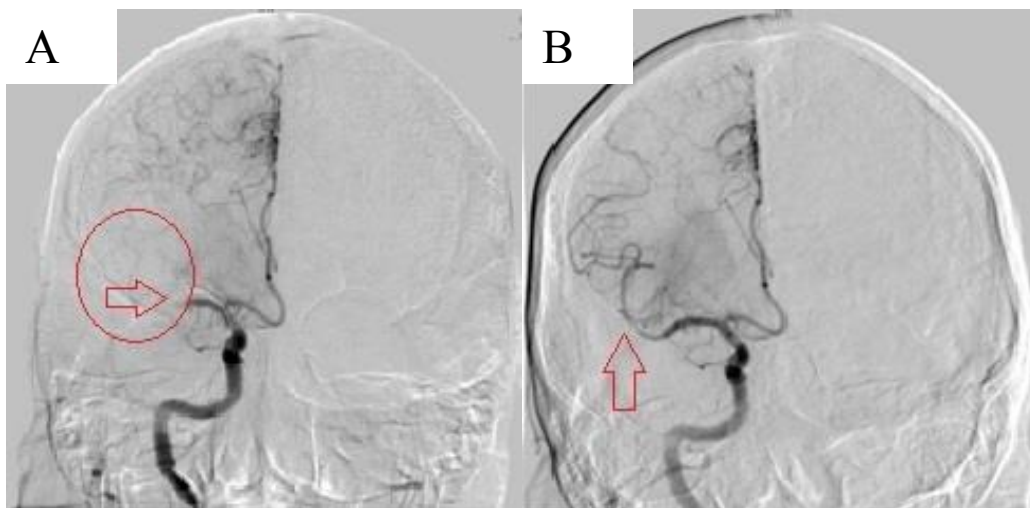


Figure 5. Cerebral angiography. A) Acute occlusion of the right middle cerebral artery (MCA) is seen (arrow) with paucity of distal flow (circle). B) Restoration of flow in the superior division (arrow) after endovascular thrombectomy using stent retriever.

Magnetic Resonance Imaging (MRI)

Brain magnetic resonance imaging (MRI) imaging protocols for acute ischemic stroke include T1- and T2-weighted sequences, fluid attenuated inversion recovery (FLAIR) sequence, perfusion-weighted imaging (PWI), and DWI with corresponding ADC maps (46). These sequences can confirm the diagnosis of ischemia and guide the selection of patients for IV-tPA and other reperfusion strategies (46).

Conventional brain MRI sequences are not sensitive for detecting cytotoxic edema in the acute phase, whereas T1 and T2 weighted images can detect vasogenic edema and can help in differentiating acute versus subacute stroke (55-57). T2-weighted and FLAIR images can detect acute ischemic tissue within 3-8 hours after stroke onset, seen as hyperintense signals, with loss of grey-white matter differentiation and sulcal effacement similar to that seen with CT (55-57). FLAIR sequences are also useful in detecting subarachnoid hemorrhages (seen as bright signal) by suppressing the CSF signal (dark), as compared to T1 and T2 weighted images.

The gradient recalled echo (GRE) or susceptibility weighted image (SWI) sequences of MRI are more sensitive for detection of blood products and chronic hemorrhages, particularly chronic microbleeds, due to the paramagnetic effect of the hemosiderin. (58). These are seen as “blooming” effects and black on GRE images. They are used to assess the burden of underlying chronic vascular disease in stroke patients (59).

In comparison to T2 weighted and FLAIR sequences, DWI is the most sensitive (88-90%) and specific (95-100%) imaging technique for detecting acute ischemic change (60-64). Changes can be seen within a few minutes of symptom onset (60-64). Acquisition is based on the ability of diffusion weighted MRI to quantify motion of water molecules accumulated intracellularly in the injured neurons relative to extracellular space. This allows identification of ischemic cells on the DWI images which appear bright (46, 65). This should always be correlated with the ADC maps. Therefore, an increased signal on DWI (hyperintense) together with a decreased signal on ADC map represents an area of brain infarction (Figure 6). This sequence complement is known as restricted diffusion. DWI and ADC maps together with T2-weighted images and FLAIR sequences can be used to distinguish acute lesions from subacute or older infarcts (66, 67). In general, lesions appearing hypointense on ADC map are usually < 7-10 days old whereas lesions seen as isointense or hyperintense are more likely > 7-10 days old (66, 67). Lesions on DWI can also be used to identify stroke etiology. For example, isolated lenticulostriate lesion points to lacunar infarct whereas multiple lesions in different vascular territories suggest a cardioembolic source. Large artery atherosclerosis can manifest as scattered lesions within one vascular territory (6).

Perfusion-Weighted Imaging (PWI)

The combination of DWI and PWI is commonly used in clinical practice to evaluate the extent of irreversible tissue damage and to identify ischemic penumbra (68, 69). DWI along with ADC can identify tissue with permanent damage, whereas areas without signal change on DWI-ADC, but abnormal signal on PWI, represent salvageable tissue at risk (68,69). This area is the ischemic penumbra. A mismatch is considered significant if the penumbra is at least 20% of the ischemic core volume (70). The mismatch pattern is found in about 70% of all patients with anterior circulation stroke within 6 hours of onset, and may represent an indication for reperfusion treatment (69).

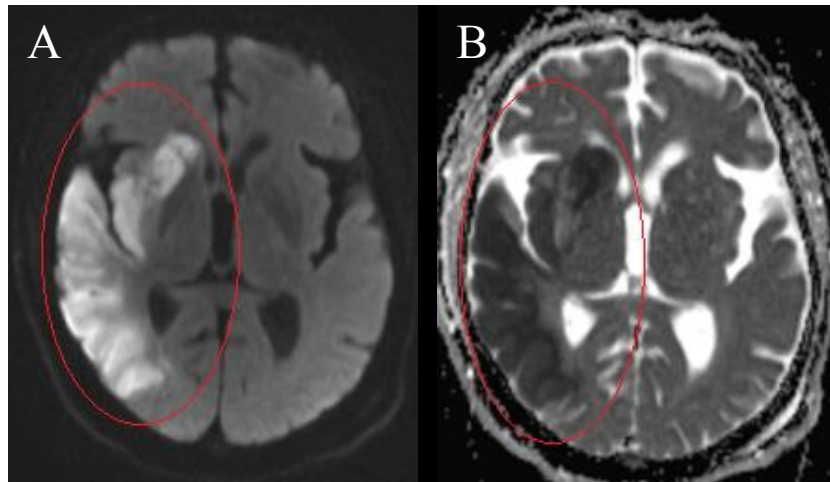


Figure 6. Magnetic resonance imaging (MRI) diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC). A) DWI showing area of hyperintensity in the right middle cerebral artery (MCA) distribution (circle). B) ADC showing hypointensity in the same MCA distribution (circle). The combination of DWI hyperintensity and ADC hypointensity is known as restricted diffusion.

Magnetic resonance perfusion (MRP) parameters are similar to the ones seen on CTP (Table 1). However, these are more difficult to quantify as compared to CTP. Time to peak (TTP) and MTT are preferred for identifying hypoperfused tissue and cerebral brain perfusion; MTT and CBF denote ischemic penumbra and can predict the final infarct volume in absence of reperfusion (70, 71). In contrast to the CTP, there is availability of contrast-induced PWI technique which incorporates the use of gadolinium based contrast through the cerebral vasculature and measures various perfusion parameters but with lesser accuracy as compared to CTP.

MRP, as compared to CTP, has the advantage of imaging the entire brain parenchyma. MRP is more precise in predicting the tissue at risk and hence the final infarct volume and does not carry the hazard of radiation exposure or exposure to contrast agents as with CT perfusion protocol.

MR Angiography (MRA)

Magnetic resonance angiography (MRA) is a noninvasive technique used to evaluate extracranial and intracranial vessels and to identify the site of vascular occlusion or stenosis in patients with ischemic stroke (72). Several MRA techniques have been developed to image intra- and extra-cerebral vessels. They include 2-dimensional time-of-flight (TOF), 3-dimensional TOF, multiple overlapping thin-slab acquisition (MOTSA), and contrast enhanced MRA (CE-MRA) (73).

Intracranial MRA has a sensitivity of 60-85% for stenosis and 80-90% for occlusions compared with CTA or digital subtraction angiography (DSA) (74). As compared to CTA, it can avoid the use of contrasted agents. In some cases, it overestimates the degree of vessel stenosis and motion artifacts as it is based on time of flight of blood flow.

Similarly, CE-MRA is more accurate with a greater sensitivity and specificity (95% and 90% respectively) than Doppler ultrasound for detecting extracranial vessel morphology, including carotid artery occlusions, stenosis, or dissections (75). As with MRI, it cannot be used in patients with pacemakers, metallic implants, and contraindications to MR contrast agents. Its use is limited in patients with severe claustrophobia. It also poses a significant risk of inducing

nephrogenic interstitial fibrosis, secondary to use of gadolinium contrast agents in patients with renal dysfunction.

Conclusion

With the introduction of thrombolytic therapy in the treatment of acute ischemic stroke and a narrow therapeutic window (up to 4.5 hours from symptom onset in select patients), timely diagnosis is essential. CT imaging is required in the evaluation of acute stroke as it is quick and readily available. Several MRI modalities like DWI and ADC mapping are now being studied in the acute ischemic stroke diagnosis and management. Evaluation of cerebral vasculature in patients with ischemic stroke is important for endovascular therapy consideration. It is important to remember when considering an imaging modality that time is brain.

Notes

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