"DIFFUSION-WEIGHTED MR IMAGING VERSUS CT BRAIN – DIAGNOSTIC ACCURACY IN HYPERACUTE STROKE"

by

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under the guidance of

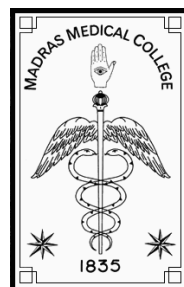## Prof. T.S. SWAMINATHAN

Professor Emeritus, The Tamilnadu Dr. M.G.R. Medical University

for the partial fulfillment of award of degree of Doctor of Philosophy (Ph.D)

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This is to certify that the work contained in this thesis "**DIFFUSION - WEIGHTED MR IMAGING VERSUS CT BRAIN – DIAGNOSTIC ACCURACY IN HYPERACUTE STROKE**" is a bonafide and genuine research work done by **Dr. I. GURUBHARATH** in the Department of Radiology, Madras Medical College, Chennai, under my guidance and is to my satisfaction during 2012-2015 in partial fulfillment of the requirement of **THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY** regulations for the award of the **degree of Doctor of Philosophy (Ph.D.)**. The thesis had not previously formed the basis for the award to the above candidate of any Degree, Diploma, associateship, Fellowship or other similar title.

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DECLARATION

I, Dr. I. Gurubharath hereby declare that I have actually carried out the project "**DIFFUSION-WEIGHTED MR IMAGING VERSUS CT BRAIN – DIAGNOSTIC ACCURACY IN HYPERACUTE STROKE"** independently under supervision and guidance in this institute.

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ABSTRACT

"DIFFUSION-WEIGHTED MR IMAGING VERSUS CT BRAIN – DIAGNOSTIC ACCURACY IN HYPERACUTE STROKE."

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Purpose:

To compare the diagnostic accuracy of non-enhanced computed tomography (NECT) and Diffusion-weighted magnetic resonance imaging (DW MRI) in a consecutive series of patients at presentation to the radiology department with symptoms of hyperacute stroke and aiding the clinicians in instituting the treatment protocol at the earliest.

Materials and Methods:

Clinical data, NECT and DW MRI and conventional MR images obtained in 200 consecutive patients with suspected hyperacute stroke were examined. Results of the diffusion-weighted imaging and NECT were compared with each other and correlated with the final discharge diagnosis.

Results:

Of the 200 patients with symptoms and signs of stroke within the hyperacute stroke window period, diffusion-weighted images indicated stroke in 180 patients. Diffusion-weighted images were negative in 20 patients. The 20 patients with negative DWI were diagnosed with stroke mimics. Of the 200 patients, NECT was positive in 99 patients with imaging features of early infarction signs. Statistical reviews yielded 96.7% sensitivity (95% CI, 92.8%-98.7%) and 90% Specificity (95% CI, 68.3%- 98.7%) for diffusion-weighted MR imaging and NECT had a sensitivity and specificity of 88% (95% CI, 80.9%- 94,3%) and 63.5% (95% CI, 37%-71,5%) respectively. The DWMRI had a higher accuracy rate of 96% (95% CI, 92.3%, 98.2%) than with 50.5% in NECT (95%CI 43.3%, 57.6%).

Conclusion:

DWMRI is replacing NECT in the imaging of hyperacute stroke patients. DWI and NECT imaging done with the same delay after onset of symptoms of hyperacute stroke resulted in significant differences in diagnostic accuracy. The study concludes with higher accuracy rate of diffusion-weighted MR imaging in diagnosing hyperacute stroke than NECT. The size of the lesion measured by DWI scans and apparent diffusion coefficient (ADC) values are potential imaging parameters for predicting the clinical outcome in hyperacute stroke patients. Our study supports the inclusion of DWMRI in the routine imaging protocol for diagnosing hyperacute stroke and thus aiding the clinicians in deciding the treatment protocols at the earliest.

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Introduction

INTRODUCTION

The specialty of Radiology has become an integral part of evidence-based medicine and decision-making. Also advancing trends in medicine puts emphasis on radiology for initial diagnosis, follow-up and increasingly the treatment of the patients. With the invention of CT and MRI scanners the field of radiology has achieved tremendous leap in the field of medicine.

Stroke is one of the important causes of premature death and disability in India. The survivors of stroke continue to live with neurological deficits and the costs of rehabilitation and care plays a major factor in the management of stroke. [1, 2]

Stroke is the third leading cause of death with important economical and social implications .The World Health Organization defined stroke as a "Neurological Deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours." Transient ischemic attack falls under the 24 hours time frame.

TYPES OF STROKE

Ischemic Stroke

The vascular supply to part of the brain is reduced which results in dysfunction of the brain tissues in that area. Ischemic stroke accounts for 85%

of stroke. The common causes for ischemic stroke include large artery atherosclerosis, thrombosis, embolism, small vessel occlusion, systemic hypoperfusion, and cryptogenic stroke without obvious explanation.

Hemorrhagic Stroke

This type of stroke, which accounts for 15 to 20 % of stroke, includes intraparenchymal and subarachnoid hemorrhage.

Clinical Features of Stroke

Stroke can present as abruptly as any of the following: hemiparesis with or with out sensory deficits, visual field loss, dysarthria, ataxia, facial droop, visual field deficits, monocular visual loss and in combination with other symptoms.

Stroke Mimics

The clinical stroke mimics generally falls in to two categories namely non- ischemic lesions and vasogenic edema syndromes which mimics like acute infarction. Non-ischemic syndromes include peripheral vertigo, migraines, seizures, functional disorders, metabolic disorders, dementia and amyloid angiopathy. Vasogenic edema syndromes include posterior leucoencephalopathies, eclampsia, HIV encephalopathy, and hypertensive encephalopathy.

The National clinical guidelines for stroke from the Royal College of Physicians firmly recommend neuroimaging for all patients with clinical symptoms of stroke. Within 24 hours of the stroke event, appropriate and early neuroimaging is essential for patient care and has proved to be cost effective. [3]

Stroke refers to neurological insult of vascular origin which consists of either a parenchymal injury, transient or permanent and a vascular lesion.

Infarctions according to the time course may be classified as hyperacute stroke, which is less than 6 hours from the time of symptom onset, acute stroke which ranges from 4 hours to 4 days, subacute stroke which ranges from 4 days to 3 weeks and chronic stroke which ranges from 3 weeks to 3 months.

Cerebral ischemia is one of the leading causes of the acute onset of severe neurological symptoms in stroke patients. Fibrinolysis is an accepted treatment of cerebrovascular insult during the first three hours after onset of symptoms and up to six hours in selected patients. The initial hours of stroke are the most critical period in order to salvage the brain tissue. Thus, morphologic details related to early treatment decisions, such as the exact volume and size of the infarction, can be crucial.

Hence accurate diagnosis at the earliest is needed in order to decide the treatment in these patients. NECT is the most commonly used modality to exclude cerebral hemorrhage. Diffusion-weighted MR imaging is very sensitive

and relatively specific in detecting hyperacute/acute ischemic stroke. The findings of DWI have demonstrated high levels of diagnostic accuracy. In this study, we prospectively compared NECT and diffusion-weighted MR imaging in hyperacute stroke patients. NECT scan was first done in all the patients in order to exclude the intracerebral hemorrhage.

Regardless of the cause, adenosine triphosphate (ATP) gets rapidly depleted in neuronal ischemia, which leads to failure of the membrane-bound, ATP-dependent ionic channels responsible for neuronal resting membrane potentials and the generation of action potentials. An intracellular gradient is created due to the accumulation of intracellular ions, including calcium ions and leads to intracellular accumulation of water causing cytotoxic edema.

The endothelial cells of the brain are more resistant to ischemia than neuroglial cells and neurons. The integrity of blood-brain barrier becomes compromised approximately 3-4 hours after the onset of ischemia and plasma proteins can pass into the extracellular space. The reperfusion occurs when there is passage of intravascular water. This process begins six hours after the onset of stroke and reaches a peak 2-4 days after the onset of stroke. Hemorrhagic transformation of the infarct may be accompanied with reperfusion, which is usually related to the site and volume of the infarct, and occurs more commonly in large cortical infarcts.

Signal changes in MRI scans, due to ischemic stroke follow the vascular distribution of the narrowed blood vessel, which is indicative of cerebrovascular disease and helps in differentiating it from other disease entities.

The primary neuroimaging modality used for the assessment of stroke is with computed tomography (CT) although its primary role is to exclude stroke of hemorrhagic type, the other principal role includes assessment of various types of vascular abnormality. CT of hyperacute ischemic stroke will typically appear normal in the first few hours of stroke onset. [4, 5, 6, 7, 8]

CT is highly sensitive to acute hemorrhagic stroke. Diffusion-weighted magnetic resonance imaging (DW MRI) shows far greater contrast and is superior in demonstrating the ischemic tissue within minutes of cerebral ischemia/infarction and has a reported sensitivity and specificity of 88-100 and 86 to 100 percent respectively. [9, 10, 11, 12, 13]

Diffusion-weighted images show higher interobserver and intraobserver reproducibility than CT. [14]

The treatment strategy in ischemic stroke is to salvage the ischemic tissue and aiming to restore functionality and morphological recovery. The timely diagnosis of hyperacute/acute cerebral ischemia is critical with therapeutic interventions in the form of thrombolysis, which is the mainstay of reperfusion

therapy. Neuroimaging plays a critical role in identifying the appropriate candidates for reperfusion therapy. [15, 16]

Clinical assessment to diagnose ischemic stroke or hemorrhagic stroke is mostly insufficient and further mandates the need for appropriate neuroimaging modalities like MRI and CT.

The primary event in ischemic stroke is an acute vascular occlusion usually in the form of thrombosis or as an embolus. The incidence of hemorrhagic stroke is probably less than ischemic stroke and accounts for up to 15%. The most critical factor in ischemic stroke is the cerebral blood flow (CBF) as the brain needs continuous supply of nutrients. [17] The lack of sufficient cerebral blood flow to perfuse the brain tissue results in insufficient oxygen and glucose delivery to support cellular homeostasis.

Normal cerebral blood flow ranges from 50-60ml / 100g/min. When there is a fall in the cerebral blood flow volume to less than 50% the consequent events lead to cessation of synaptic transmission. When the cerebral blood flow falls more rapidly further leading to neuronal death. [18]

Thrombolysis as an initial treatment of stroke dates back to the 1950s. Three studies during that time utilized intravenous streptokinase as thrombolytic agents, and due to increased mortality and hemorrhagic complications the study was stopped. [19, 20, 21, 22]

Further studies using tissue plasminogen activator (tPa) like the ECASS (European Cooperative Acute Stroke Study) and NINDS (National Institute of Neurological Disorders and Stroke) demonstrated both safety and efficacy in a sub-group of patients. [22, 23]

The study conducted by ECASS II and the ATLANTIS (Alteplase thrombolysis for acute non-interventional therapy in ischemic stroke) demonstrated failed therapeutic benefits of intravenous tPA administered more than 4 hours after onset of symptoms. [24]

In the present day intravenous tPA is the treatment of choice for hyper acute ischemic stroke presenting within 3.5 to 6 hours of stroke symptoms onset, excluding hemorrhagic stroke.

Noncontrast computed tomography (NCCT) is the widely used imaging modality to evaluate patients presenting with stroke symptoms and signs. The main advantages of CT scan are its availability, cost effectiveness and its ability to identify hemorrhage. The early changes of ischemia include hypo density of brain parenchyma and cerebral edema as a result of increase in intra and extra cellular water. [25]

The potential advantage of CT is its widespread availability in many hospitals 24 hours a day. The sensitivity of CT during the first six hours of

cerebral ischemia was 64% in the ECASS reading panel with an accuracy of 67%.

The important NECT finding of early brain ischemia includes mass effect, hypo attenuation of grey matter structures, and presence of one or more hyperattenuating arteries. The CT finding of hypodense gray matter becoming isodense to adjacent white matter, represents the blurring of grey-white matter junction. The insular ribbon sign is a typical example of blurring of grey-white matter. Another example of blurring of grey-white matter junction is the hypo attenuation of the basal ganglia, which becomes isodense to the adjacent white matter structures like the internal capsule.

CT demonstration of mass effect includes the narrowing of Sylvian fissures primarily in MCA infarction.

Hyperdensity of arteries can be seen in any cerebral vessel but most frequently seen in MCA thrombosis. Hyperdensity of the arteries is primarily a result of stasis of flow due to arterial thrombus. [26]

Cortical sulcal effacement i.e. loss of precise delineation of the gray-white matter interface in the margins of the cortical sulci which is primarily due to localized mass effect.

Obscuration of lentiform nucleus, which presents as decreased attenuation of the lentiform nucleus and loss of the delineation of lentiform nucleus.

These changes may not be present early after onset of ischemia or may be subtle to be identified by the radiologist. In the early days before the advent of diffusion-weighted imaging, non-enhanced CT has been the primary neuroimaging modality for early stroke assessment, but it may not be sensitive or accurate enough in order for reliable detection of hyperacute stroke.

During the subacute phase of stroke, the attenuation value of the infarcted tissue decreases further, mass effect increases and these changes will be seen involving the grey and white matter.

During the subacute phase of stroke, the attenuation value of the infarcted tissue approaches to that of surrounding normal brain thereby masking the infarct, which is known as the fogging phenomenon. This fogging effect is attributable to reopening of capillaries in the region with resultant hyperemia. [27]

False positive areas of hypodensities can be seen due to beam hardening artifacts in the posterior fossa due to the skull base. Various lesions may produce focal areas of hypodensity with or without mass effect, including encephalitis, perivascular spaces, and infiltrative tumors with vasogenic edema.

Contrast Enhanced CT

Contrast enhancement following cerebral infarction is usually seen during the second and third week post ictus. The contrast enhancement pattern varies in the form of patchy, ring like, homogeneous or gyriform enhancement. Early contrast enhancement corresponds to large volume infarction. This is due to disruption of the blood-brain barrier with increased vascular permeability or from reperfusion from collateral circulation.

DIFFUSION-WEIGHTED MRI:

The image contrast provided by diffusion-weighted imaging is different from that provided by conventional MR imaging techniques. DWI is particularly sensitive for detection of hyper/acute ischemic stroke. DWI also aids in differentiation of acute stroke from the conditions that manifests with sudden neurological deficits.

Diffusion occurs as a result of constant motion of water molecules. The heat associated with human body temperature energizes the water molecules causing the water molecules to randomly move in a constant phase. This phenomenon of random movement of water molecules is known as Brownian motion. In biological tissues, the diffusion is not truly random as the tissue has structure. Vascular structures, axon cylinders, and cell membranes limit or restrict the amount of diffusion .The diffusion properties are affected by

chemical interaction of water and macromolecules. Water diffusion in brain is referred to as apparent diffusion. To perform diffusion studies, one need to apply field gradients in addition to radio frequency and gradient pulses used for conventional MR imaging. When there is no net movement, dephasing of spins occurs during the application of first pulse and rephasing of the spins occurs during the application of second pulse.

There are two types of DW images.

- **Trace or diffusion** images are those where damaged tissue that has restricted diffusion (low ADC) is brighter than normal tissues where diffusion is free (high ADC). This is because spins in restricted tissue are refocused as they remain in the same place during the application of both gradients. However, in normal tissue with random diffusion, refocusing is incomplete and signals cancel. If motion varies rapidly, diffusion attenuation occurs and signal is lost in that area. Hence abnormal issue is brighter than normal tissue.

- **Apparent diffusion coefficient maps** are acquired via post-processing by sampling the ADC for each voxel of tissue and allocating signal intensity according to its value. Therefore restricted tissue, which has a low ADC, is darker than free diffusing areas that have a high ADC. The contrast is therefore the mirror of the trace images. This is useful when T2 shine through is a problem.

T2 shine through occurs when lesions or areas with a very long T2 decay time remain bright on the DW or trace image. It is therefore difficult to know whether they represent an area of restricted diffusion or not. By producing ADC maps it is possible to differentiate between areas with a low ADC and those with a long T2 decay time. On the trace image the infarcted tissue is bright, while on the ADC map it is dark. The ADC map enables differentiation of this area from the other high signal intensities seen on the ADC map. These areas represent tissues with a long T2 decay time, not those with a low apparent diffusion coefficient.

During the evolution of time (TE), a pair of field gradients is used to perform "diffusion encoding". Each gradient in the gradient pair will last a time, with strength G (usually in units of mT/m), and the pair is separated by time.

A formal analysis will tell us that the intensity of the signal will depend on all these parameters, given by $S = S_0 \times \exp(-b \times ADC)$ where ADC is the apparent diffusion coefficient, and b is the gradient factor, also called the b-factor. S_0 is the signal intensity obtained when no diffusion gradients are used. The diffusion coefficient calculated in this way is usually called "apparent" because it is often an average measure of much more complicated processes in the tissues.
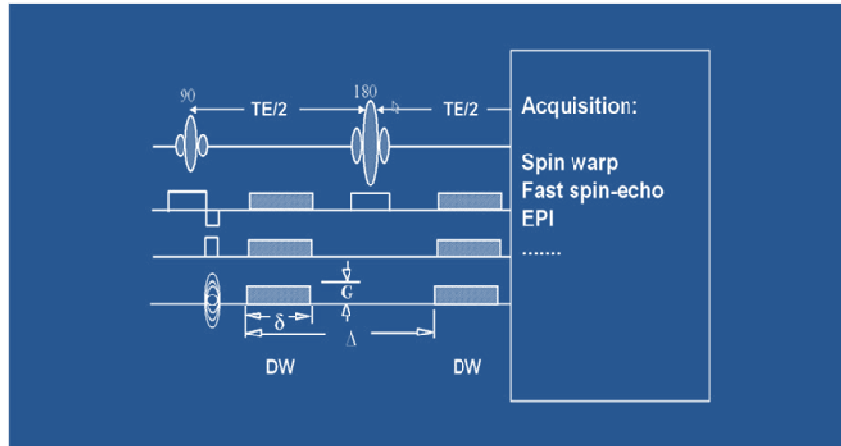
Fig. 1: A Pulse sequence for diffusion imaging. The shaded areas denote field gradient pulses.

As the diffusing spins are moving inside the fielded gradient, the field affects each spin differently. The alignment of the spins with each other is thus eliminated. The measured signal is a summation of tiny signals from all individual spins, the misalignment, or "dephasing", which is caused by the gradient pulses results in a drop in signal intensity; lower signal is attributed to increase in diffusion distance.

In order to help detect areas of ischemia, apparent diffusion coefficient (ADC) maps are used and areas, which are bright on diffusion and dark on ADC, are suggestive of acute infarct. ADC maps are absolutely necessary because, in the initial diffusion image signaling some areas of high signal such as vasogenic edema will appear bright. The reason being diffusion sequence is T2 weighted and the "shine through" effect will cause some bright signals, but these high signal areas, which are not secondary to acute infarct, are easily

detected on the ADC maps and allow for an accurate initial diagnosis. As time progresses, the appearance of the diffusion and ADC abnormalities will reverse as the stroke moves into a sub acute phase (more than 24 hours to 5 days). This specific signal patterns that are identified on MR diffusion help the radiologist to date the time of onset, progression and resolution of strokes.

Diffusion-weighted images are acquired by combining echo-planar imaging (EPI) or fast gradient echo sequences with two large gradient pulses applied after excitation. When the moving spins undergoes phase shift, the gradient pulses cancel each other out if the spins does not move.

In normal tissues signal attenuation occurs with random motion and high signal appears in tissues with restricted diffusion. The amount of attenuation depends on the amplitude and the direction of the applied diffusion gradients.

Diffusion gradients applied in the X, Y and Z-axes are combined to produce a diffusion-weighted image (isotropic image). When the diffusion gradients are applied in only one direction, signal changes reflect direction of axons (anisotropic image). In order to achieve enough diffusion-weighting strong diffusion gradients must be applied.

The sensitivity of diffusion is controlled by a parameter '*b*' that determines the diffusion attenuation by alteration of the time duration and

amplitude of the diffusion gradient. Typical **'b'** values range from 500 s/mm2 to 1000 s/mm2.

freely diffusing water   restricted water
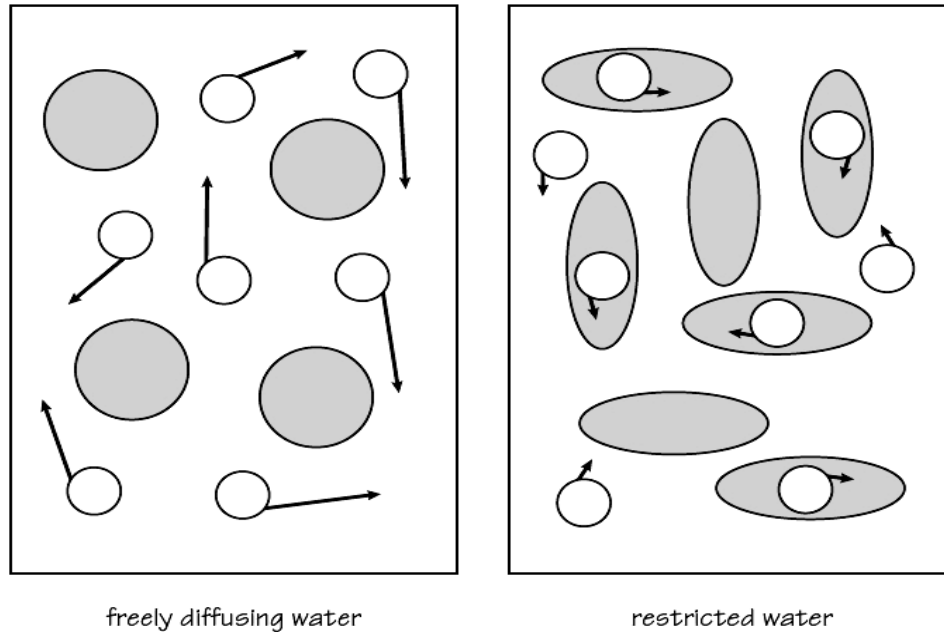
Fig. 2: Schematic representation of freely diffusing water and restricted water.

Diffusion-weighted imaging has the potential advantage to detect ischemic changes within minutes of onset. Decreased proton movement is detected as a decreased ADC. Diffusion-weighted imaging is sensitive to the microscopic random motion of the water molecule protons, a value called apparent diffusion coefficient (ADC), which is measured and captured by this type of imaging. The water molecules align in the direction of the field gradient. Phase shift occurs in their transverse magnetization relative to that of a stationary one, and this phase shift is directly related to the signal intensity of the image. ADCs in ischemic areas are lower by 50% or more compared with

those of normal cerebral regions, and they appear as bright areas on DWI and ADC changes occur as early as 10 minutes following the onset of cerebrovascular insult.

Cytotoxic edema appears following potassium/sodium pump failure, which results from failure of energy metabolism due to ischemic insult. This occurs within minutes of the onset of ischemia and this produces an increase in cerebral tissue water of up to 3-5%. The possible explanation for the decrease in ADC values is the reduction in intracellular and extracellular water molecular motion.
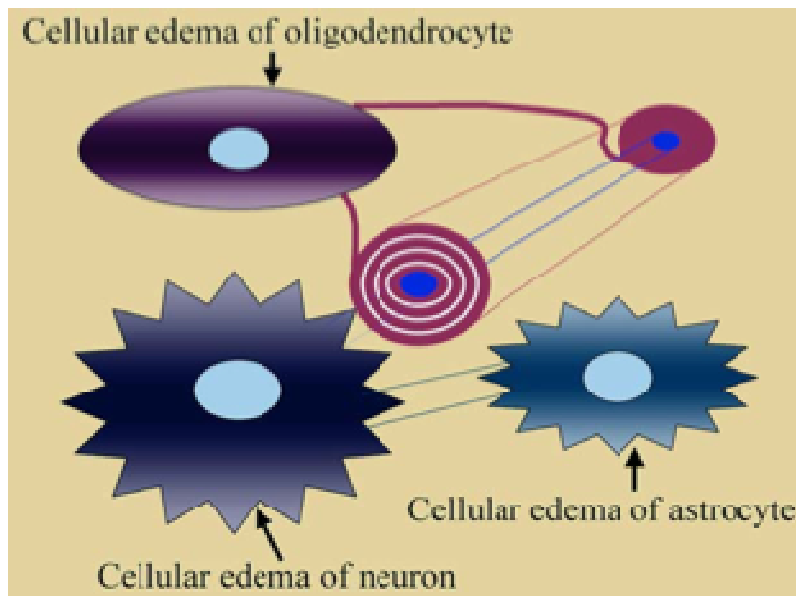
Fig. 3: Cytotoxic edema occurs in astrocytes and oligodendrocytes and these cells are vulnerable to ischemia.

The diffusion of water molecules is safeguarded by biologic barriers in the brain tissue (e.g., cell membranes and cellular organelles). The behavior of

water molecules is asymmetrical and may show uneven distribution of the ADC when measured in one direction; this uneven distribution may give a negative impression of a lesion. ADC values are measured in 3, 6, or more directions, and ADC maps are formed to produce a direction-insensitive measurement of the diffusion.
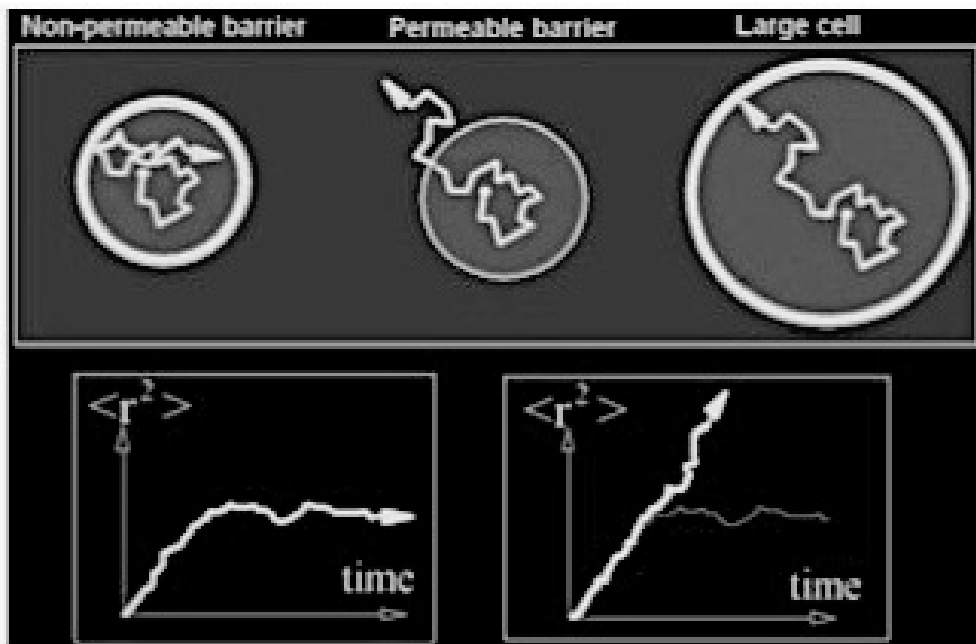
Fig. 4: The behavior of diffusion among cellular structures depends on the mean displacement ($<r^2>$) during the measurement time and size of cellular structure.

The ADC reduction also occurs in other conditions, such as hypoglycemia, status epilepticus, and global ischemia, and it should always be evaluated in relation to the clinical history and condition of the patient.

The technique most commonly used to acquire diffusion weighted imaging is an ultrafast, echo-planar imaging (EPI). Echo-planar imaging

decreases scanning time significantly and prevents movement artifacts. The acute decrease in ADC is gradually normalized to baseline at 5-10 days after ischemia (pseudo normalization) and it even exceeds normal levels as time passes, and aids in differentiating acute, sub-acute and chronic infarctions. Normal diffusion weighted images in patients with stroke like symptoms should be evaluated for non-ischemic cause of the symptoms.

The diffusion-weighted signal intensity is increased during the hyperacute stage with corresponding low ADC manifested as dark signal in the ADC map. During the acute stage of stroke, the signal intensity on DW imaging further increases with a corresponding lower ADC than the hyperacute stage. As the infarct progresses to subacute stage, there is pseudonormalization of the ADC, which is due to the persistence of cytotoxic edema, development of vasogenic edema and disruption in cell membrane. The hyperintense signal usually decreases within 1-2 weeks but is slightly hyperintense where ADC is usually normalized. In the chronic stage, there is almost complete necrosis of the cells and the ADC is increased with a hyperintense signal on the ADC maps with low signal intensity on DW imaging.

The other early MRI findings in patients with hyperacute stroke are hypointense (blooming) artery sign of acute intravascular thrombus on susceptibility weighted images (SWI sign), hyperintense vessel sign on FLAIR

sequence which is indicative of slow flow, and arterial occlusion on magnetic resonance angiography.

The reperfusion strategies in the treatment of hyperacute ischemic stroke primarily depend on the rapid and accurate identification of patients who will benefit from therapy. The time-dependent efficacy of thrombolytic therapy combined with the limited sensitivity of unenhanced CT early in the course of acute stroke has resulted in the common scenario of thrombolytic administration in the face of a negative CT. Studies have demonstrated that up to one-fifth of patients with a clinical diagnosis of stroke are categorically determined to have a stroke-mimic, and many of these patients received unnecessary thrombolytic therapy. [28, 29, 30, 31]

The superior sensitivity of diffusion study early in the course of stroke may not only decrease the unnecessary administration of thrombolytic therapy but may also allow for modified reperfusion protocols that mandate imaging evidence of ischemia before treatment.

Since the criteria to define patients who will benefit from reperfusion therapy are refined, it has become increasingly evident that large volume strokes are associated with an increased risk of hemorrhagic transformation. It is also clear that non-enhanced CT cannot adequately define the volume of ischemia early in acute stroke, resulting in poor inter-rater reliability, with less experienced readers. The data reviewed here also demonstrate the superiority

and reliability of DWI in delineating the extent of infarction, even early in the course of illness. MRI also offers the advantage of being able to discern the age of infarct. The presence of a subacute lesion may increase the likelihood of hemorrhagic transformation with administration of thrombolytic therapy.

Definitive management goal is aimed at removing the blockage of the vessels by thrombolysis or thrombectomy. Thrombolysis with recombinant tissue plasminogen activator in hyperacute ischemic stroke, when given within 3 hours of symptoms onset results in overall benefit of 27% with respect to living without disability. [31] After four and half hours, intravenous thrombolysis worsens the outcomes. Intra-arterial fibrinolysis has been found to improve outcomes with acute ischemic stroke. [32]

Apart from early detection of ischemic stroke, diffusion-weighted imaging also aids in differentiation of acute stroke from stroke mimics, differentiation of abscess from necrotic tumors, differentiation of epidermoid cyst from arachnoid cyst, differentiation of herpes encephalitis from diffuse temporal gliomas, assessment of active demyelinating diseases, differentiating benign from malignant tumors, tumor staging, and assessment of the extent of diffuse axonal injury.

In diffusion-weighted imaging the diffusion measurement occurs in one direction. The advantage of short acquisition time, no post processing, easy

interpretation, better patient tolerance makes DWI and ADC an ideal MR sequence for hyper acute and acute stroke imaging.

The neuroimaging technology has a crucial role in the diagnosis and treatment of stroke. In the recent years, significant advances in imaging techniques enable the clinicians to define the neuroanatomy and physiology in greater details. The imaging diagnosis and management of hyperacute stroke in first few hours remains crucial, where our aim is to identify the patients eligible for thrombolytic therapy and other therapeutic protocols in order for the patients to a have a good clinical outcome.

Aims & Objectives

AIMS & OBJECTIVES

1. To study the diagnostic accuracy of Diffusion-weighted MR imaging with non-enhanced CT in the diagnosis of hyperacute stroke.

2. To study the role of Diffusion-weighted MR imaging and non-enhanced CT in diagnosing hyperacute ischemic stroke and deciding thrombolytic treatment / therapeutic protocols aimed at reversing the cerebral ischemic insult.

Review of Literature

REVIEW OF LITERATURE

Barber et al [33] study observed that NECT and DWI are comparable for detecting and quantifying the signs of brain ischemia in acute stroke when the modalities are of good quality and when assessed systematically using Alberta stroke program early computed tomography score (ASPECTS). But the study does not imply that the two modalities are equivalent. The ASPECTS values were low for diffusion MR images demonstrating that DWI is more sensitive than CT assessing the hyperacute stroke. The sensitivity is high for each individual CT ASPECTS value and the specificity in cortical areas i.e. M2-M6, ranges from 40 to 60%. This implies that CT is visualizing disease process such as cytotoxic edema, where DWI mainly visualizes the signal changes and gives a better anatomical definition. The study also reveals that DWI has a higher sensitivity in detecting anterior and posterior circulation hyperacute and acute stroke whereas the magnitude of CT is small within the first six hours. DWI also helps in confirming the location and etiology of stroke for example in case of shower of emboli from cardio embolic stroke.

Gonzalez et al [34] conducted a blinded study of 18 patients who underwent imaging within six hours of symptom onset where DWI, conventional MRI and NCCT were performed. The study observed the importance of contrast to noise ratio (CNR) .The region of interest was placed at the location of stroke. A second ROI was measured from a normal appearing location in the contralateral

hemisphere. The mean Hounsfield unit (CT) and the signal intensity (MR) were obtained for each region of interest and the CNR was calculated. The CNR percentage was calculated as 100 x (SL-SN)/SN where SL is the signal intensity in the stroke location and the SN is the signal intensity of the normal cerebral parenchyma. The improved signal to noise ratio of DWI is attributable to decrease in the diffusion of water in ischemic tissue due to cytotoxic edema. When the b value is too low there will not be sufficient diffusion weighting. The study observed that when the b value of around 1000 sec/cm^2 will be the optimal imaging value of DWI. There is a 20 fold higher percentage of CNR for DWI of acute ischemic stroke compared with CT scans or T2 weighted image and thus explains the improved sensitivity of DWI in detection of hyperacute/acute stroke. The window settings of the image and the CNR percentage allows for the estimation of stroke detection. The study also observed that in the setting of negative diffusion restriction will spare extensive diagnostic evaluation and can prevent the unnecessary risks of anticoagulation.

Schaefer et al [35] in their study observed that conventional MR imaging has demonstrated poor differentiating features of vasogenic edema from cytotoxic edema associated with acute infarction. Conventional T2-weighted images produce high signal intensity in gray and white matter in the case of cytotoxic edema. Vasogenic edema on T2-weighted images usually produces high signal intensity in white matter but can involve the adjacent gray matter also. HIV encephalopathy can mimic acute arterial infarction. DW MR imaging

can reliably differentiate vasogenic from cytotoxic edema. Cytotoxic edema demonstrates restricted diffusion whereas vasogenic edema is characterized by elevated diffusion; the reason behind this is due to relative increase in mobility of water in the extracellular compartment.

In diffusion-weighted imaging the vasogenic edema appears hypointense as there is both T2 and diffusion addition. If the vasogenic edema is hyperintense it can mimic hyperacute or subacute infarction. ADC images show cytotoxic edema due to ischemia to be hypointense for 1-2 weeks and vasogenic edema will be hyperintense. The study shows that DW MR images should always be compared with the ADC images. Misdiagnosis of vasogenic edema syndrome as acute cerebral ischemia may lead to unnecessary and inadvertent use of thrombolytic, antiplatelet agents and anticoagulants. Misdiagnosis of acute infarction as vasogenic edema syndrome will discourage the proper treatment, which could lead to the risk of recurrent cerebral infarction.

Huang et al [36] studied the possible differences between the evolution of cerebral watershed infarction and that of territorial thromboembolic infarction by using DWI, T2 MR and ADC maps in a study group of 14 patients. The evolution time of ADC is rapid for thromboembolic infarction than for watershed infarction. The difference is mainly attributed to the different pathophysiological hemodynamic features of the two-infarction type. The difference in ADC evolution time indicates that type of infarction plays a vital role in determining the progression of infarction. The study observes that the

size of diffusion abnormality stabilizes in a time frame of 18 to 24 hours following the onset of symptoms. The ADC map value time frame for predicting the final ischemic infarct volume is limited to about 1 day after the onset of symptoms. The study states that the signal intensity changes on DW images were studied as a single parameter. High signal intensity was constantly observed during acute and sub-acute stages. This abnormal signal intensity declined after two weeks of onset of symptoms.

Burdette et al [37] study observed the time course of signal intensity changes on diffusion-weighted images in 212 patients referred for suspected brain infarction over a period of 6 months. The study demonstrated the presence of diffusion restriction in patients who presented within 24 hours of brain infarction and in up to 94% of patients scanned during the first 2 weeks after ictus. There was a decline in the percentage of abnormal diffusion with time and no signal intensity abnormality was noted in stroke patients scanned more than 2 weeks after the onset of symptoms. Since diffusion-weighted images are produced with a modified spin echo pulse sequence with long TE and TR values, the signal changes reflects the changes in diffusion constant, spin density and T2. This known as T2 shine through is a possible reason for prolonged duration of high signal intensity in DWI. However the ADC can eliminate this T2 shine through phenomenon maps.

Arenillas et al [38] study observed the prediction of early neurological deterioration in hyperacute middle cerebral artery ischemic stroke by means of

diffusion and perfusion weighted imaging. The study demonstrates that DWI lesion volume gained within the hyperacute phase of stroke after intracranial ICA or MCA occlusion is a powerful predictor of further neurological deterioration. The early neurological deficit is mainly determined by the severity and the extent of early ischemic injury. Large hyperacute hypo density and diffusely attenuated corticomedullary contrast in CT scan have been shown to be highly specific but moderately sensitive in predicting fatal ischemic brain edema and stroke outcome. Based on this context the study has shown that DWI and PWI are much reliable and sensitive in the detection of early ischemic pathology. Large hyperacute DWI lesions reflect a severe early ischemic insult with a rapid progression from ischemia to infarction due to proximal arterial occlusion and poor collateral circulation. The study observes that early DWI volume is a considered a primary marker of the intensity of the molecular response initiated by the brain ischemia which relates to the early neurological deficit. The study supports that the severity of initial ischemia determines the risk of developing massive cerebral edema, which leads to neurological deterioration.

Kim et al [39] studied the impact of high b value DWI in hyperacute ischemic stroke in a 1.5 T MRI scanner. The study compared the DW images obtained with a b value of 1000s/mm2 with a b value of 2000 s/mm2 in 94 patients of clinically suspicious hyper acute ischemic stroke. The study shows when increasing the b value the signal intensity of normal grey matter decreases

progressively relative to normal white matter. When the b values are greater than 2000, there is a reversal of gray white matter pattern in contrast to b value of 1000. The b value of 2000 revealed relative hyper intensities to cortical gray matter more specifically in corona radiata, lower brain stem and the posterior limb of internal capsule. The b value increase from 1000 to 2000 showed an increased contrast to noise ratio (CNR) by 23%. The study observed that higher b value DWI is more advantageous in the detection of hyper acute ischemia not only in territorial lesions but also the smaller lesions in internal capsule and the brainstem.

Lansberg et al [40] compared the DWI with NECT in acute stroke in 19 patients. The study showed diffusion weighted imaging identified hyperacute stroke in all patients and CT identified correctly in 43 to 63 % of patients. DWI sensitivity for the detection of more than 33% MCA involvement was 57 to 86% and for CT is 14 to 43%. There was a strong correlation of acute lesion DWI volume with the final infarct volume whereas there was no significant correlation between CT volume and the final infarct volume.

Hacke et al [41] studied the clinical course and prognostic signs in malignant middle cerebral artery territory infarction. 55 patients with complete middle cerebral artery territory infarction caused by occlusion of either distal ICA or proximal MCA trunk were studied. The study showed a survival rate of 22 % and the cause of the mortality was due to transtentorial herniation. The study assessed the prognosis of complete MCA stroke is poor and can be

estimated by early clinical and imaging data within the first few hours of symptom onset.

Linfante et al [42] studied the effectiveness of DWI in acute phase of posterior circulation stroke and correlated with the National Institute of Health Stroke Scale Score (NIHSS). Posterior circulation stroke differs in etiology, clinical presentation and prognosis. CT provides suboptimal imaging in detection of acute phase of posterior circulation infarction. The lesion volume on DWI was found to have a good correlation with the 24-hour NIHSS score in ischemia of anterior circulation. DWI is more effective than conventional T2 weighted images in patients with posterior circulation stroke. There is also no significant correlation between the DWI lesion volume and NIHSS score.

Morita et al [43] evaluated the value of DWI using a semi-quantitative score, which is being modified from ALBERTA stroke program early CT score (ASPECTS) for predicting the neurological deterioration in patients with hyper acute ischemic stroke who had underwent thrombolytic therapy. Twenty-two treated patients were examined and were divided in to deteriorated group and non-deteriorated group. The study compared the DWI score, ASPECTS and DWI volume of the 2 groups, examined the correlations between these scores and initial NIHSS score or DWI volume. The DWI score and ASPECTS tend to be lower in the deteriorated group than the non deteriorated. This method may be used to evaluate the ischemic lesion on DWI and predict more accurately than DWI volume or ASPECTS. On comparing the DWI score with the DWI

volume, there was a large variation in the DWI volume with low DWI scores and large variation in DWI scores with small DWI volume.

Schellinger et al [44] assessed the safety and efficacy of MRI based thrombolysis within and beyond 3 hours compared with the standard CT based thrombolysis. The study showed that overall MRI based thrombolysis appears to be safer and more effective than standard CT based thrombolysis for acute ischemic stroke. The impact of MRI based patient selection is accentuated beyond the 3-hour time frame. The study observed that within the 3-hour time window, the choice of imaging modality may be at the discretion of the clinician and also depends on the institutional protocol. After the 3-hour time window, a considerable number of patients can be treated with thrombolysis based on the pattern of penumbra detected by MRI. The study also observes that safety and efficacy of MRI based thrombolysis beyond 3 hours compares well to standard CT based thrombolysis.

Olsyzycki et al [45] studied the reliability of DWI vs. FLAIR MR imaging in 29 patients of hyperacute stroke with reference CT in these patients. The pathologic hyperintense lesions were well visualized in 20 patients by means of DWI whereas FLAIR MR also detected discrete hyperintense lesions of the same locations in 19 patients. The study concluded that DWI MR imaging in patients with early cerebral ischemia was superior and clearer than FLAIR imaging.

Dg et al [46] studied the comparison between multiphasic perfusion CT and diffusion and perfusion MRI in predicting the final infarct growth, volume and clinical outcome in 19 patients of hyper acute ischemia untreated with thrombolysis. DWI and perfusion MRI was obtained within 2 hours after CT and lesion volumes were compared with infarct volume and clinical outcome and mismatch on MRI and CT was compared with the final infarct growth. The study observed that the lesion volume on CT peak perfusion map and MRI rCBf correlated well with the infarct volume and clinical score. DWI relative blood flow or CT mismatch was more conclusive in predicting the infarct growth when compared with the DWI mean transit time mismatch.

Schellinger et al [47] studied the feasibility of diffusion and perfusion MRI for the initial evaluation and follow up monitoring of patients undergoing thrombolytic treatment. The study assessed the clinical scores namely the Scandinavian stroke scale (SSS), National Institute of Health Stroke Scale (NIHSS), Barthel index and Rankin scale at days 1, 2, 5, 30 and 90. The study performed the volumetric analysis of the volumes of infarct on day 1, 2, 5 by DWI, Perfusion weighted imaging and T2 weighted imaging. Out of 24 patients studied 20 patients had demonstrated vessel occlusion. 11 patients were recanalized and 9 patients did not undergo recanalization. Despite the various diagnostic potentials of DWI and PWI in hyperacute stroke, there exist substantial doubts regarding the utility, availability and cost effectiveness of these methods. Stroke MRI was performed within average time of 1, 2 hours

after CT and 3.4 hours after onset of symptoms in 24 patients. Intravenous thrombolysis was administered without any unnecessary delay within an average time of 3.2 hours after onset of symptoms. Four out of eight patients were imaged within 30 minutes after IV thrombolysis and another 3 patients were imaged within 1.5 hours. The study demonstrated the feasibility of stroke MRI in hyper acute stroke patients. MRI acts an important diagnostic tool in assessing the pathophysiological aspects of hyper acute stroke. DWI identifies the infarcted cerebral parenchyma in less than 1 hour after the onset of symptoms, probably within few minutes thus providing cumulative evidence in the early brain ischemia. The study categorically states that with the availability of MRI, times consuming diagnostic efforts with different modalities are not warranted, as the intra and extra-cranial vessel status is reliably assessed and the presence of intracerebral hemorrhage can also be excluded.

Lee et al [48] studied the impact on stroke subtype diagnosis of early DWI and MRA. The study analyzed 46 patients with acute cerebral ischemia who underwent DWI and MRA within 24 hours of onset of symptoms. The initial diagnosis was assessed with the use of 2 most widely used formal stroke subtype classifications namely the TOAST and oxfordshire methods that were applied before DWI and MRA were performed. Modified TOAST and oxfordshire methods were applied based on the results of day 1 DWI, MRA and DWI plus MRA. The gold standard of final TOAST and oxfordshire diagnosis were taken during the time of discharge. DWI and cervical cephalic MRA has

been accepted with a good potential to identify the site of cerebral ischemia and the site of large vessel occlusion/disease within the early onset of stroke thus providing the pathophysiological information that will aid in improving the accuracy of stroke subtype diagnosis.

Bisdas et al [49] compared perfusion CT with Diffusion -weighted magnetic resonance imaging in assessing the hyperacute ischemic brain. 20 patients underwent CT perfusion and DWI studies within 3 hours after stroke onset. The cerebral blood flow was used to delineate the ischemic area, infarct and the penumbra. The volume of ischemic lesion on CT perfusion was correlated with the volume of DWI abnormalities. The study concluded that both the imaging modalities are superior in assessment of hyperacute cerebral infarct and there was a significant correlation between the two modalities .CT perfusion allows differentiation of the infarct core and penumbra with positive predictive value of the follow up volume of the infarct and the prognosis.

Chen et al [50] assessed the accuracy of DWI MR technique with fluid inversion prepared diffusion (FLIPD) MR imaging in depicting acute ischemic stroke at 3 T scanner. DWI was performed in 75 consecutive patients with acute ischemic stroke. FLIPD MR images were obtained with a value of 1500 sec / ^{mm2} had shown decreased sensitivity for acute ischemic stroke when compared with DWI MR Images obtained with a b value of 1000 sec / ^{mm2}. The study concluded that FLIPD MR Images with a b value of 1500 sec / ^{mm2} is less

accurate for detection of acute ischemia due to decreased sensitivity and negative predictive value.

Yoo et al [51] studied the outcomes of patients with acute ischemic stroke by combining acute diffusion-weighted imaging and mean transit time lesion volumes with the National Institute of Health Stroke Scale (NIHSS). The study comprised of 54 patients with acute stroke who had MRI within 9 hours of symptom onset and 3-month follow-up with modified Rankin scale. The study found that all the patients with DWI volume > 72 ml and an NIHSS score > 20 had poor outcomes. The patients with DWI volume of < 47 ml and a NIHSS score of <8 had good outcome. The study concluded that by combining quantitative DWI and MTT with NIHSS has a good prediction of clinical outcomes and is found to be superior to NIHSS alone.

Schramm et al [52] observes that although stroke MRI has advantages over other imaging modalities in detecting acute stroke, there is a potential disadvantage of non-availability of MRI facilities in emergency units. Thus there is an absolute need for an accurate diagnostic tool that rapidly detects hemorrhage, vessel status, and extent of the ischemic insult and estimation of tissue at risk. The study determined the diagnostic accuracy of the combination of non-contrast CT, CT angiography and CT source imaging in comparison with stroke MRI protocols within 6 hours of onset. On analysis of 20 stroke patients who underwent the combined modality imaging, vessel occlusion was present in 16 patients. The volume of CT source images significantly correlated with the

initial diffusion weighted imaging lesion volumes and with the outcome lesion volumes. The patients with infarct growth had poor collaterals and had experienced worse clinical outcomes.

Barber et al [53] article determined the incidence, diagnostic value and reliability of MCA dot sign in NECT. The hyperdensity associated with embolic occlusion of the branches of middle cerebral artery in the sylvian fissure also known as MCA dot sign. 100 patients with signs of thromboembolic stroke and early signs of CT ischemia were studied.

Hyperdensity of the main middle cerebral artery (HMCA) is an early warning of large cerebral infarction, brain edema and poor prognosis. The HMCA sign was seen in 5% of CT scans where the MCA dot sign was seen in 16%. The study concluded that MCA dot sign is reliably an early marker of thromboembolic occlusion of the distal branches of middle cerebral artery and has better outcome than HMCA sign.

Pexman et al [54] studied the importance of Alberta stroke program early CT score (ASPECTS) for assessing CT scans in patients with acute stroke. The ASPECTS was developed to increase the reliability and utility of baseline CT examination with a reproducible grading system to detect the early ischemic changes in patients with acute ischemic stroke of anterior circulation before standardizing treatment. The score divides the middle cerebral artery territory in to 10 regions of interest thus providing a topographic scoring system for a quantitative approach, which does not necessitate the need for estimating the

volumes from two-dimensional images. The study concludes that the inter and intra observer reliability of ASPECTS was good to excellent and proved to be superior to the $1/3^{rd}$ rule.

Tomura et al [55] retrospectively analyzed in 25 patients who underwent early CT scan with signs of embolic infarction of the middle cerebral artery observed an obscured outline or partial disappearance of the lentiform nucleus and effacement of cortical sulci. These findings were recognized in 23 of 25 patients and it appeared earlier. The study observed that the obscuration of lentiform nucleus is an important early sign of cerebral infarction.

Sanghvi et al [56] analyzed the importance of CT imaging in diagnosis and management of early stroke. CT has proven to been an effective first line investigation for acute ischemic stroke as it is widely available as well as time tested modality. With the advent of modern CT scanners non-enhanced CT scan of the brain can be acquired within few minutes and thus plays an important role in the management of acute ischemic stroke. In selected cases the CT perfusion and CT angiogram study may be added. As CT has higher sensitivity to detect hemorrhage, the need for thrombolysis is thus avoided. CT imaging has been employed in all major studies of stroke therapy namely NINDS, ECASS, and PROACT. There exists a considerable difference of opinion between clinicians with regard to practice of acute stroke therapy. Formal imaging protocol for acute stroke should be devised and should be made patient centric.

Kloska et al [57] in a study of forty-four patients, who underwent

multidetector row CT within eight hours (mean 3 hours) of symptom onset, assessed the detection of stroke and prediction of extent of infarction with unenhanced CT, perfusion CT and CT angiography. The evaluation was performed with history of suspected acute stroke but without detailed clinical information. The baseline unenhanced CT scans evaluated the extent of ischemia/final infarction and the follow-up images were assessed with the Alberta stroke program early CT score. The ct perfusion maps were studied to assess the percentage of the ischemic hemisphere. The CT components were compared with magnetic resonance images after a mean time of 2.3 days. Nonenhanced CT, CT perfusion and CT angiography showed sensitivities of 55.3%, 76.3 % and 57.9% respectively. The study concludes that multimodal CT evaluation improves the detection rate and prediction of the final infarct size when compared with unenhanced CT, perfusion CT and CT angiography alone.

Lev et al [58] performed non-enhanced CT in 21 patients with hyperacute middle cerebral arterial stroke to assess improved non-enhanced CT detection by using variable window width and center level settings with soft copy images. The images were reviewed with standard window width settings of 20 and 80 HU and soft copy settings initially centered at a level and width of 32 and 8 HU. The sensitivity and specificity for stroke diagnosis with a standard viewing parameter were 57% and 100%. The study concluded that that in nonenhanced CT of brain, the detection of ischemic brain is improvised by soft copy view

with variable window width and center level to facilitate the contrast between normal and edematous parenchyma.

Takahashi et al [59] proposed a method called adaptive partial medial filter (APMF) to improve the visibility of gray-white matter interface in CT. The presence of quantum noise on CT images limits the diagnosis of hyperacute stroke by which the early signs of hyperacute stroke like the loss of grey white matter interface may be difficult to detect. The adaptive partial median filter reduces the local noise without blurring of the anatomical details by using variable filter shape and size according to the pixel distribution of object around a center pixel. CT images of 26 patients with acute stroke (<5 hours) were studied and APMF was applied to all CT images. The study concluded that a 78% noise reduction with APMF was obtained and thus the visibility of gray white matter interface is improved which helps the radiologist detect the early CT signs in emergency settings.

Hopyan et al [60] evaluated the diagnostic benefits and inter and intraobserver reliability of combined CT protocol in diagnosis of clinically suspected stroke. A total of 191 patients with stroke symptoms of less than 3 hours were studied. The sensitivity of combined CT modalities namely non-enhanced CT, CT perfusion and CT angiography increased by 12.4% over that with non-enhanced CT and CT angiography. The study observed that an incremental protocol, which includes CT perfusion, raised the accuracy in stroke diagnosis and the inter and intraobserver agreement.

Ma et al [61] studied the diagnostic value of CT perfusion in hyper acute cerebral infarction patients and determined the correlation of time period from onset of stroke symptoms to examination and CT perfusion imaging parameters. Non-enhanced CT and CT perfusion were done on 75 patients with acute brain infarction. The NIHSS, Barthel index and modified Rankin scale were assessed on the same day, 14 and 90 days after stroke onset. The study observed that areas of cerebral blood flow (CBF) of the ischemic region correlated well with NIHSS on the day of symptom onset. Cerebral blood volume and time to peak (TTP) of the ischemic region correlated well indices of clinical outcome on the day of presentation, day 14 and 90 The CT perfusion evaluates the severity and prognosis of acute cerebral infarction and the most sensitive parameter is the area of abnormal perfusion.

Parsons et al [62] studied the correlation of early ischemic changes on non-enhanced CT with concurrent assessment of cerebral perfusion and compared their rates of progression to infarction in a study group of 40 patients of anterior circulation ischemic stroke. The early changes of ischemia on non-enhanced CT namely the parenchymal hypodensity and isolated focal swellings were assessed. The perfusion values were calculated for cortical areas from CT perfusion maps, cerebral blood volume maps, cerebral blood flow and mean transit time. Cerebral blood volume was low in parenchymal hypo- attenuation regions and increased in areas of isolated focal swelling. The hypo-attenuated parenchyma progressed to infarction but the isolated focal swelling region had

lower rate of infarction The majority of hypoperfused region appears normal on nonenhanced CT. CT perfusion can reliably assess the subsequent infarction for normal appearing areas on nonenhanced CT.

Song et al [63] in a study of 45 patients evaluated the frequency of hyper dense middle cerebral artery sign on patients with severe ischemic attack in the middle cerebral artery within 3 hours of symptom onset and compared the baseline scans and 90 day outcomes between hyper dense middle cerebral artery sign group and non hyper dense middle cerebral artery group. The positive group with hyperdense middle cerebral artery sign had significant neurological deterioration 24 hours after onset and developed severe MCA infarction. This sign detected by non-contrast CT should be considered as an alarming sign among patients with MCA territory infarction.

Goldmakher et al [64] studied the utility of hyperdense basilar artery in detecting thrombosis and predicting the outcomes in patients with posterior circulation stroke. . Non-enhanced CT scans were obtained within 24 hours of symptom onset in 95 patients suspected of posterior circulation stroke. With a cutoff score of >/ = 4, hyperdense basilar artery sign had sensitivity of 71%, specificity of 98%, 83% positive predictive value, and 95% negative predictive value for basilar artery occlusion. The study concluded that in patients with signs and symptoms of posterior circulation stroke, the presence of HDBA sign on unenhanced CT is a strong predictor of thrombosis of basilar artery.

Nakano et al [65] found the incidence of parenchymal hypodensity within 3 hours after ischemic onset among patients with angiographically proved embolic middle cerebral artery occlusion and to assess the correlation of subtle hypodensity in the deep middle cerebral artery territories with involvement of the lenticulostriate arteries in the presence of ischemia. 50 CT images were evaluated by three neurosurgeons who were aware of the clinical history and CT images were obtained within 3 hours of onset of embolic occlusion. Subtle hypodensities in the region of Insular cortex, posterolateral putamen and lentiform nucleus were evaluated assigning increasing grades I, II and III respectively. A grade I CT sign was considered a negative finding for lenticulostriate artery involvement, whereas grade II and III CT signs were considered to be positive findings and these findings were angiographically confirmed. They concluded that involvement of the lenticulostriate arteries might be presumed by precise evaluation of subtle, CT revealed hypoattenuation in the deep MCA territories, even within 3 hours of ischemic onset.

Von Kummer et al [66] in their study assessed the reliability of detecting signs of hemispheric infarction on CT scans obtained within 6 hours of the onset of symptoms and predicted the interobserver agreement. From two series of 750 patients with recent onset of middle cerebral artery stroke a neurologist selected12 normal and 33 abnormal CT studies showing the hyperdense middle cerebral artery sign (HMCAS), brain swelling and parenchymal hypodensity, these selections served as the reference source for a non-blinded analysis of the

initial and follow-up CT scans. Six neuroradiologists then reviewed the CT scans twice, first blinded and then not blinded to clinical symptoms. The chance-adjusted agreement was moderate. The conclusion derived were that even with no clinical details, neuroradiologists can assess subtle CT signs of cerebral infarction within the initial six hours of symptom onset with moderate interobserver agreement.

Kimura et al [67] assessed the relationship between DWI Alberta stroke program early CT score (ASPECTS) and patients outcome in 49 consecutive patients with anterior circulation stroke who presented within 3 hours of onset of symptoms. The National institute of health stroke scale score was obtained before and 7 days after intravenous thrombolytic therapy. Patients with a DWI ASPECTS > 5 should be considered for thrombolytic therapy and DWI ASPECTS appears as a valid tool for predicting bad clinical outcome.

Arnould et al [68] compared the CT and MR imaging in detecting and categorizing hyperacute ischemic stroke early hemorrhagic transformation and observed that MR had better intra and inter observer agreement than CT and also better depiction of hemorrhage. In MRI the highest sensitivity was demonstrated by echo planar gradient recalled echo (GRE) T2* weighted sequence. Bleeding categorization observed from CT to MR and between MR images showed equivocal upward shifts.

Kidwell et al [69] study on 42 patients with symptomatic cerebral TIA in comparison with the 23 completed stroke patients observed that out of the TIA patients 48% demonstrated focal abnormalities, which was neuroanatomically relevant on diffusion weighted imaging and apparent coefficient imaging. But the signal changes noted in the DWI or ADC were less pronounced and smaller in volume in comparison with the stroke patients. The study concluded that the ischemic signal changes noted in the diffusion MRI of TIA patients corresponded to the TIA symptom duration and thus having significant clinical correlation.

Chen et al [70] in their study predicted the risk of infarct growth in 22 patients with middle cerebral artery infarction and clinical outcome from prominent vessel sign identified on the first susceptibility weighted imaging (SWI) after acute stroke .The extent of prominent vessel sign was significantly correlated with the infarct growth ($p<0.001$) and early clinical outcome .The study concluded that prominent vessel sign on the first susceptibility weighted image after acute MCA stroke is a useful predictor of early infarct growth . Large prominent vessel sign with in the MCA region is related to poor clinical outcome and could be useful for clinical assessment of stroke.

Lam et al [71] in their study assessed the prognostic value of CT in hyperacute middle cerebral artery infarcts by correlating the total CT score, NIHSS score and CT features in 16 patients. The extent of infarct, total CT score and attenuation of corticomedullary differentiation were associated with

30-day mortality (p<0.05). The extent of infarct >67% gave sensitivity, specificity, PPV, NPV rates of 86%, 100%, 100% and 90% respectively. A CT score >4 gave sensitivity, specificity, PPV and NPV rates of 86%, 78%, 75% and 88% respectively .CT features and admission NIHSS scores are important predictors of survival in hyperacute extensive MCA infarcts.

Materials and Methods

MATERIALS AND METHODS

The study was approved by the scientific committee and ethical committee clearance obtained before commencing the study.

Study design:

The prospective study was conducted in Radiology department at Madras Medical College Chennai. The study was conducted between July 2012 and July 2015.

Study population:

The study group includes a sample of 200 patients who came to the Department of Radiology within 6 hours of onset of stroke symptoms. NECT and MRI were done in all the patients and the results were studied.

Inclusion criteria:

Patients who presented within 6 hours of onset of symptoms of stroke including subtle focal neurological deficits.

Exclusion criteria:

Patients with hemorrhagic stroke were excluded from the study. Patients with surgical clips and contraindications for MR imaging, were excluded from the study.

Consent:

Informed consent was taken from all the patients enrolled in the study as per the guidance of the ethical committee.

Patient evaluation:

A complete prospective evaluation of all patients was carried out as per the proforma attached.

Imaging Methods and Analysis:

Clinical data was collected from all patients and all of them underwent unenhanced CT and MRI imaging.

CT:

Non-enhanced CT scans were performed first on the patients with a standard CT protocol (5 mm slice thickness, 120 kv, 180 mA at 2 secs and with appropriate window width and window level).

MRI:

Imaging was performed on a 1.5 Tesla MR system equipped with standard head imaging coil and high-speed gradients. The DWI was performed using single shot, gradient echo, echo planar pulse sequence with diffusion gradient b values of 0 and 1000 s/mm2 along all 3 orthogonal axes over 18 axial sections (18, 7 mm –thick sections with no intersection gap, matrix 96 x 128,

field of view 240 mm with single acquisition) Diffusion weighted images were automatically post processed to give trace images from the primary data. ADC maps were derived. ADC trace maps were obtained on the basis of the DWI that was acquired over the 3 principal axes. The mean ADC of the ischemic lesions was calculated. Regions of interest were placed to exclude the sulcal and ventricular cerebrospinal fluid, which has high ADC value.

MR imaging sequences include, axial diffusion weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR), Sagittal and axial T1 weighted images, axial T2 weighted images, Gradient sequence (GRE) and multislab three-dimensional time of flight magnetic resonance angiography (TOF MRA). The conventional scanning protocol included an axial 5 mm thick T2 weighted sequence (3000/100/20), coronal FLAIR sequence with 4 mm thickness (TR/TE 800/112, T1 -2800 msec) sagittal and axial 5 mm thick T1 weighted spin echo sequence (TR/TE-550/15). The total image acquisition and reconstruction processing time with the MR sequences was 12 minutes on average. (Range 10 - 14 minutes).

Results

STATISTICAL ANALYSIS AND RESULTS

The study group includes a sample of 200 patients who came to the department of radiology within six hours of onset of stroke symptoms. Nonenhanced CT and diffusion-weighted MRI including the conventional MRI were done in all the patients and the image findings were studied. Demographic variables and clinical variables are given in frequencies with their percentage. Male Female age difference were analysed using student independent t-Test. The statistical Agreement between DWMRI and NECT were calculated using Cohen Kappa Agreement statistics. The association between NECT and DWMRI findings was calculated using McNemar's Test. Diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value of DWMRI and NECT in hyperacute stroke patients were calculated using diagnostic statistics. $P<0.05$ was considered significant.

AGE DISTRIBUTION

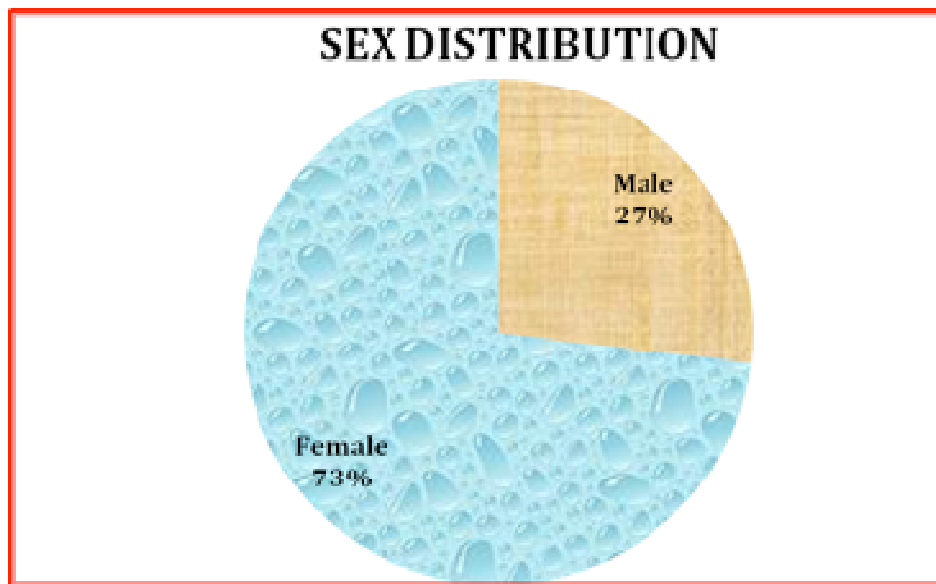| AGE IN YEARS	NO. OF PATIENTS	PERCENTAGE
21-30	16	8.0%
31-40	13	6.5%
41-50	34	17.0%
51-60	59	29.5%
61-70	44	22.0%
71-80	34	17.0%
TOTAL	200	100.0%
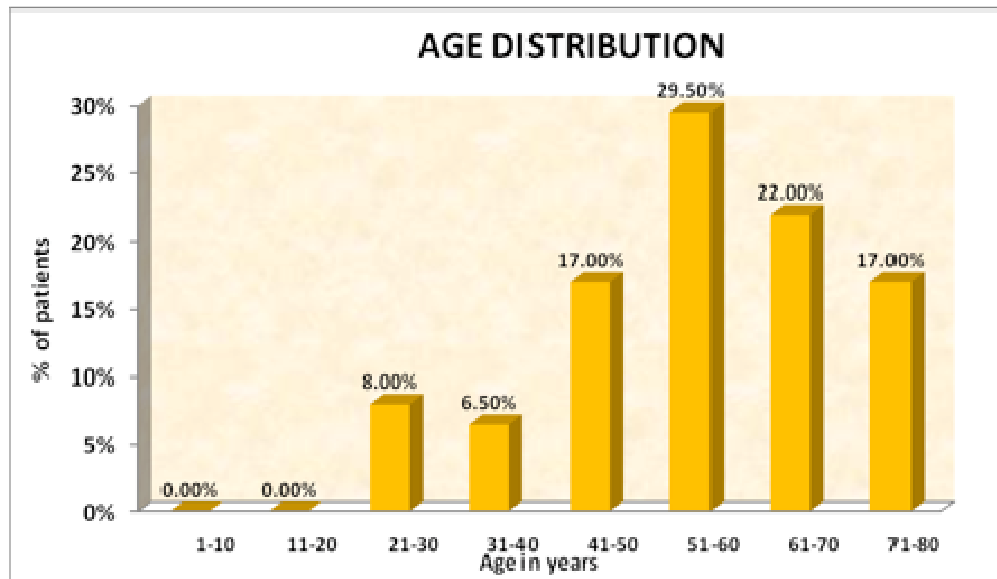
Fig. 5: Age Distribution

The Commonest age group involved was between 51 to 60 years, accounting for 29.5% of the cases. The age group ranged from 21 to 80 years.

SEX DISTRIBUTION

GENDER	NO. OF PATIENTS	PERCENTAGE
Male	54	27.0%
Female	146	73.0%
Total	**200**	**100.0%**

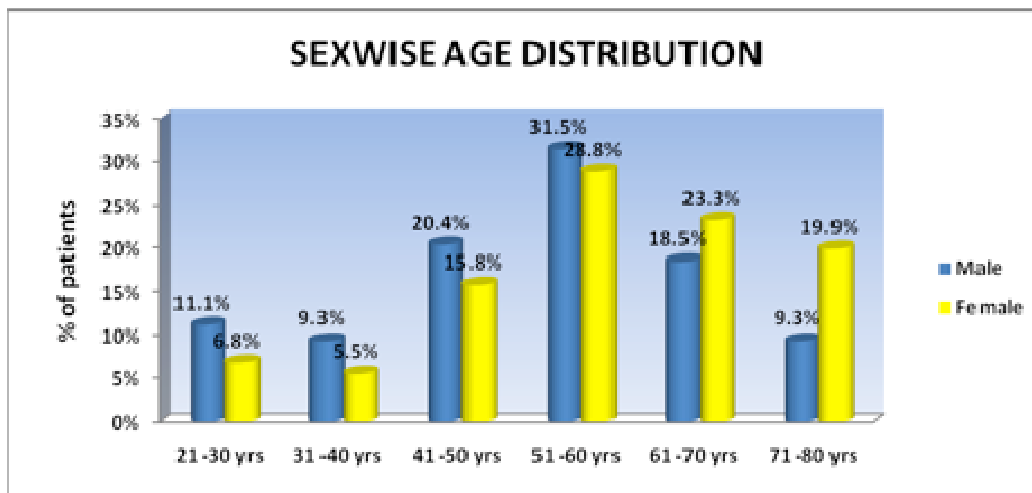*Fig. 6: Sex Distribution*

There existed a female preponderance in the study population with 73% females and 27% male subjects.
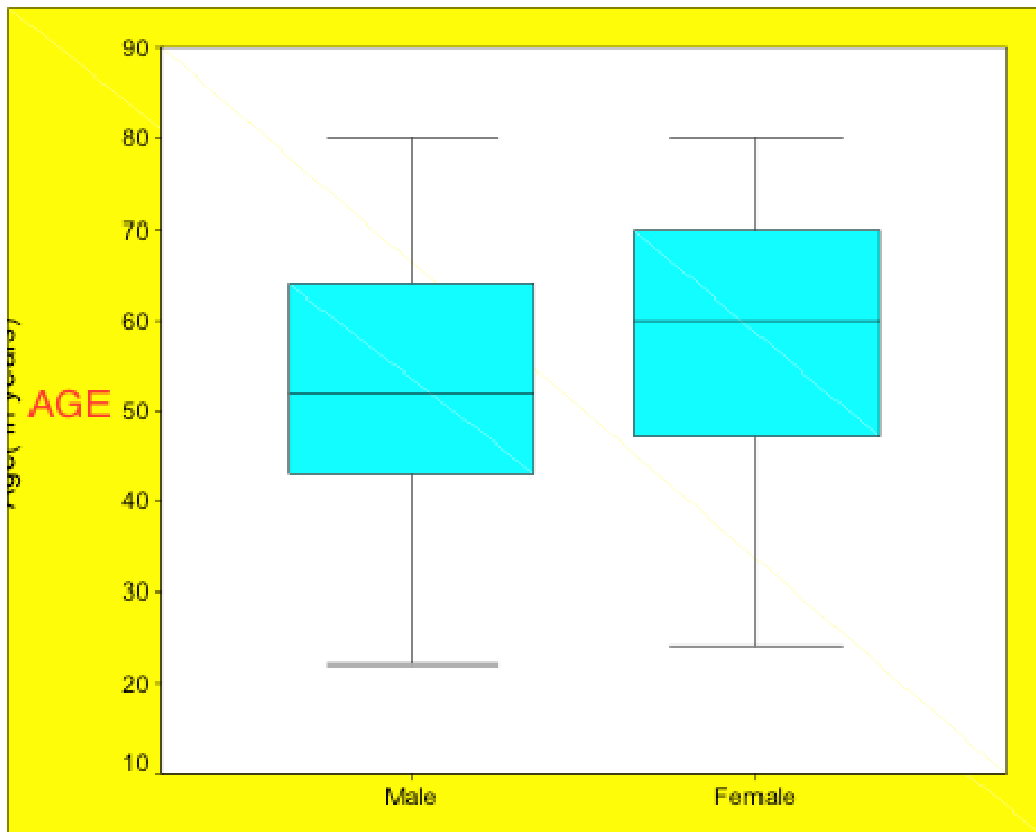
AGE and SEX DISTRIBUTION

Age	Sex			
	Male		Female	
	n	%	n	%
21-30 yrs	6	11.1%	10	6.8%
31-40 yrs	5	9.3%	8	5.5%
41-50 yrs	11	20.4%	23	15.8%
51-60 yrs	17	31.5%	42	28.8%
61-70 yrs	10	18.5%	34	23.3%
71-80 yrs	5	9.3%	29	19.9%
Total	**54**	**100.0%**	**146**	**100.0%**

Fig. 7: Sexwise Age Distribution

MEAN AGE

Sex	N	Mean	Std. Deviation	Student Independent t-test
Male	54	52.41	14.80	t=2.36 p=0.02* significant
Female	146	57.94	14.71	

Fig. 8: Mean Age

SEVERITY OF STROKE BASED ON NECT AND DWMRI FINDINGS

Imaging	NUMBER	PERCENTAGE
LACUNAR /SMALL STROKE	11	6.1%
MODERATE STROKE	68	37.8%
MODERATE TO SEVERE	63	35.0%
SEVERE	38	21.1%
Total	**180**	**100.0%**
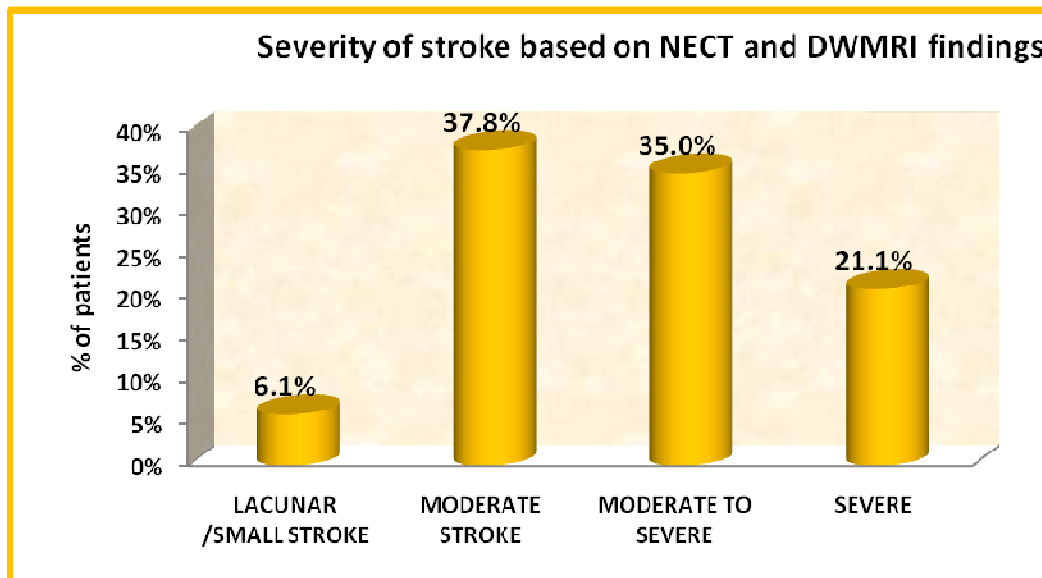
Fig. 9: Severity of stroke based on NECT and DWMRI findings

IMAGING – NECT FINDINGS

| NECT	NUMBER	PERCENTAGE
Hyperdense MCA sign	26	13.0%
Loss of gray white interface, insular ribbon sign	44	22.0%
Loss of Gray-white interface, obscuration of lentiform nucleus.	29	14.5%
Normal CT	101	50.5%
Total	200	100.0%
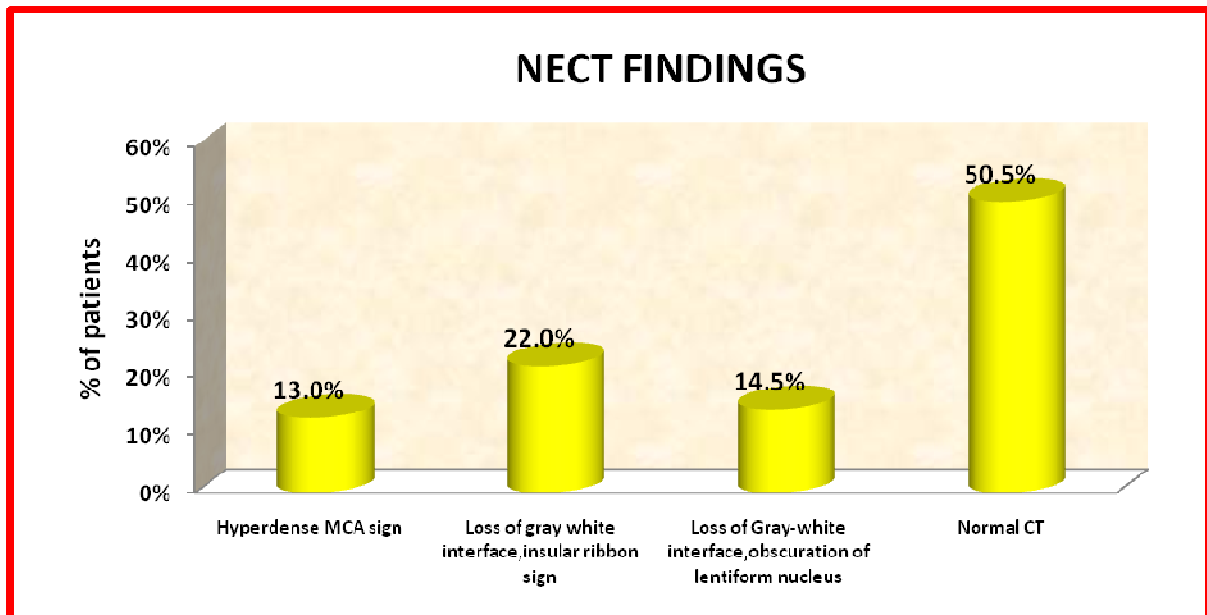
Fig. 10: NECT Findings

DW MRI RESTRICTION –TERRITORIAL DISTRIBUTION

DWI Restriction and ADC	NUMBER	PERCENTAGE
MCA	86	44.0%
ACA	52	32.0%
PCA	08	7.0%
PICA	07	3.5%
ACA and MCA (ICA occlusion)	27	13.0%
Total	180	100.0%
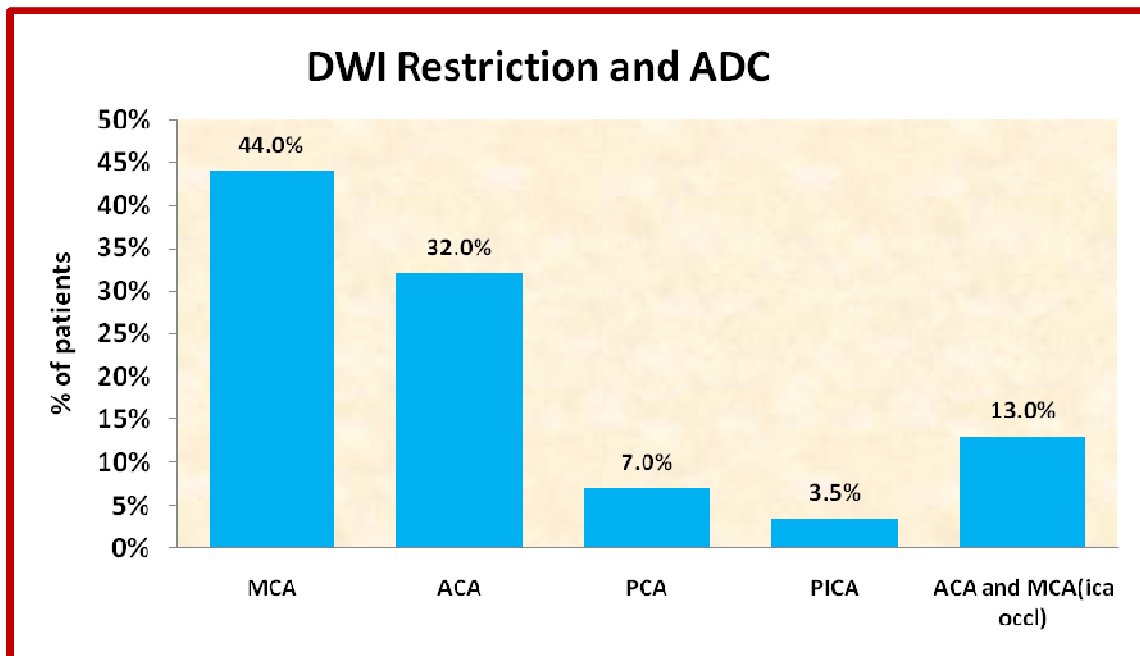
Fig. 11: DWI Restriction and ADC

DWIMRI Modality Statistics

		STROKE		
		RESTRICTION	NO RESTRICTION	
DWMRI	RESTRICTION	174	6	180
	NO RESTRICTION	2	18	20
		176	24	200

|	Estimate	95% confidence interval
Sensitivity	96.7%	92.8% - 98.7%
Specificity	90.0%	68.3% - 98.7%
Accuracy	96.0%	92.3%- 98.2%
Positive predictive value	98.9%	95.9 % - 99.8%
Negative predictive value	75.0%	53.2% - 90.2%

ROC Curve for DWMRI

MRI scan ROC Curve
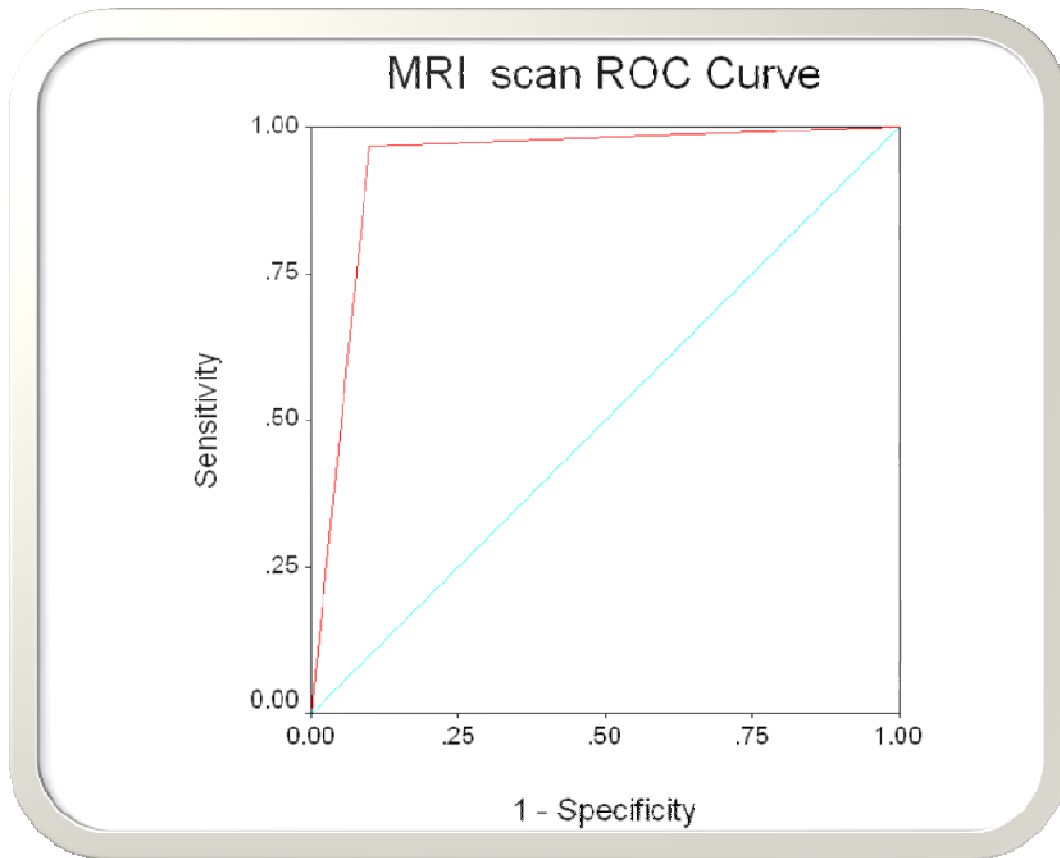
NECT modality statistics

		STROKE		
		POSITIVE	NEGATIVE	
NECT	POSITIVE	88	11	99
	NEGATIVE	88	13	101
		176	24	200

NECT	Estimate	95% confidence interval
Sensitivity	88.8%	80.9% - 94.3%
Specificity	63.5%	37.0% - 71.5%
Accuracy	50.5%	43.3%- 57.6%
Positive predictive value	50.0%	42.3 % - 57.7%
Negative predictive value	54.2%	32.8% - 74.4%

ROC Curve for NECT

CT scan ROC Curve
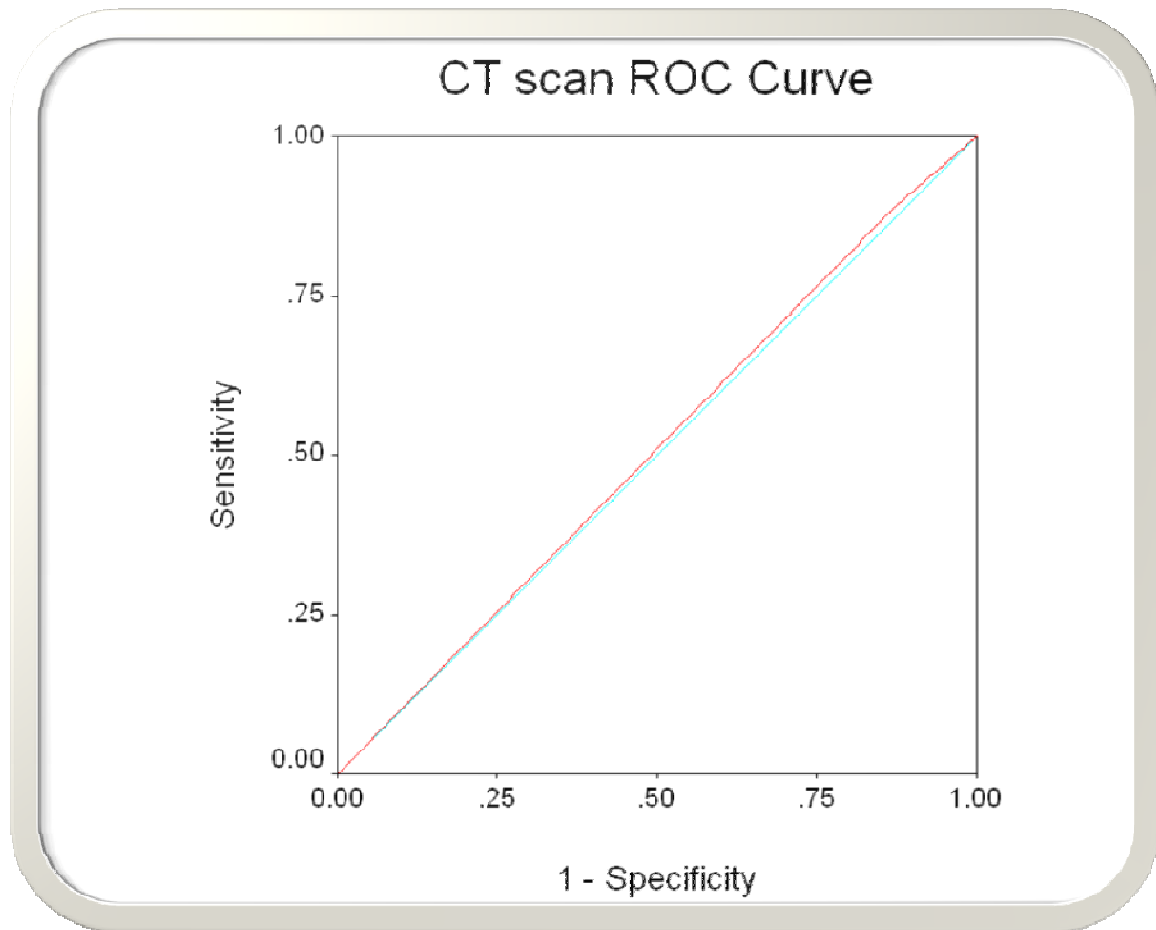
MCNEMARS TEST FOR DWMRI

		STROKE		
		RESTRICTION	**NO RESTRICTION**	
DWMRI	**RESTRICTION**	174	6	**180**
	NO RESTRICTION	2	18	**20**
		176	24	**200**
Mc Nemars test= 25.3 P=0.001				

There is a significant difference between MRI and CT results according to McNemar's test.
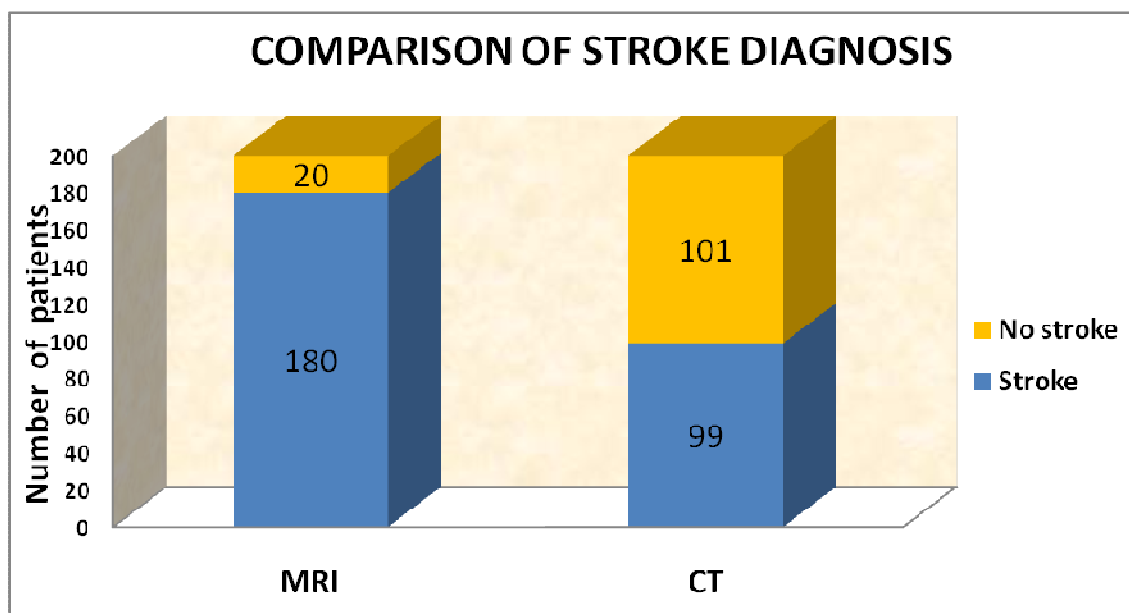
MCNEMARS TEST FOR NECT

		STROKE		
		POSITIVE	**NEGATIVE**	
NECT	**POSITIVE**	88	11	**99**
	NEGATIVE	88	13	**101**
		176	24	**200**
Mc Nemars test= 59.9 P=0.001				

There is a significant difference between MRI and CT results according to McNemar's test.

DW MRI Vs CT Imaging analysis

	Image findings	% of findings	Proportion with 95% Confidence interval
MRI	180/200	90%	90.0%(85.2% -93.6%
CT	99/200	49.5%	49.5%(42.6%-56.4%)

Fig. 12: Comparison of Stroke Diagnosis

KAPPA AGREEMENT STATISTICS

DWMRI

		STROKE		
		RESTRICTION	**NO RESTRICTION**	
DWMRI	**RESTRICTION**	174	6	180
	NO RESTRICTION	2	18	20
		176	24	200
Kappa agreement statistics κ= 0.79 P=0.001				

There is a good agreement between MRI and actual results according to kappa agreement statistics.

NECT

		STROKE		
		Positive	**Negative**	
CT	**Positive**	88	11	99
	Negative	88	13	101
		176	24	200
Kappa agreement statistics κ= 0.05 P=0.43				

There is a slight agreement between CT and actual results according to kappa agreement statistics.

Interpretation

0   = No agreement

0.01 - 0.20   = Slight agreement

0.21 - 0.40   = Fair agreement

0.41 - 0.60   = Moderate agreement

0.61 - 0.80   = Substantial agreement

0.81 - 1.00   = Almost perfect agreement

Clinical data and images obtained in 200 consecutive patients with suspected hyperacute stroke were examined. Results of NECT and DWI were analysed and correlated with the final neurologic discharge diagnosis. Of the 200 patients, who underwent imaging, a final diagnosis of hyperacute stroke was made in 180 patients after full clinical evaluation and neurological imaging. The results of the imaging studies were stratified and reported according to the time of symptom onset in hours that had elapsed between the triage and radiological examination.

Diffusion-weighted MR imaging had an advantage that was most pronounced in the period of less than or equal to 6 hours following the presentation to the radiology department. Of the 200 patients, Restricted diffusion was observed in 180 patients with 96.7% sensitivity (95% CI 92.8%-

98.7%) and 90% Specificity (95% CI: 68.3%- 98.7%). CT had a sensitivity and specificity of 88% (95% CI, 80.9%- 94.3%) and 63.5% (95% CI: 37%-71,5%) respectively. The DWI had a higher accuracy rate of 96% (95% CI: 92.3% - 98.2%) than with 50.5% in CT (95%CI: 43.3% - 57.6%). Diffusion-weighted imaging appeared to have a superior negative predictive value of 75% (95% CI: 53.2% - 90.2%) and a good positive predictive value of 98.9% (95 % CI: 95.9% - 99,8%) than with a CT negative predictive value of 54.2% (95 %CI: 32.8% - 74.4%) and a positive predictive value of 50% (95% CI: 42.3% - 57%). Of the 180 patients 86 patients (44%) demonstrated restricted diffusion in MCA territory, 52 patients (32%) in ACA territory, 27 patients (13%) in ACA and MCA (ICA Occlusion) (27%), 8 patients (7%) in PCA territory and 7 patients (3.5%) in PICA territory. 20 patients with no restricted diffusion were analysed with conventional MR. 3 patients had venous infarct, 2 patients had factitious disorder and 1 patient had an unexplainable vasogenic edema.

14 patients out of the 20 patients were classified as stroke mimics. Of the 14 patients with stroke mimics, 8 patients had seizure disorder, 3 patients were diagnosed with peripheral vertigo, 2 patients with underlying metabolic disorder and 1 patient with space occupying lesion. Of the 200 patients with signs and symptoms of stroke within 6 hours stroke window, CT was negative in 101 patients with no evidence of early ischemic signs. 99 patients within the

hyperacute stroke window showed early ischemic signs in CT namely the hyperdense MCA sign, insular ribbon sign, loss of grey white matter interface, obscuration of lentiform nucleus and mass effect.

The parenchymal hypoattenuation and cerebral edema were analysed in five different regions (frontal, temporal, parietal, basal ganglia and insular ribbon). The extent of early ischemic signs was estimated on NECT and DW images relative to the anticipated size of the ischemic territory. When the five regions were considered independently, the sensitivity was higher for DWI than NECT. For both modalities sensitivity was highest for the insular ribbon and basal ganglia.

With DW imaging the consensus on the presence of parenchymal hyperintensity was present in 180 of 200 patients (sensitivity 96.7%; McNemar 25.4, p =0.001) with excellent kappa value of 0.79. Overall the consensus on the presence of early ischemic signs on NECT was achieved in 99 of 200 patents (Sensitivity, 88% ; McNemar 59.9, P = 0.001) with a poor kappa value of 0.05. The hyperintense ischemic lesions on diffusion- weighted images were more distinct and easier to identify than the early ischemic signs on NECT resulting in overall better kappa values.
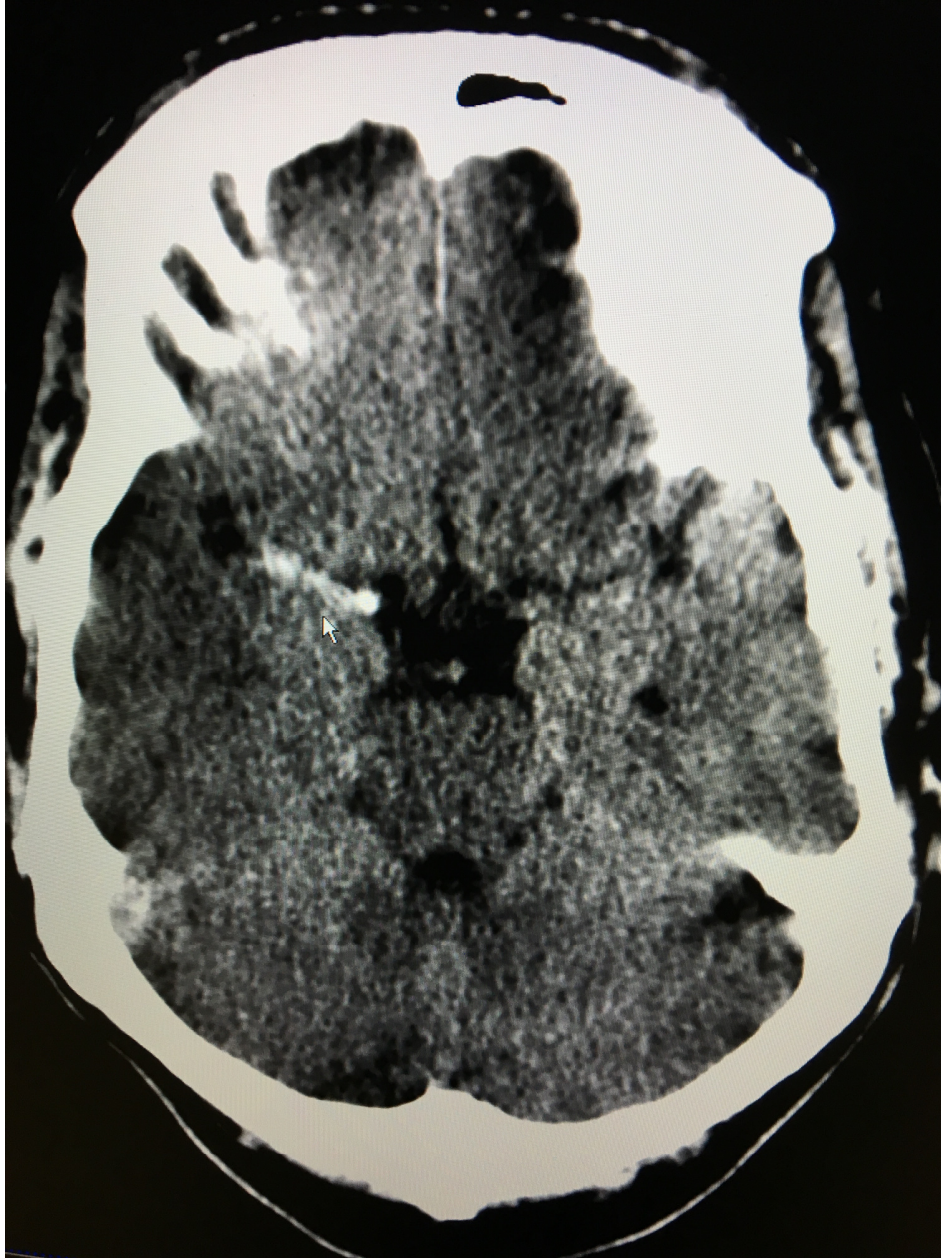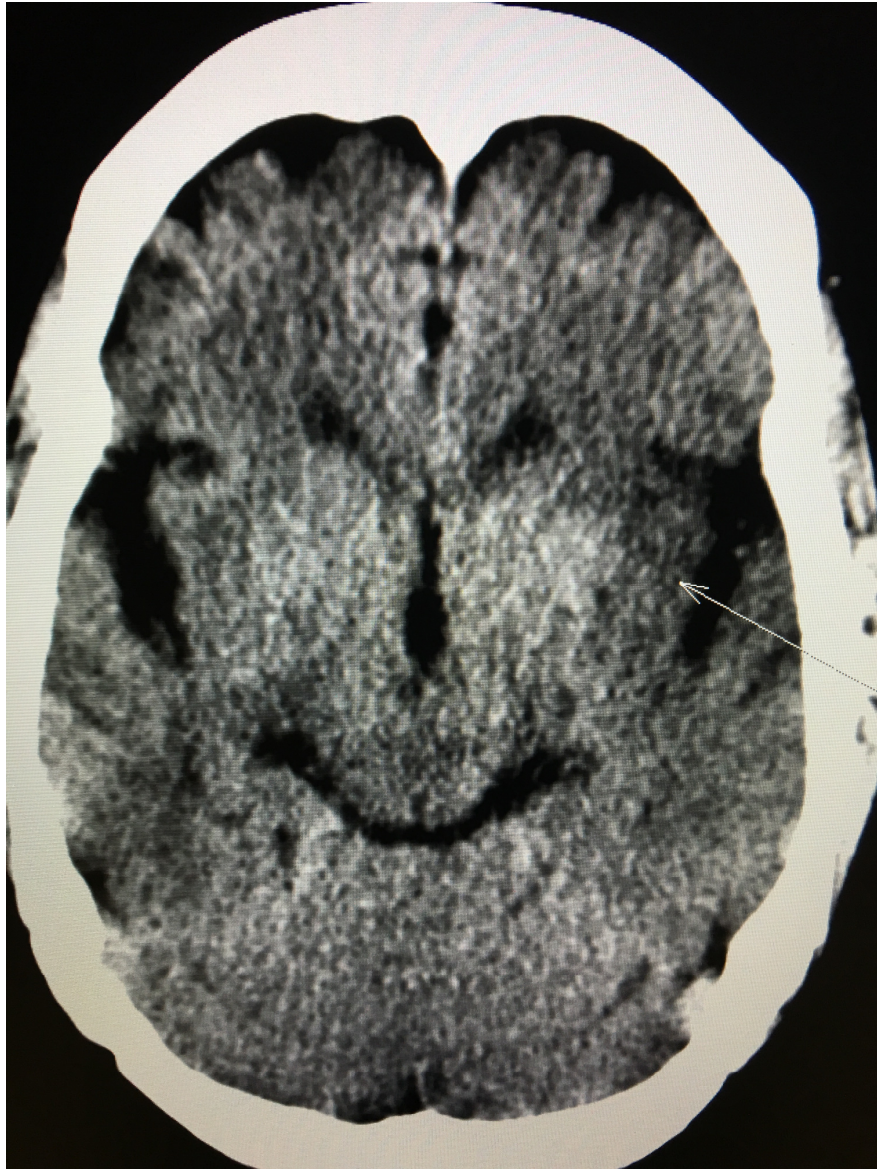
Illustrative Cases

ILLUSTRATIVE CASES

Case 1

Case-1. Axial image from a non-enhanced CT scan of brain of a 56-year-old male with symptoms of stroke. Increased density is observed at the M1 segment of right middle cerebral artery corresponding to thrombosis.

Case 2

Case-2. Axial non-enhanced CT of 48-year-old female with symptoms of stroke. CT reveals loss of normal left lentiform nuclear attenuation consistent with cytotoxic edema, as compared with the normal-appearing right lentiform nuclei. Obscuration of lentiform nucleus also called the blurred basal ganglia is seen in middle cerebral artery infarction and is one of the earliest and most frequently seen sign.
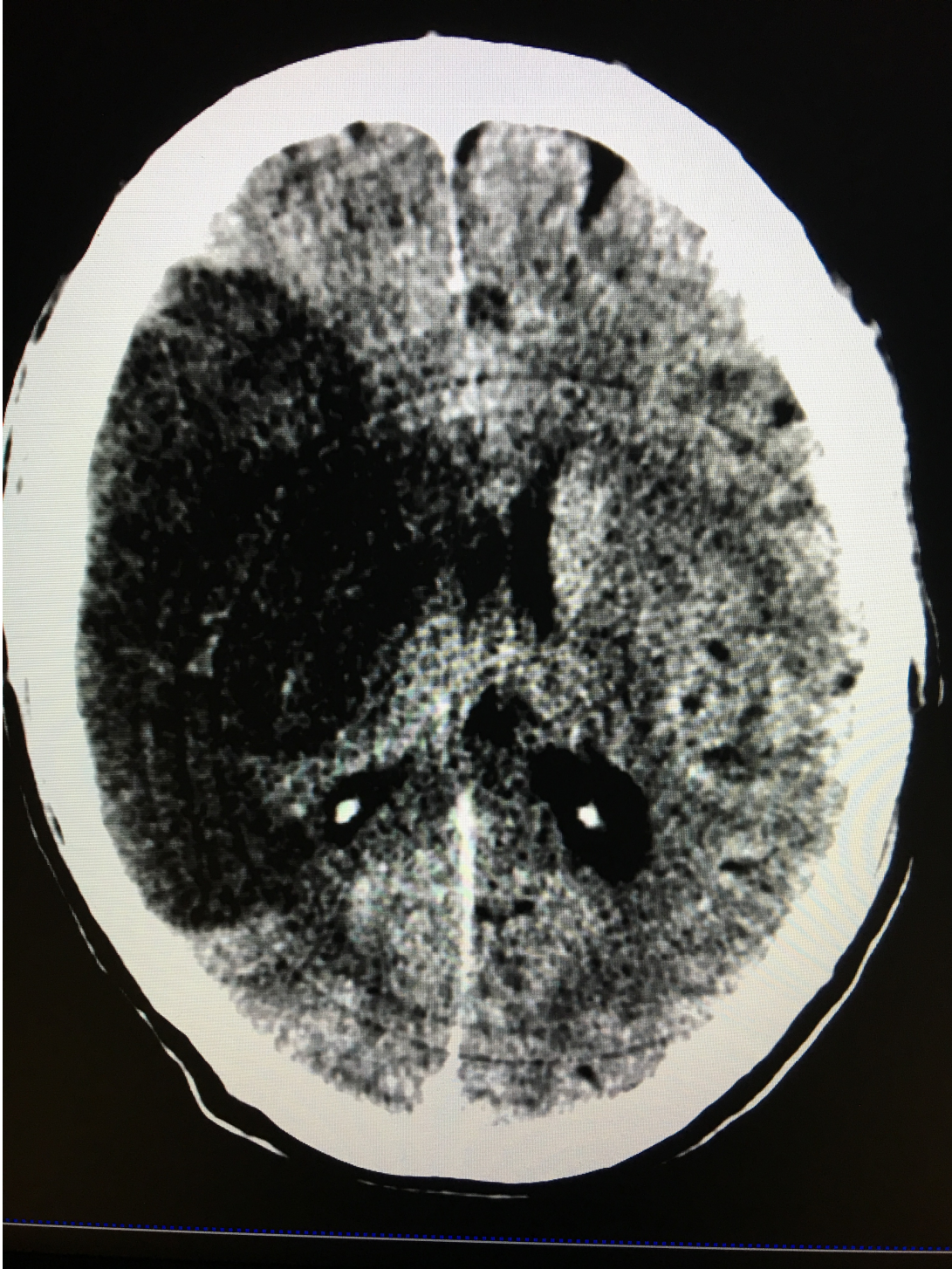
Case 3
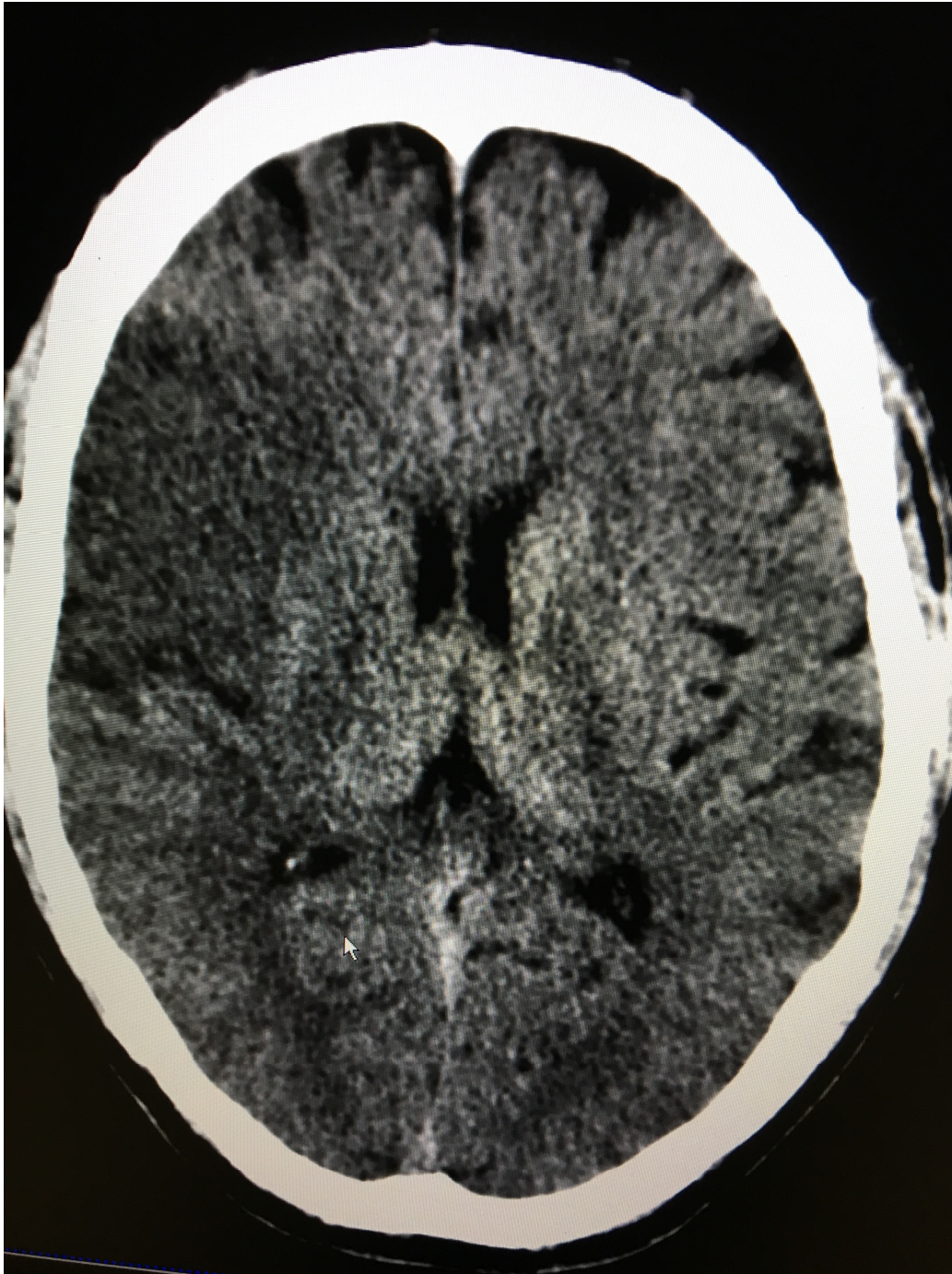
Case-3. Axial non-enhanced CT of 63 year male with symptoms of stroke showing loss of grey white interface in the right MCA territory. Sulcal effacement due to edema is also observed.

Case 3 – Follow up

Case-3 - Follow up: CT on the 3rd day of this patient showed increasing mass effect and hypodensity in the affected territory - Acute phase of Infarction.

Case 4

Case-4. Axial NECT of a 38-year-old male with stroke symptoms show loss of the left insular stripe –insular ribbon sign, which is one of the earliest indications of MCA infarction. Normal stripe is a thin white line (gray matter) adjacent to the darker gray line (subcortical white matter). With ischemia insular stripe is lost and homogenous appearance is noted.
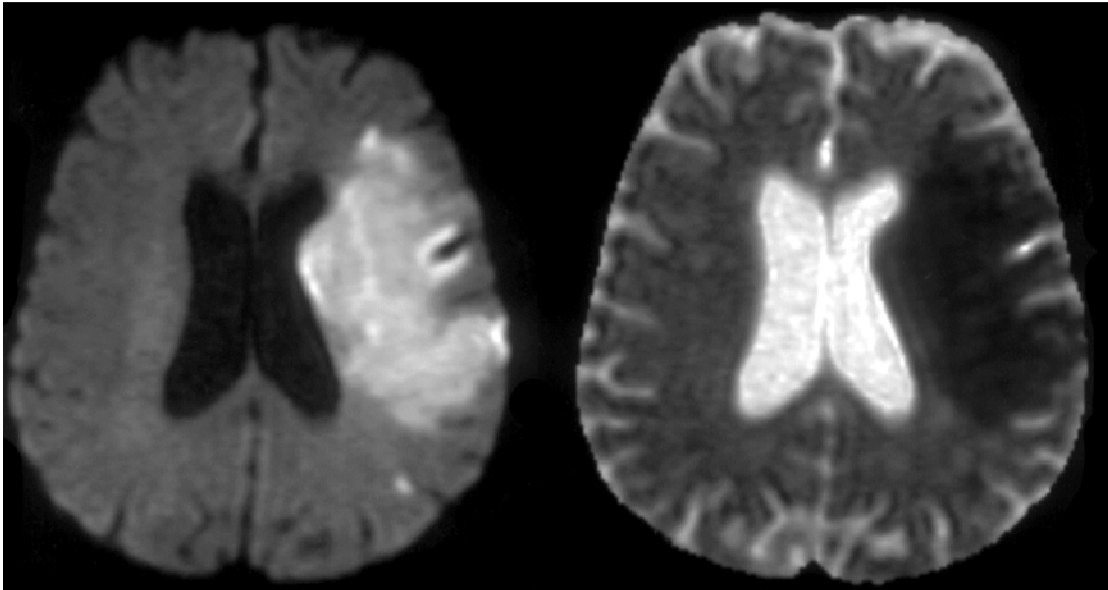
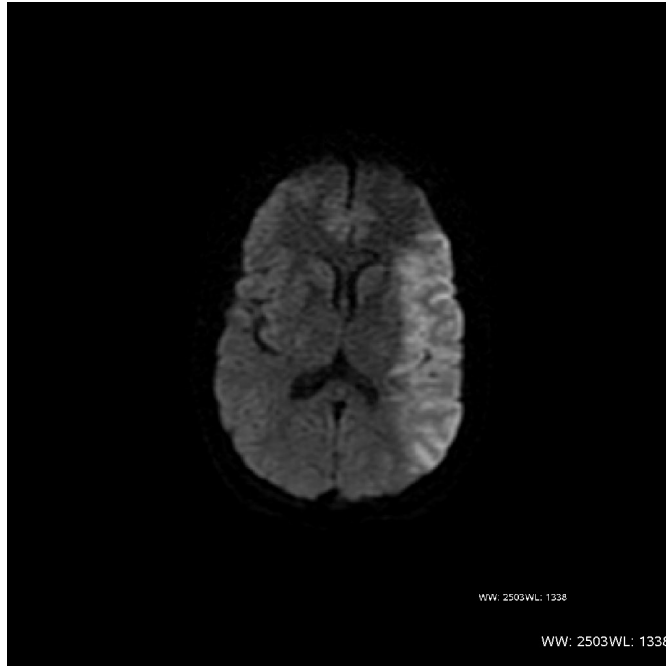**Case-5.** DWI image of a 57-year-old female patient with symptoms of stroke onset within 3.5 hours shows restricted diffusion in left MCA territory with corresponding low signal in ADC image.

Case 5

WW: 1804WL 980
WW: 1804WL: 980

Case-5. MRA of the same patient shows no flow in the left MCA. Axial reconstruction showing an abrupt cutoff (occlusion) of the left middle cerebral artery.

Case 6

Case-6. DWI of 52-year-old male patient with symptoms of stroke onset within 4 hours shows restricted diffusion in left MCA territory.
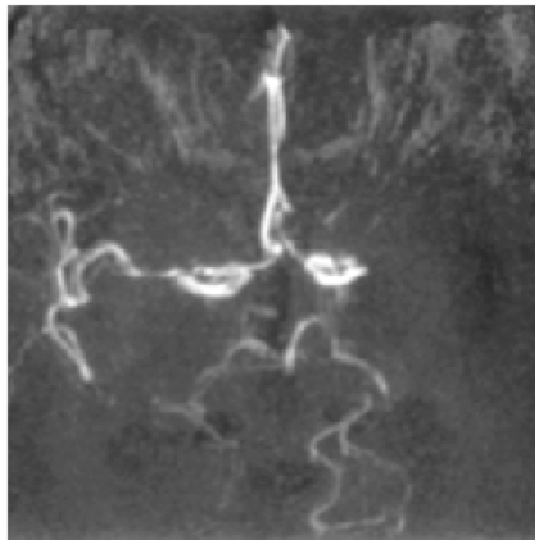

Case-6. MRA of the same patient shows no flow in the left MCA. Axial reconstruction showing an abrupt cutoff of the left middle cerebral artery.

Case 7
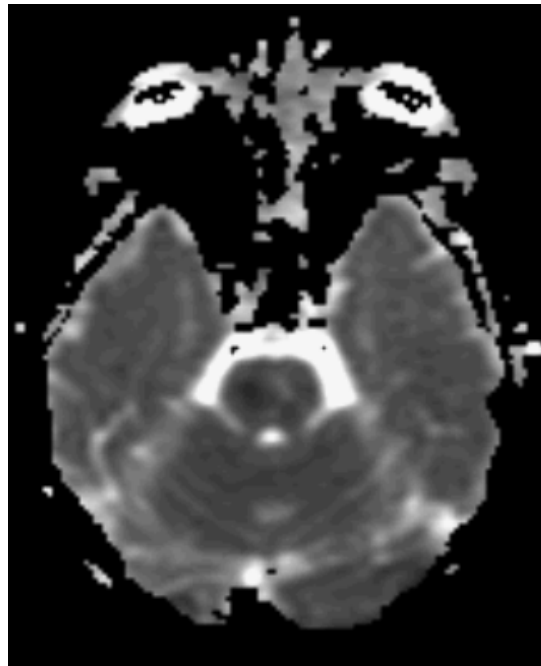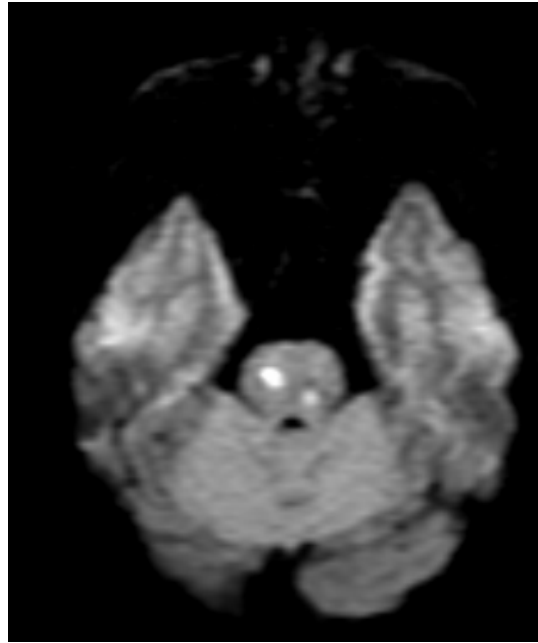
Case-7. DWI image of a 65 years male presented within 4 hours of stroke symptoms shows restricted diffusion in the Pons with corresponding low signal intensity in ADC.

Case 8
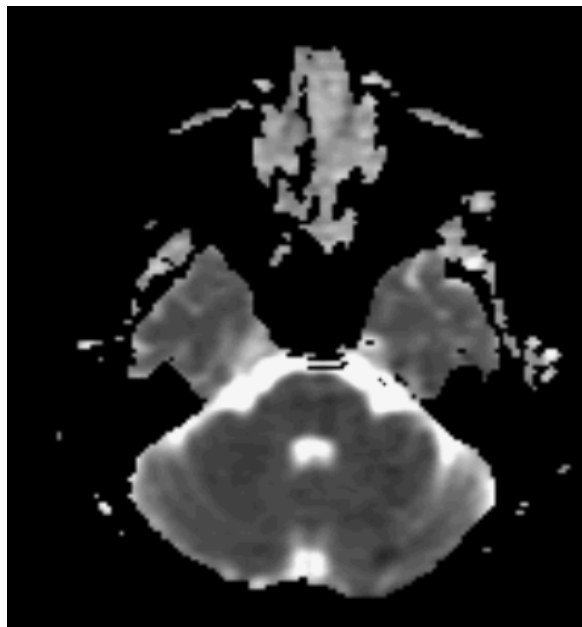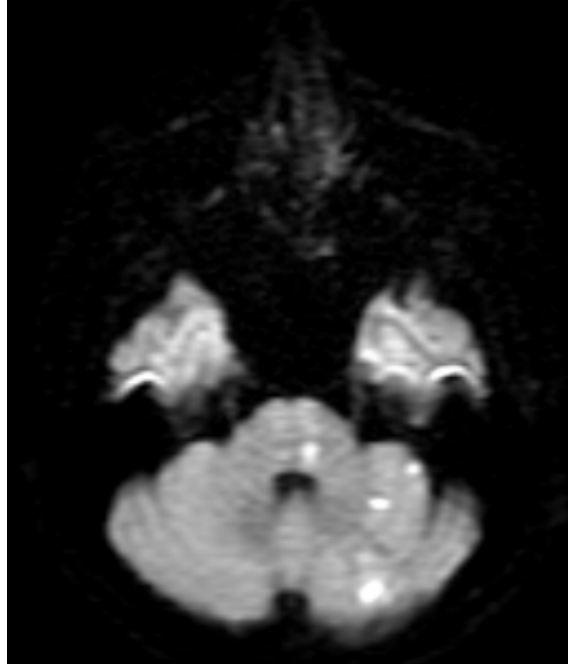
Case-8. DWI image of a 33-year female within 4 hours of stroke symptoms shows restricted diffusion in the medulla and left cerebellar region with corresponding low signal intensity in ADC.

Case 9
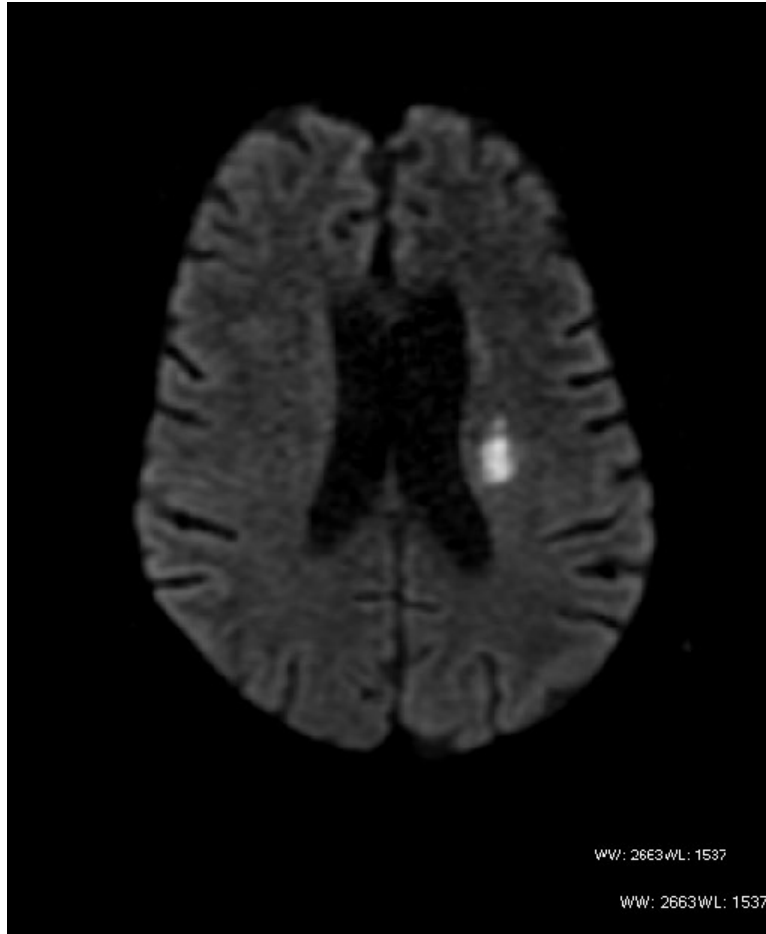
Case-9. DWI of 66-year male within 4 hours of symptom onset showing a lacunar infarct in left corona radiata.

Case 10
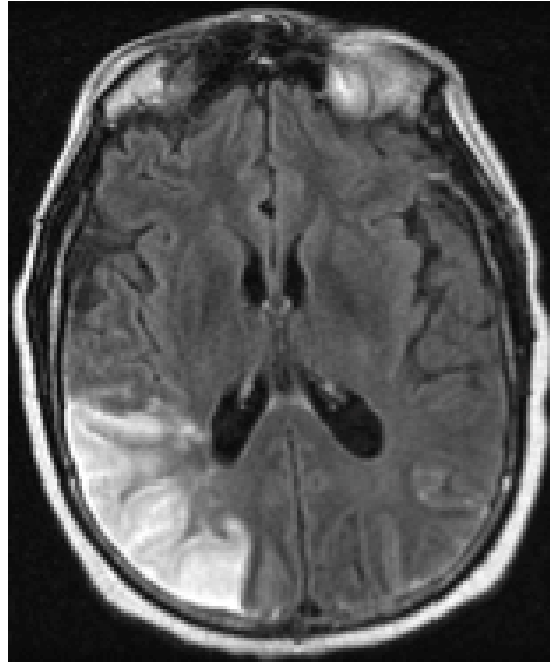
Case-10. DWI of 59-year-old female presenting within 5 hours of stroke symptoms shows hyperintensity in right posterior parietal region. MR angiography of circle of Willis demonstrates small caliber of right Sylvian branches of MCA when compared to the normal.

Case 11
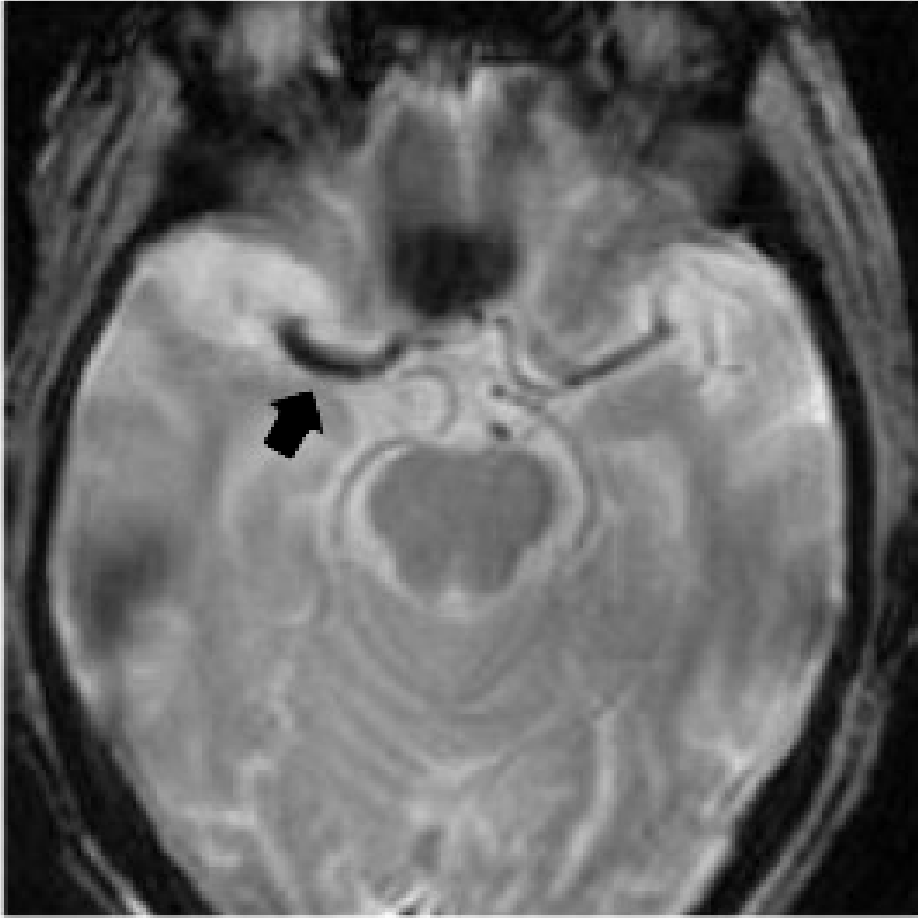
Case-11. Susceptibility weighted image (SWI) of a 48-year male within 4 hours of stroke symptoms show susceptibility sign in the right proximal MCA.
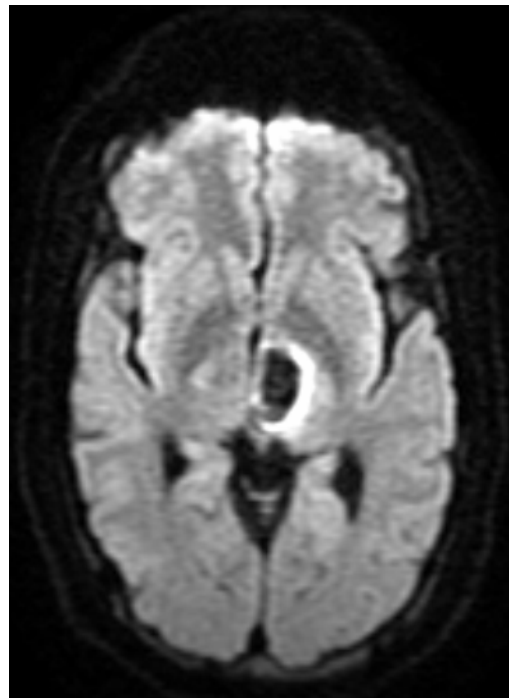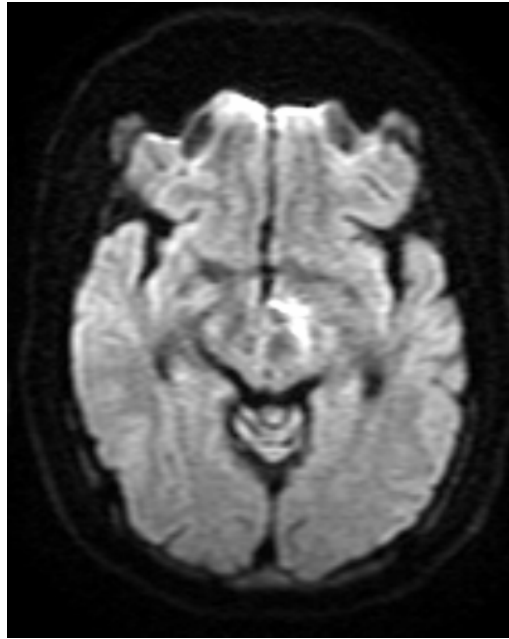
Case 12. Follow up DWI image of a 67 year Male patient shows restricted diffusion with hemorrhagic transformation in the left Thalamus during the subacute phase of infarction.
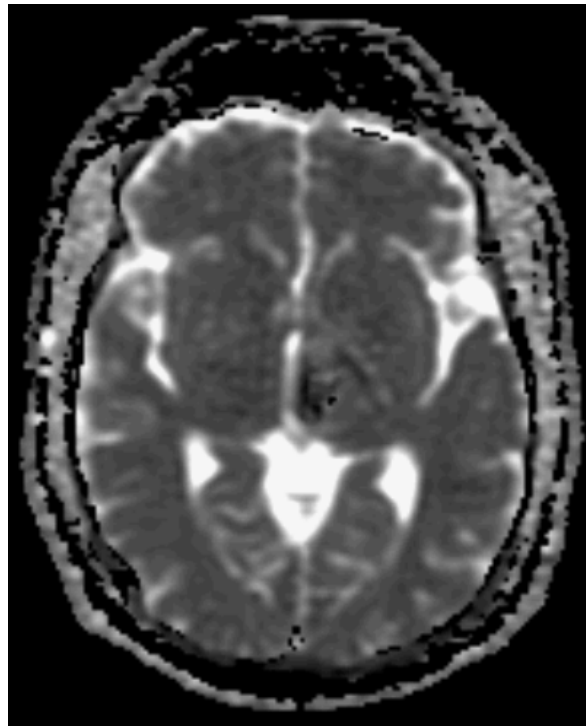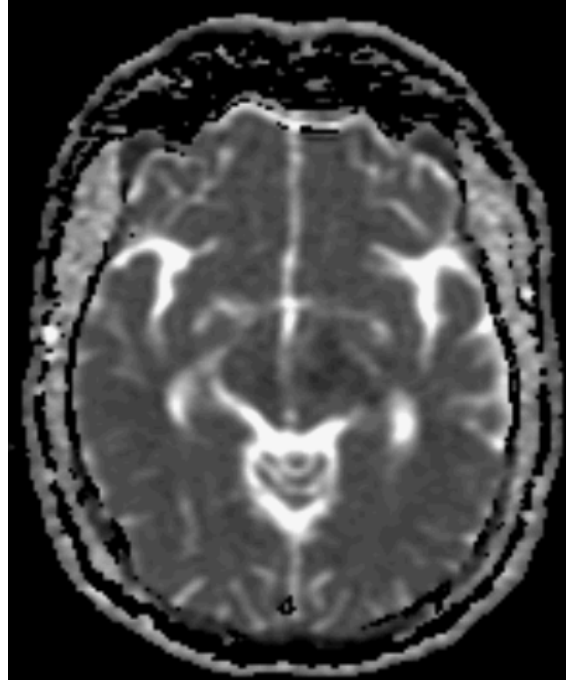
Case-12. The corresponding ADC of the same patient with subacute infarct with hemorrhagic transformation in left thalamus.

Case 13

Case-13. Follow up CT image of acute infarction on day 3 of a 49-year female patient showing hypodensity in bilateral occipital region**.**
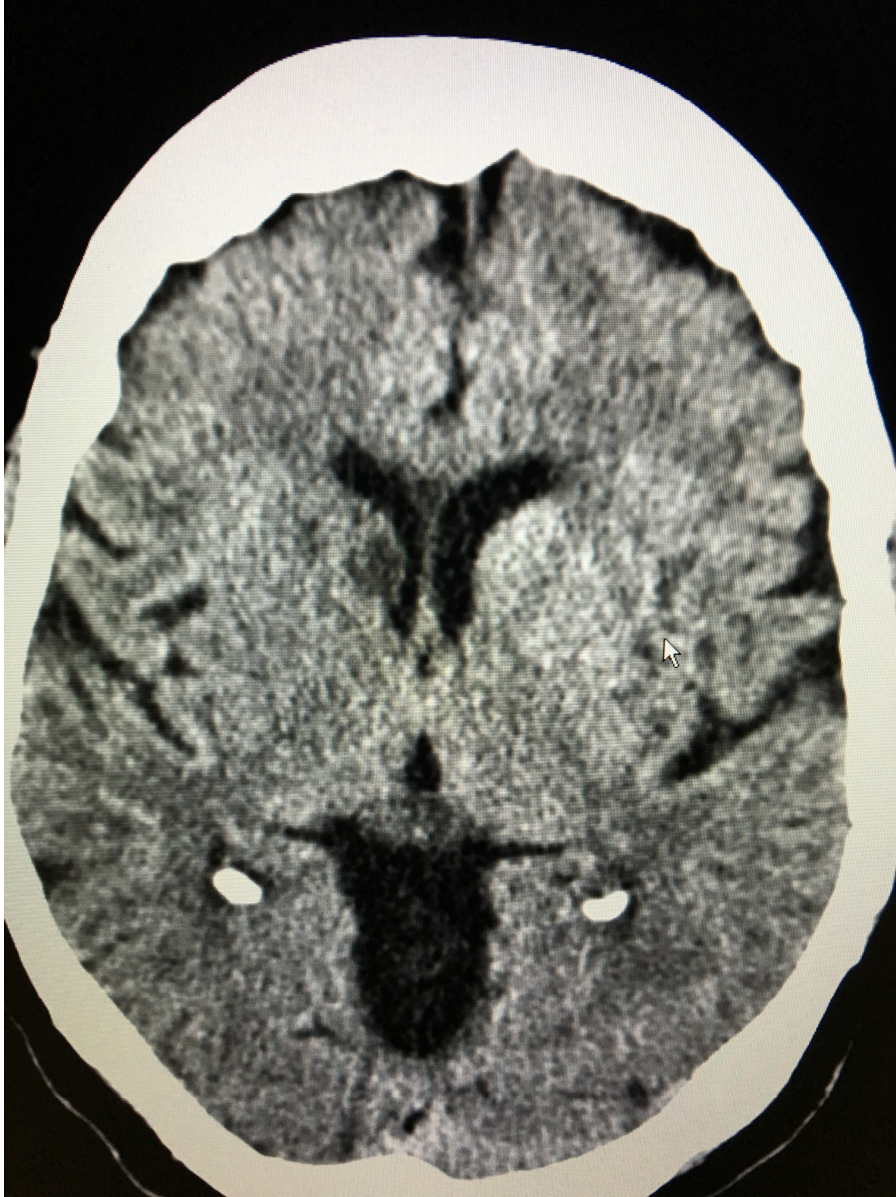
Case-14. Follow up CT image on day 12 of a 69-year-old male patient of acute

lacunar infarction in head of right caudate nucleus.

Case 15

Case-15. Follow up CT image of acute infarction of a 57-year female patient showing hemorrhagic transformation of a subacute infarct in the right basal ganglia.

Case 16

Case-16. Follow up CT image of a 76-year female patient showing marked hypodensity in the Left MCA territory with similar density to cerebrospinal fluid corresponding to chronic infarction.

Case 16
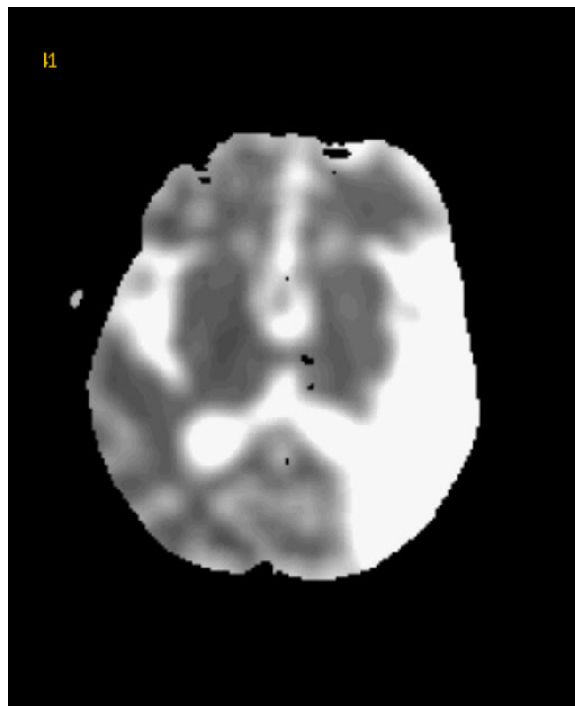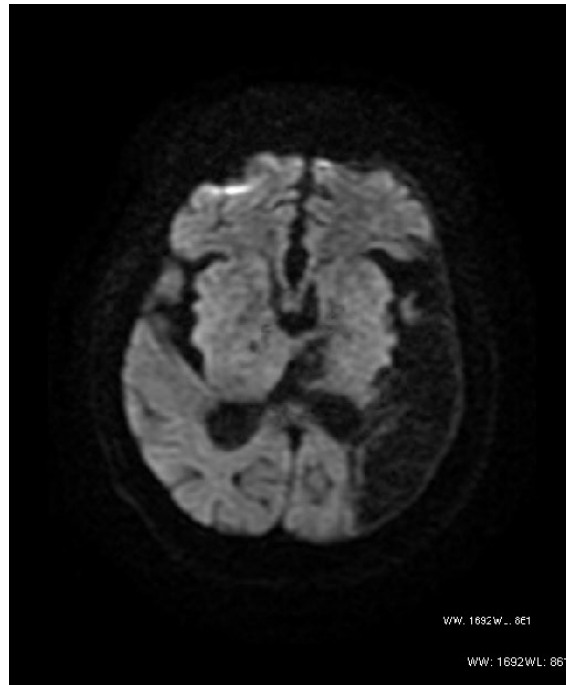
Case-16. DWI with corresponding ADC of   the same patient with chronic

infarction showing hypointensity on DWI and hyperintensity on ADC.
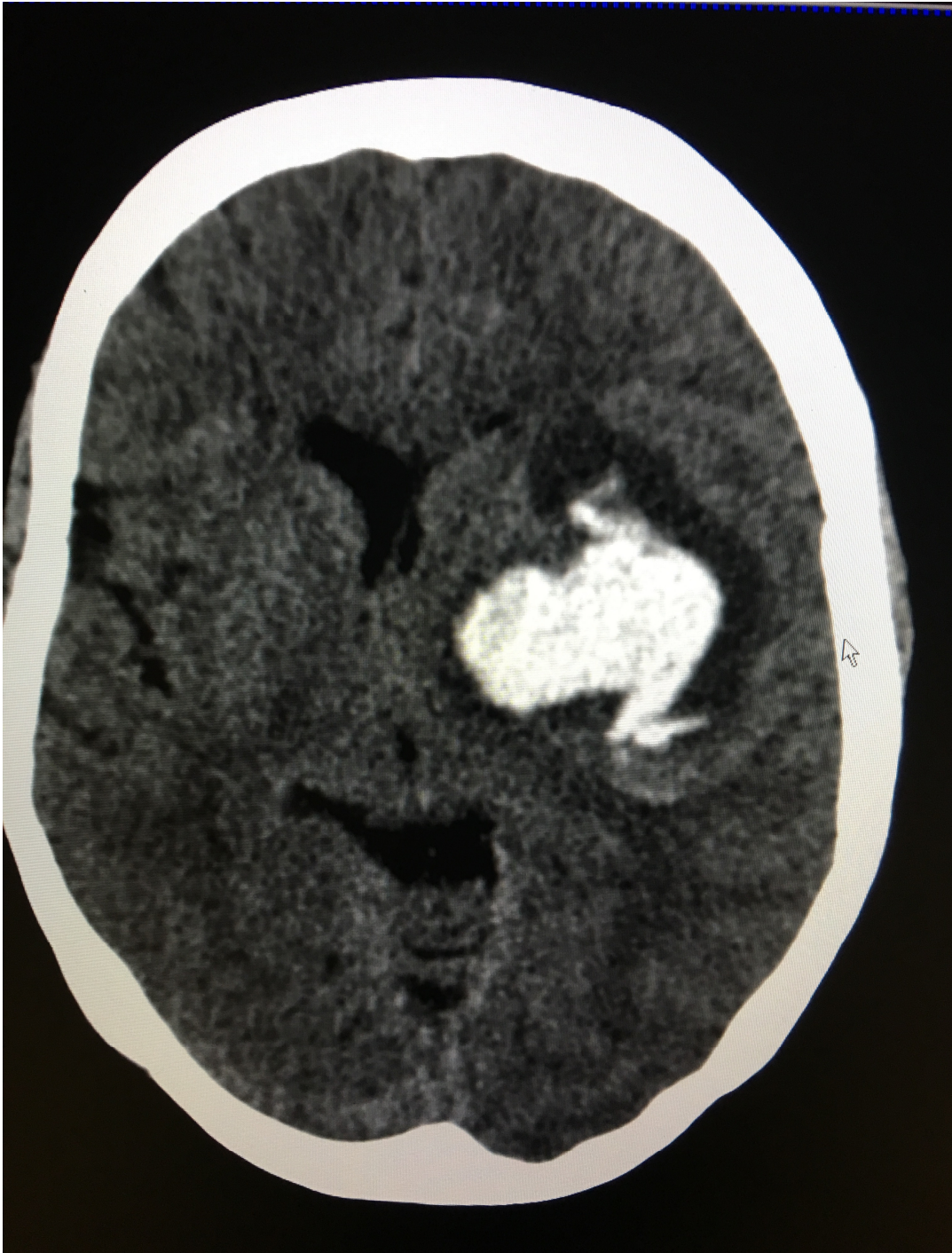
Case-17. Axial CT image of 48-year-old hypertensive female showing intracerebral hemorrhage in left capsulo-ganglionic region. Patients with hemorrhagic stroke were excluded from the study.

Discussion

DISCUSSION

The study was designed to evaluate and to compare nonenhanced CT and DWI in diagnosis of hyperacute stroke under similar clinical scenario. The study randomized the patients with signs and symptoms of hyperacute stroke with respect to the sequence of imaging modalities. The reperfusion strategies employed in the treatment of acute ischemic stroke mainly depends on early and precise identification of patients who will benefit from thrombolytic therapy. The efficacy of thrombolysis combined with the poor and limited sensitivity of nonenhanced CT in the early stage of acute stroke has led to the administration of thrombolytic therapy in the absence of positive CT findings. Diffusion-weighted MR imaging has demonstrated superior sensitivity early in the course of ischemia and allows for modified reperfusion protocols that necessitate imaging evidence of ischemia before institution of treatment.

The study observes that non-enhanced CT cannot adequately estimate the volume of ischemia in hyperacute stroke and showed poor inter-rater reliability. The large volume strokes have an increased risk of hemorrhagic transformation after thrombolytic therapy. The data in our study reveals the superiority of DWI in assessing and delineating the extent of infarction in hyperacute stroke. MRI can also evaluate the age of infarct. The potential advantage of non-enhanced CT is to identify and define acute intracerebral hemorrhage, which is an

absolute contraindication to thrombolysis. However Schellinger et al [72] observed that unenhanced CT and MRI have equal sensitivity for detecting hemorrhage. The study also observes that with the advent of echo-planar imaging, it is faster to acquire images in a single shot requiring only 100 ms. Multishot imaging requires only 200 ms per image thus providing the possibility of image acquisition of brain in less than 2 minutes. The study also observes that 24-hour availability of MRI offered significant advantages in diagnosis and therapeutic implications and offered the advantage of time and effort reduction.

Lansberg et al [40] in a prospective study of 19 hyperacute stroke patients observed a higher accuracy and sensitivity of diffusion-weighted imaging compared with CT. In this study, CT was done first and the median delay between CT and diffusion-weighted imaging was 1.2 hours. In our study the higher sensitivity and detection rate of diffusion-weighted imaging is associated with increase in edema over time. The study also observes that the inter-rater variability in detection of infarction was excellent for diffusion-weighted imaging than CT.

The Alberta Stroke Program Early CT score (ASPECTS) used a ten point topographic scoring system for quantitatively assessing acute ischemia on CT imaging. The scoring system divides the MCA territory in to 10 regions, each of which accounts for one point in the total score. A total score of 10 is assigned

for the normal MCA territory. One point is deducted for each area involved in stroke on nonenhanced CT images. A score of 0 indicates diffuse ischemic involvement of the MCA territory. The clinical agreement of ASPECTS was superior when compared with the one-third MCA rule. Our study observed that ASPECTS system is a systematic and an ideal method that is applicable to axial sections acquired at different levels.
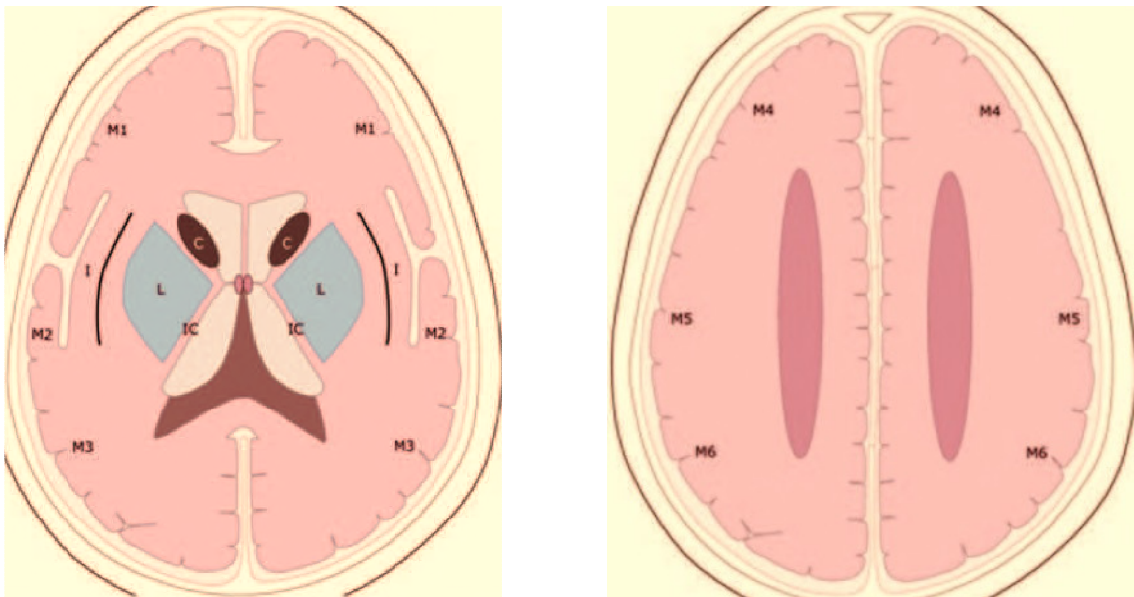
Fig. 13: 10 areas of the Middle Cerebral Artery distribution, each one of which accounts for one point in the ASPECT scoring system - the internal capsule (IC), the lentiform nucleus (L), the caudate nucleus (C) M1, M2, M3, M4, M5, M6, and the insular cortex (I).
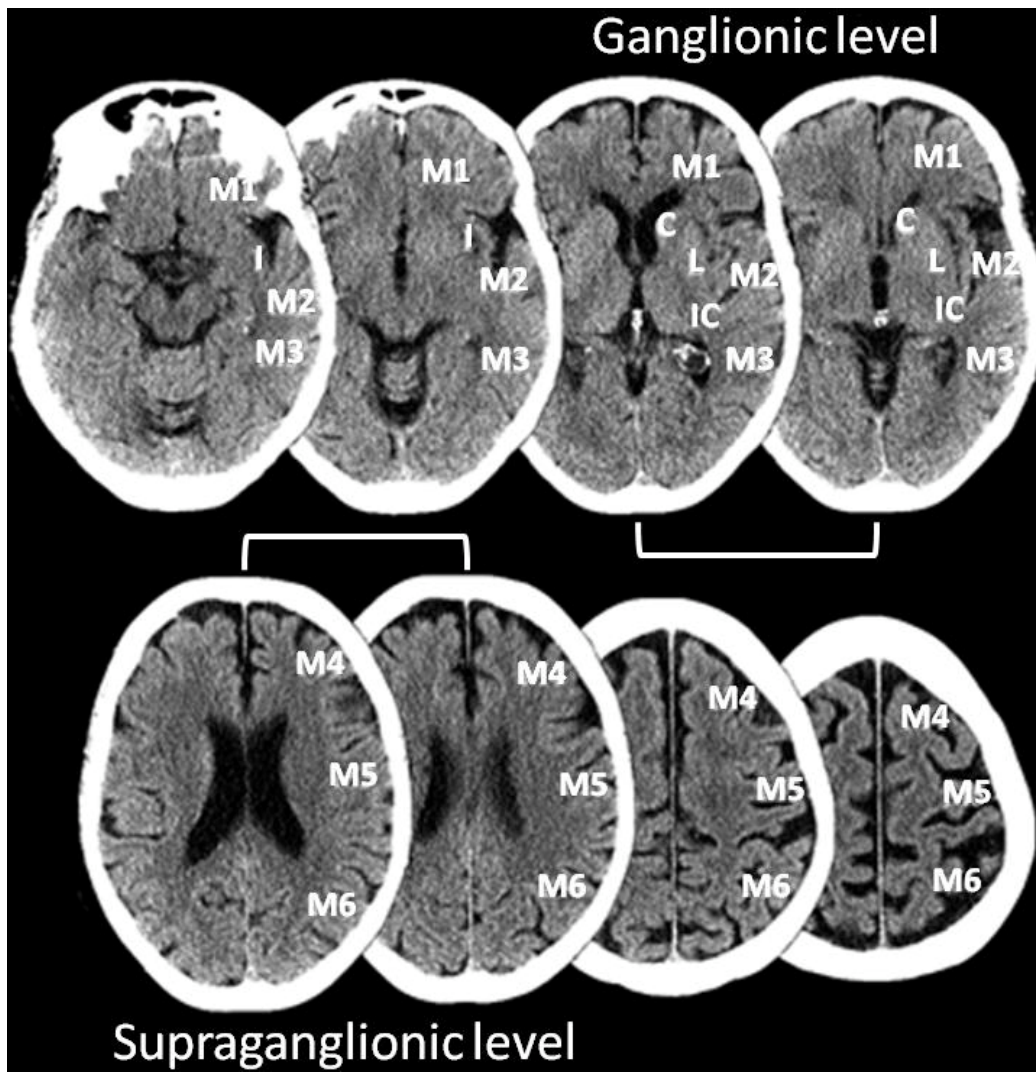
Fig. 14: Axial CT images showing the MCA territory regions, as defined by ASPECTS.
L - Lentiform nucleus. C - Caudate nucleus, I -Insular ribbon, IC - Internal capsule, M1 -
Anterior MCA cortex, M2 MCA cortex lateral to the insular ribbon, M3 - Posterior MCA
cortex, M4, M5, and M6 are the anterior, lateral and posterior MCA territories
immediately superior to M1, M2 and M3, respectively and rostral to the basal ganglia. The
image is adapted from www.aspectsinstroke.com.

Our study observes that the Alberta stroke program early CT score is a useful diagnostic tool to detect and describe the ischemic area in a detailed

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manner according to the cerebral vascular anatomy. ASPECTS is a tool established for CT within 3 hours of cerebral ischemia and has a higher agreement of different raters when compared with the one third of middle cerebral artery rule. When aspects score is implemented in to routine use, it has to be validated for the 6 hours time frame in order to make efforts to extend the therapeutic time window of 3 hours for thrombolytic therapy based on the improved imaging criteria.

The Alberta stroke program early CT score tool was instituted to provide a standard CT examination with a proper grading system. Lately ASPECTS has also been in instituted for diffusion-weighted MRI. Mitomi et al [73] in their study compared the detection rate of ischemia by DWI ASPECTS and CT ASPECTS in patients with signs and symptoms of stroke within 3 hours. The inter rater agreement for DWI ASPECTS and CT ASPECTS were calculated using kappa statistics and the concordance rates of CT ASPECTS and DWI ASPECTS scores were analyzed. The correlation coefficient of CT aspects and diffusion coefficient was established. The study observed that a higher detection rate of ischemia by DWI ASPECTS within 3 hours of stroke. Our study observed that DWI ASPECT score is sensitive and superior to CT ASPECTS scoring system for hyperacute stroke.

Our study observes that the apparent diffusion coefficient values are

found to be different for white matter and gray matter. There is a significant decrease in apparent diffusion coefficient in white matter than gray matter and the lasts for a longer period in white matter than gray matter. The possible reason for this phenomenon is attributed to early occurrence of necrosis in gray matter infarctions than in white matter infarctions. The decrease in ADC of white matter is also attributed to the cytotoxic edema occurring in various cell types such as glial cells, axons and myelin sheaths.

The DWI signal in cytotoxic edema appearing bright seems to be irreversibly damaged tissue, which leads to permanent infarction. In the early stages of ischemic insult, the decreased ADC in the ischemic penumbra represents the viable tissue and the hypo-perfused tissue is at the risk of infarction. After thrombolysis there may be reversal of abnormal signal either partially or completely.

On judging the size of the lesion, diffusion-weighted images showed better kappa value than CT. Our study detected lacunar lesions more often and the DWI has yielded a larger number of concordant ratings. It is important to assess the size of the ischemic lesion as early as possible, as larger infarctions are prone for hemorrhagic transformation following the administration of thrombolytic.

Watershed infarctions develop between two major vascular territories or within a single territory involving the supraganglionic white matter, which represents the border zone of the superficial and deep penetrating arteries. In case of thromboembolic infarction, thrombolytic therapy in the early period may be effective in limiting the size of the infarction. Contrary to thromboembolic infarction, watershed infarctions are less responsive to thrombolysis, the reason being a reduction in the perfusion secondary to reduced blood flow and poor distal perfusion pressure. There exists a difference in evolution time of ADC between thromboembolic and watershed infarction, thromboembolic infarction demonstrating early normalization. However the T2 signal intensity remains the same for both the types of infarction.

The role of diffusion-weighted imaging in identifying the stroke subtypes and the need for thrombolytic therapy is well observed in this study. The National Institute of Neurological Disorders and Stroke trial states that the lacunar stroke remains a relative contraindication for thrombolysis, the reason being the partial or complete recovery in this subtype and risk of intracerebral hemorrhage with tissue plasminogen administration. The study also observed that up to 27% small vessel ischemic strokes evolved gradually in to large cortical strokes. The DWI hyperintense signal also delineates the extent of ischemic lesions. And based on the location the small vessel strokes can be differentiated from large vessel stroke.

Hemorrhagic transformation is a common phenomenon of an embolic stroke and worse outcome is associated with clinically significant hemorrhagic transformation. Tong et al [74] studied the utility of diffusion weighted imaging in assessing and prediction of hemorrhagic transformation. The study analyzed 17 patients within 8 hours and at 1 week after the ischemic event. ADC was calculated for each pixel of the ischemic region and the values less than 550×10^{-6} correlated with the development of hemorrhagic transformation. In our study the ADC values of less than 540×10^{-6} correlated with the hemorrhagic transformation. Thus diffusion-weighted imaging is a good tool for predicting hemorrhagic transformation of an embolic stroke.

The role of combined diffusion-weighted imaging – perfusion imaging in initiation of thrombolytic therapy has gained widespread acceptance but the potential disadvantage of time limitation has led to reduced usage of this combination. Diffusion-weighted imaging and perfusion imaging combined together offers a good tool for rational thrombolytic therapy in hyperacute ischemic stroke. The identification of penumbra before attempted perfusion is an important factor. The perfusion deficits will define the potential infarcted area whereas the diffusion-weighted imaging as a whole identifies the region of irreversible infarction. Thrombolytic treatment should be instituted when there is diffusion – perfusion mismatch. Diffusion perfusion match implies a completed stroke and hence the role of thrombolysis appears to be of little role.

The candidates for thrombolysis are selected on the basis of diffusion perfusion mismatch. However because of time limitations diffusion-perfusion combination could not be performed in hyperacute stroke patients.

Based on the location stroke can be divided on supra and infratentorial one, depending on the affected vascular territory namely internal cerebral artery and its main branches like the middle cerebral artery, anterior cerebral artery and posterior circulation area. Depending on the affected region all strokes are further divided in to small, intermediate and massive. The most frequently encountered area of stroke is the MCA territory. The MCA stroke can affect the entire arterial supply including the basal ganglia or only the cortical region may be affected. This mainly depends on the level of occlusion and the state of compensatory collateral circulation from the branches of posterior cerebral and anterior cerebral arteries. Basal ganglia strokes are striatocapsular strokes, which affect the lentiform nucleus, claustrum, external capsule, and anterior genu of internal capsule and head of the caudate nucleus. The primary reason for this stroke is the occlusion of lenticulostriatal branches arising from the initial middle cerebral artery segment. The occlusion of thalamoperforating arteries leads to lacunar infarctions of the thalamus and hypothalamus in the case of watershed infarctions, combined blood supply of the long perforating arteries of white matter and deep pial branches of arteries of the cortical brain surface are affected. The occipital lobe is the second most frequent stroke

location next to MCA stroke area. The mainly affected areas include calcarine sulcus, deep penetrating arteries of thalamus, midbrain and posterior genu of internal capsule.

Caplan et al [75] divided the posterior circulation lesion sites in to 3 main vascular territories according to the New England Medical Center posterior stroke circulation registry. (1) Proximal intracranial territory includes the areas supplied by intracranial vertebral arteries, medulla oblongata and the posterior inferior cerebellar artery (PICA) supplying the cerebellar territories. (2) Middle intracranial territory includes a part of the brainstem supplied by basilar artery, Pons and a portion of cerebellum supplied by anterior inferior cerebellar artery (AICA) (3) Distal intracranial territory includes the territories supplied by rostral basilar artery, posterior cerebral arteries and their branches. The basilar artery occlusion at the level of distal segment affects the thalamus, the midbrain and posterior genu of internal capsule. The superior cerebellar artery occlusion leads to stroke in the cortex of the superior portion of the affected cerebellar region, ipsilateral portion of the vermis and the cerebellar white matter. The anterior inferior cerebellar artery occlusion leads to stroke involving the lateral region of cerebellar hemisphere. The posterior inferior cerebellar artery occlusion leads to the development of stroke in the region of lateral portion of medulla oblongata and inferior cerebellar peduncle.

In acute stroke imaging, acquiring the images of the intracranial and extra cranial vessels provides information, which will be essential for explaining the stroke mechanism. Detecting occlusion, stenosis, vascular anomaly and dissection can explain the events that have led to the cerebrovascular accident. Obtaining this information is beneficial for the treatment of patients after stabilization. Our study instituted the magnetic resonance imaging protocol for visualization of the intra and extra cranial vessels; the time of flight MRA demonstrated higher sensitivity and specificity when compared with the phase contrast MRA. The information obtained from MRA can guide anticoagulation, on cardiac evaluation and carotid endarterectomy and hence aid in prevention of future strokes.

Our study observed that the patients with symptoms and signs of small vessel ischemic disease were associated with cardiac embolism and atherosclerosis. These ischemic lesions were detected on diffusion-weighted imaging and non-enhanced CT had poor sensitivity and specificity in detecting the small vessel ischemic lesions. On admission CT provided less information as only as 18% as opposed to 95% on diffusion weighted images. The small vessel infarcts are usually seen in the basal ganglia, internal capsule, corona radiata and pons. The differential diagnosis of lacunar infarction includes the widened perivascular spaces also known as Virchow-Robin spaces and subependymal myelin pallor.

The primary goal of opening the occluded blood vessels and to restore the blood supply to the tissue at risk is achieved by way of thrombolysis in hyperacute stroke .The administration of the thrombolytic drug within the golden hour of stroke plays a crucial role in determining the prognosis. Diffusion-weighted signal sensitivity represents the irreversible changes and provides valuable information of the size of the stroke and to consider thrombolysis.

Stroke mimics can provide clinical and imaging overlaps and a systematic pattern based protocol should be followed to provide a reasonably accurate method to diagnose stroke like conditions. This facilitates appropriate and timely management. The following conditions or stroke mimics should be considered namely seizures, migraine, neoplasm, hypoglycemia, wernickes encephalopathy and hepatic encephalopathy. Careful clinical and imaging details can exclude these conditions from acute stroke.

Our study observed that diffusion-weighted MR imaging using echo planar sequences are highly resistant to movement artifacts. The images are acquired within 3 minutes and has improved sensitivity to signal changes primarily due to molecular motion. The other diffusion imaging methods include single shot fast spin echo, single shot gradient echo and single shot spin echo techniques.

Schellinger et al [76] observed equal sensitivity of non-enhanced CT and T2 weighted MRI in detecting intracerebral hemorrhage in 9 patients within 6 hours of symptom onset. Our study observed that unenhanced CT is an easy modality in identifying the intracerebral hemorrhage and excluding patients from the study group. Our study also observed that that T2 *gradient recalled echo technique and susceptibility weighted imaging techniques are highly sensitive in detecting microbleeds.

There exist various classification systems for acute ischemic stroke. The TOAST classification based on the study by Donan et al [77] stroke is classified as being due to 1) thrombosis or embolism due to atherosclerosis of a large artery, 2) embolism of cardiac origin 3) small blood vessel occlusion, 4) other determined cause and 5) undetermined cause. Stroke without an obvious etiology or explanation is termed cryptogenic and constitutes 15 – 20 % of all ischemic strokes.

Bamford et al [78] classified the ischemic stroke by Oxford community stroke project classification (OCSP) and described the anatomical localization of infarct in to the following subgroups 1) total anterior circulation infarct (TACI) 2) Partial anterior circulation infarct (PACI) 3. Posterior vertebral infarct (POCI) and 4) lacunar infarct (LACI).

Albers et al [79] study defined large vessel stroke as greater than 50 % stenosis of carotid, anterior cerebral artery, middle cerebral artery, basilar, posterior cerebral artery or vertebral arteries. These subtypes are more prone for causing significant clinical deterioration.

Schneider et al [80] stated that clot formation and potential embolism in cardioembolic stroke occurs in relation to the cardiac conditions like mitral stenosis, atrial fibrillation or flutter, myocardial infarction, thrombus in the ventricles and artificial heart valves. Small vessel strokes also known as lacunar strokes are a small ischemic lesion, which occurs, in the deep cortical tissue with no potential large vessel or cardiac etiology.

Clinical symptoms of ischemic stroke mainly depend on the anatomical location of the thrombus. The clinical presentation involves acute neurological deficits and affects motor, sensory, vision, visual – spatial perception, consciousness and language.

However the sudden neurological deficits can also be present in non-ischemic stroke like conditions like intracranial hemorrhage, vasovagal syncope, seizures, tumors and other stroke mimics. Careful clinical examination along with neuroimaging leads to proper assessment and diagnosis of ischemic stroke.

The stroke MRI protocol consists of diffusion-weighted imaging, T2/FLAIR, Gradient recalled echo and MR angiography (MRA). This imaging protocol can be performed in less than 30 minutes. Diffusion-weighted imaging provides image contrast based on the molecular motion of water. Cytotoxic edema occurs as result of transfer of extracellular water in to intracellular compartment. This leads to reduce extracellular volume and there is a reduction in the water diffusion in the extracellular matrix. This phenomenon is detected with diffusion-weighted imaging within minutes of vessel occlusion and can be quantitatively measured with the apparent diffusion coefficient mapping. The diffusion weighted imaging lesions can be partially reversible in the hyperacute phase of ischemia and the size of the DWI lesion does not necessarily reflect the irreversible damaged tissue.

Barber et al [33] study concluded that both CT and MRI provide complementary information in some aspects, but time dictates the imaging modality before making a therapeutic decision. The study observed that the ability of CT to detect early cerebral infarction is comparable with Diffusion Weighted Imaging. The study also states that non-contrast CT is versatile, accessible and faster and is a better choice in imaging of acute stroke than MRI when considering thrombolysis. Our study observed that in spite of the above advantages of CT, the sensitivity and specificity of diffusion-weighted imaging in detecting hyper acute stroke is higher.

Diffusion-weighted imaging helps in identifying the cerebral area that are most likely irreversibly damaged and not the regions that are ischemic yet viable. Our study suggests that the diffusion-weighted imaging can contribute significantly in management of acute stroke. A negative study is highly accurate in exclusion of acute brain infarctions. In many situations, a negative diffusion-weighted imaging may spare patients from extensive diagnostic evaluations and may prevent the unnecessary risk of anticoagulation.

Schwamm et al [81] in their study reported a significant statistical correlation between acute diffusion MR lesion volume and acute and chronic neurological assessment results. Strong correlation exists in cases of cortical stroke and a weak correlation in penetrator artery stroke. Our study observed similar results and observed that the location of the lesion explains the variance as a lesion in a major white matter tract may lead to significant neurological deficit than a cortical lesion of similar size.

Our study observed that diffusion-weighted MR imaging can reliably differentiate vasogenic from cytotoxic edema. The vasogenic edema syndromes include hypertensive encephalopathy, eclampsia, posterior leucoencephalopathies and venous thrombosis. Vasogenic edema may be hypointense to mildly hyperintense as these images have both diffusion and T2 contributions. When vasogenic edema appears hyperintense it can mimic

hyperacute infarction. On ADC images vasogenic edema is always hyperintense whereas the cytotoxic edema due to ischemia is always hypointense for 1 to 2 weeks. This necessitates the need of DW images to be compared with ADC images. Misdiagnosis of vasogenic edema as acute ischemia can lead to unnecessary use of antiplatelet drugs, thrombolytic, anticoagulants and vasoactive agents. Further misinterpretation of acute ischemic infarction as vasogenic edema conditions can discourage the appropriate treatment, and may increase the risk of recurrent cerebral infarction.

Our study observed that hemorrhagic transformation usually occurs during the first week after the development of stroke symptoms. Few factors like lysis of embolus, which occurs when endothelial cells of the vessel are damaged by ischemia and thus results in hemorrhage of the infarcted region. The incidence increases with the use of thrombolytic therapy, anticoagulant therapy, coexisting conditions like hypertension and increased stroke severity. The ischemic lesions with a relatively greater percentage of low ADC values have increased risk for hemorrhagic transformation than lesions with smaller percentage of ADC values.

Our study found that the higher sensitivity of diffusion-weighted imaging is primarily due to the varying temporal evolution of early ischemic signs on CT and signal intensity changes on diffusion weighted images. The early ischemic

signs are as a result of net water uptake in ischemic tissues whereas the diffusion-weighted imaging is sensitive to extracellular to intracellular water shift, which occurs with ischemic cell depolarization. The development of early ischemic changes on CT scans and diffusion-weighted imaging signal changes primarily depends on the severity of ischemia. The sensitivity of CT scan depends on the duration as well as the location, size and type of the infarct. Normal CT scans are observed when the ischemia is confined to the white matter, as the net water is exclusively visible earlier in gray matter. Moseley et al [82] in their study found that conventional spin echo MR is sensitive to accumulation of tissue water and this provides the signal contrast in ischemic parenchyma .The conventional spin echo MRI becomes more hyperintense during the first 24 hours.

Our study observed early ischemic stroke signs in CT namely the hyperdense artery sign, insular ribbon sign and mass effect to be of significant importance in establishing the diagnosis of early ischemia. The hyperdense artery sign suggests that a major blood vessel is occluded and this vessels territory is at risk for cerebral hypoperfusion. Serious clinical implications are seen in ICA and MCA trunk occlusion than the occlusion of MCA, ACA or the PCA branches, as the involved territory is larger. The involved territory, which may undergo ischemic necrosis or not depends on the collateral blood supply. The insular ribbon is an area of gray-white differentiation and is located

between the sylvian fissure and the basal ganglia. Loss of insular stripe is one of the early findings of MCA stroke. Mass effect is very subtle during the early hours after arterial occlusion. Brain swelling detected within the hyperacute stage indicates severe edema and is associated with poor prognosis.

Eichel et al [83] in their study employed a diffusion-weighted imaging only protocol for differentiating stroke from stroke mimics. The common stroke mimics studied were peripheral vertigo, seizures acute confusion, and migraine. Their study concluded that a short DWI only protocol can effectively differentiate stroke from stroke mimics and the findings of restricted diffusion are increased in patients with multiple signs and symptoms. The stroke mimics we came across were migraine, seizures, tumors, metabolic disorders and positional vertigo and these conditions presented with DWI negative results, as the primary event is nonischemic in nature. Of the 14 patients with stroke mimics, 8 patients had seizure disorder, 3 patients were diagnosed with peripheral vertigo, 2 patients with underlying metabolic disorder and 1 patient with space occupying lesion.

Our study found that hyperintense vessels in FLAIR images with acute ischemic stroke have been linked to slow flow in collateral circulation. Patients with hyperintense vessels on FLAIR images have been shown to proceed to large area of ischemia and subsequently more severe clinical impairment.

Hyperintense vessels are a common finding associated with proximal vessel occlusion and predicts arterial occlusion with a higher diagnostic accuracy.

Imaging of cervical vessels should be done as a part of radiological evaluation of patients with acute ischemic stroke. Rl et al [84] in their study concluded that noninvasive imaging of cervical arteries should be performed in the imaging workup of patients with transient ischemic attacks. (TIA). The imaging techniques employed for assessing the intra/extra cranial vessels include diagnostic ultrasound, CT angiography (CTA), MR angiography (MRA) and digital subtraction angiography (DSA). Our study employed 3D MRA as a routine protocol for acute stroke imaging. Each imaging technique has its own advantages and disadvantages in specific clinical situations. DSA is the reference standard imaging technique to assess the degree of vessel stenosis. Complete or near complete stenosis, the so-called the string sign is most precisely detected by DSA followed by contrast enhanced MRA and CTA. The susceptibility vessel sign is the MRI correlate of hyperdense middle cerebral artery sign observed on NECT. Our study observed that the hyperdense MCA sign in CT was inferior to the MRA in identifying MCA occlusion. The hyperdense artery sign carries a risk of severe cerebral ischemia and poor clinical outcome. The absence of MCA flow on MRA indicates the presence of hypoperfused region that is of greater volume than the diffusion weighted lesion and can detect the hypoperfused tissue at the risk of infarction.

The subtypes of stroke may be related to different lesion patterns. Our study classified DWI lesions as single, scattered or multiple lesions in a single vascular territory and multiple in more than one vascular territory. Cardiac emboli are commonly associated with cortical and subcortical lesions in the anterior and posterior circulation (P<.01). Multiple lesions in the anterior circulation were associated with large artery arteriosclerosis. (P<.01) Microangiopathy related image pattern was more commonly seen in patients with hypertension. DWI adds significant etiological information of the small subcortical infarctions when the cause of stroke appears quite uncertain based on clinical aspects only. DWI aids in confirming the clinical diagnosis and facilitates the recognition of certain patterns of ischemia .The high contrast of the DWI lesions facilitates the detection of lesions, which are less than 1 mm, or less in diameter. Smaller lesions including small lacunar infarcts, punctate cortical infarcts and DWI bright dots in patients with TIA are accurately assessed. DWI bright dots confirm the clinical TIA syndrome as ischemic. UG et al[85] studied the clinical usefulness of DWI in subacute minor stroke in a study group of 103 patients and concluded that DWI detects a clinically ischemic lesion in more than half of minor stroke patients presenting more than two weeks after the event, but only in small proportion of patients with TIA. Ischemic stroke in young patients requires more extensive investigation in order to find the underlying etiology than elderly patients. The primary causes include cardioembolism, premature atherosclerosis, immunological and hematological

disorders, vasculitis of central nervous system and connective tissue disorders.

CT stroke settings for identifying the lesions is markedly improved by using an adequate centre level and narrow window width .The narrow window width with higher contrast images are more sensitive in detecting both grey and white matter changes and the hyperdense MCA sign than the standard brain review settings. Our study observed that window width and level settings are essential in identifying the subtle parenchymal changes in early phase of ischemia. The use of window width and center level settings of 8 HU and 32 HU, compared with the standard window settings of 80 HU and 20 HU respectively improved the sensitivity for detecting early ischemic changes from 54 % to 67% without affecting the specificity.

Tisserand et al [86] in their study observed that pronounced FLAIR hyperintensity with DWI hyperintensity, which represents the DWI/FLAIR match, might indicate that the time of stroke onset is likely to be greater than 4.5 hours. Our study observed that DWI hyperintensity with no FLAIR hyperintensity represents a hyperacute lesion i.e. DWI/FLAIR mismatch. The above study findings are observed when the there is a DWI/FLAIR match, the stroke onset is likely to be > 4.5 hours. Our study observed that the DWI/FLAIR mismatch with quantitative or qualitative analysis can determine the sensitivity and specificity of more than 90% about the time of stroke onset.

Goyal et al [87] studied the role of endovascular treatment within 6 hours of stroke symptoms and concluded that endovascular techniques in selected patients is superior to the standard medical management, including thrombolysis, in improving the neurological outcomes in patients with early occlusion of the proximal anterior circulation. However in our study it is of primary importance to focus on patients for receiving intravenous thrombolysis without further delay emphasizing the acute management of ischemic stroke based on early imaging studies. Patient selection should be based on absent contraindication for intravenous tissue plasminogen activator therapy, which includes history of previous intracranial hemorrhage, NECT and DWI demonstrating multilobar infarction (hypodensity/restricted diffusion >1/3 cerebral hemisphere) and patients with bleeding disorders.

Conclusion

CONCLUSION

DW MRI is increasingly replacing NECT in the imaging of hyperacute stroke patients. DWI and NECT imaging performed with the same delay after onset of symptoms of hyperacute stroke resulted in significant differences in diagnostic accuracy.

When compared with NECT, DWI was more accurate for identifying hyperacute infarction and more sensitive for detection of ischemia. The study concludes with higher accuracy rate of diffusion-weighted MR imaging in diagnosing hyperacute than NECT. Our study supports the inclusion of DW MRI in the routine imaging protocol for diagnosing hyper acute stroke.

We conclude that diffusion-weighted imaging is a highly reliable and superior imaging method than NECT in detecting ischemia in hyperacute stroke patients and thus aiding the clinicians in deciding the treatment protocol at the earliest.

Impact of Study
& Recommendations

IMPACT OF STUDY & RECOMMENDATIONS

- This study implicates the need for inclusion of DW MRI in the routine protocol of imaging hyperacute stroke patients.

- We recommend a study, which can be done on a larger sample population, which can strategically prove the significance of the above systematic approach for imaging diagnosis outlined by us and to streamline the imaging preferences according to clinical diagnosis and thereby avoiding unnecessary investigations.

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Annexures

ABBREVIATIONS

ACA   :   anterior cerebral artery

AICA   :   anterior inferior cerebellar artery

ADC   :   apparent diffusion coefficient

APMF   :   adaptive partial medial filter

ASPECTS   :   Alberta Stroke Program Early CT Score

ATLANTIS :   Alteplase thrombolysis for acute non-interventional therapy

                    in ischemic stroke

CBF   :   cerebral blood flow

CBV   :   cerebral blood volume

CT   :   computed tomography

CTA   :   computed tomography angiography

DSA   :   digital subtraction angiography

DWI   :   diffusion-weighted imaging

EPI   :   Echo Planar Imaging

ECASS   :   European cooperative acute stroke study

FLAIR   :   fluid-attenuated inversion recovery

GRE   :   gradient recalled echo

HMCAS   :   the hyperdense MCA sign

ICA   :   internal carotid artery

M1   :   M1 segment of the middle cerebral artery

M2   :   M2 segment of the middle cerebral artery

M3   :   M3 segment of the middle cerebral artery

M4	:	M4 segment of the middle cerebral artery
MCA	:	middle cerebral artery
MRI	:	magnetic resonance imaging
MRA	:	magnetic resonance angiography
NECT	:	nonenhanced computed tomography
NIHSS	:	National Institutes of Health Stroke Scale
NINDS	:	National Institute of Neurological Disorders and Stroke
NPV	:	negative predictive value
OCSP	:	oxfordshire community stroke project
PACI	:	Partial anterior circulation infarct
PCA	:	posterior cerebral artery
POCI	:	Posterior vertebral infarct
PPV	:	positive predictive value
PROACT	:	The Prolyse in Acute Cerebral Thromboembolism
PICA	:	Posterior inferior cerebellar artery
PWI	:	perfusion-weighted imaging
LACI	:	lacunar infarct
rtPA	:	recombinant tissue plasminogen activator
SWI	:	susceptibility-weighted imaging
TACI	:	total anterior circulation infarct
TIA	:	transient ischemic attack
VA	:	vertebral artery

PROFORMA

DEPARTMENT OF RADIOLOGY

Madras Medical College,
Chennai – 600 003, Tamil Nadu.

TITLE: "DIFFUSION-WEIGHTED MR IMAGING VERSUS CT BRAIN – DIAGNOSTIC ACCURACY IN HYPERACUTE STROKE."

_____

NAME   :   AGE / SEX :
STUDY NO   :   DATE   :
CLINICAL HISTORY :
RISK FACTORS   :

TECHNIQUE		LOCATION	OBSERVATION
NECT			
MRI	DWI		
	T1		
	T2		
	FLAIR		
	GRADIENT		
	MRA		
DIAGNOSIS			
FOLLOW UP			

_____

"DIFFUSION - WEIGHTED MR IMAGING VERSUS CT BRAIN – DIAGNOSTIC ACCURACY IN HYPERACUTE STROKE"
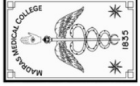
by

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under the guidance of

Prof. T.S. SWAMINATHAN

Professor Emeritus, The Tamilnadu Dr. M.G.R. Medical University

for the partial fulfillment of award of degree of Doctor of Philosophy (Ph.D)

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY CHENNAI – 600 032.

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