

Role of Diffusion-weighted Imaging in Acute Stroke Management using Low-field Magnetic Resonance Imaging in Resource-limited Settings

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ABSTRACT

A variety of imaging modalities exist for the diagnosis of stroke. Several studies have been carried out to ascertain their contribution to the management of acute stroke and to compare the benefits and limitations of each modality. Diffusion-weighted imaging (DWI) has been described as the optimal imaging technique for diagnosing acute ischemic stroke, yet limited evidence is available on the value of DWI in the management of ischemic stroke with low-field magnetic resonance (MR) systems. Although high-field MR imaging (MRI) is desirable for DWI, low-field scanners provide an acceptable clinical compromise which is of importance to developing countries posed with the challenge of limited availability of high-field units. The purpose of this paper was to systematically review the literature on the usefulness of DWI in acute stroke management with low-field MRI scanners and present the experience in Nigeria.

Key words: Acute stroke; diffusion-weighted imaging; low-field strength; magnetic resonance imaging

Introduction

The primary aim of imaging in acute stroke is to determine the ischemic tissue at risk. This requires imaging techniques that are able to accurately depict tissue that can be salvaged within the narrow window available for making therapeutic interventions.^[1-3] Intravenous and intra-arterial stroke therapies are restricted by the time from stroke onset. For effective intravenous tissue plasminogen activator approach, the time window is 3–4.5 h.^[3,4] For intra-arterial therapies, the maximal time window is 6 h for thrombolytic and up to 8 h for mechanical therapies. This narrow window period reflects the idea that “Time is Brain.”^[4] In addition, the variability of the narrow window available for penumbral salvage prompts the need for a highly sensitive imaging technique in acute ischemic stroke (AIS).^[1,4] A variety of imaging modalities exist for

the diagnosis of AIS. Several studies have been carried out to ascertain the contribution of all imaging modalities to the management of acute stroke and to compare the benefits and limitations of each modality in a single study. Diffusion-weighted imaging (DWI) has been described as the optimal imaging technique for the diagnosis and management of AIS.^[3,5,6] Although high-field magnetic resonance imaging (MRI) systems are desirable for DW imaging,^[7] low-field scanners provide an acceptable clinical compromise which is of importance to developing countries posed with the challenge of limited availability of high-field units.^[8] This paper reviews the usefulness of DWI in acute stroke management with low-field scanners and presents our experience in a Nigerian tertiary hospital.

Methodology

The key words (DWI, MRI, acute stroke) were entered as search terms into the Anglia Ruskin University (ARU) advanced library search engine. Articles published over the last 5 years (from 2009 to 2014) in English language yielded 1523 results. The result was filtered to include full-text reviews from peer-reviewed journals beyond ARU library collections, and these yielded 179 results. This was further tailored down to include articles from MEDLINE (NLM) and PMC (PubMed Central) to come up with 109 results

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out of which all articles relevant to the study were selected. Only articles pertaining to medical imaging and stroke were included in the study. Most of these studies had at least two of the key words in the abstract. Studies relating to pediatrics, cancer, and animal studies were excluded from the selection and studies relevant to low-field strength imaging were randomly selected.

The Global Burden of Stroke

Stroke is the third leading cause of morbidity and mortality in adults following ischemic heart disease and cancer.^[2,9] Blacks have twice the risk of stroke compared to whites and women have a higher risk for stroke than men.^[2,9] Ischemic stroke accounts for approximately 85% of stroke.^[1,2,4,6,10,11] There are more than 50 million stroke and transient ischemic attack (TIA) survivors worldwide.^[2] Between 15% and 30% of stroke survivors are permanently disabled^[2,9] while 20% remain in need of institutional care for about 3 months after the stroke event.^[2] The total estimated worldwide economic cost of stroke is about \$68.9 billion.^[1] High blood glucose level (≥ 7 mmol/L), hypertension, myocardial infarction, coagulopathies, diabetes mellitus, and ageing are considered risk factors for stroke^[1,2,6] and current evidence reveals that a third of stroke victims are under the age of 65.^[2]

An Overview of Acute Ischemic Stroke

Ischemic stroke is primarily caused by intracranial thrombosis due to atherosclerosis or extracranial embolus arising from extracranial arteries.^[1,2,4,6,10,11] When an artery is occluded, the core of the brain tissue supplied dies rapidly. Tissue surrounding the infarct core, however, remains viable for a period of time as a result of minute blood supply from collateral vessels. If there is early recanalization, this penumbra could be saved and protected from infarction [Figure 1]. The extent and salvageability of the penumbra are not only time-dependent

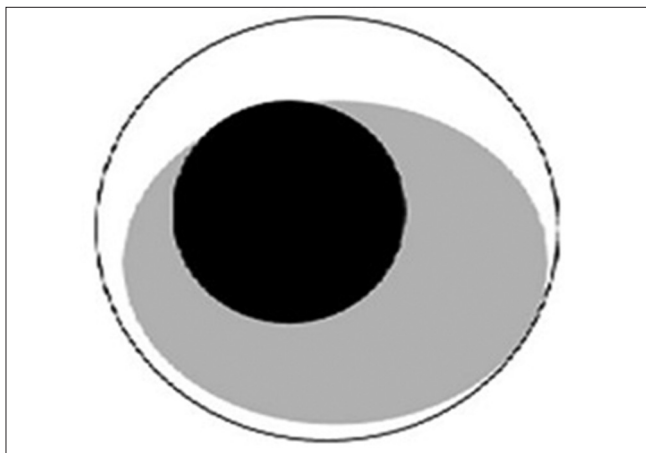


Figure 1: A schematized model of ischemic tissue with different degree of tissue damage: White = benign oligemia, grey = penumbra (tissue at risk), and black = infarct core (irreversibly damaged tissue)^[14]

but varies between patients from <3 h to well above 48 h. The location of vessel occlusion, efficacy of collateral supply, and location of the ischemic lesion are some important factors that influence inter-patient variation.^[1,3]

A TIA results in focal neurological deficits similar to ischemic stroke but lasting <24 h. However, most TIAs resolve within 1 h and 90% terminate completely after 4 h.^[2,12]

The availability of modern imaging techniques has revolutionized our understanding and definitions of TIAs. Early definitions of stroke and TIA focused on the duration of symptoms and signs. Current imaging observations have shown that the duration and reversibility of brain ischemia are variable. Brain tissue that suffers ischemia can, in some patients, survive without permanent injury for a considerable period of time – several hours or even, rarely, days – while in most other individuals, irreversible damage (infarction) occurs quickly. Modern imaging can now differentiate between infarcted and underperfused and reversibly injured cerebral tissue. Because of the variability of duration, it is now generally agreed that a fixed time designation should not be the primary distinguishing factor between stroke and TIA. Time should be a secondary consideration when adequate imaging is unavailable.^[13]

The word “transient” generally indicates a lack of permanence. DWI and other modern brain imaging techniques may show evidence of brain infarction in some patients in whom symptoms and signs of brain ischemia are clinically transient. It is therefore from an imaging perspective, misleading to designate the ischemia as transient. Similarly, ischemia may produce prolonged symptoms and signs (and so qualify in older definitions as strokes), and yet no permanent brain infarction may have occurred as detected or revealed by imaging.^[14]

The primary aim of imaging in acute stroke is to differentiate hemorrhagic from ischemic stroke or to exclude stroke mimics (such as hypoglycemia and seizure) in a timely manner. Additional information derived from imaging includes early detection of infarction, assessment of vascular distributions and perfusion and determination of the penumbra all of which serve to guide treatment decision.^[1-3,7]

Appraisal of Low-field Diffusion Weighted Imaging

Although low-field strength MRI units are characterized by low signal and consequently are of lower image quality compared to high-field systems, surprisingly, evidence reveals that both systems demonstrate sub-acute ischemia on DWI equally well. And as such could be used as a screening tool for patients with suspected stroke.^[15] In addition, low-field MRI units are usually constructed with permanent magnets.^[16] This allows for an open configuration design which permits

better access for monitoring patients and allows quick access for interventions such as anesthesia or even intravenous thrombolysis.^[15] Reduced safety considerations, low power requirements with associated low operating cost, and increased patient comfort in terms of claustrophobia and patient size constraints are added benefits.^[16]

Though MRI offers improved image resolution and as such is able to identify a wider range of acute and chronic cerebrovascular pathologies than computed tomography (CT);^[2,3] the inability to obtain thinner slices on low-field scanners compared to high-field units might increase the possibility of missing small lesions which may occur in lacunar strokes.^[15]

The improvements made on high-field MRI systems have drastically reduced the acquisition time of MRI sequences leading to an increase in the use of MRI for imaging in acute stroke.^[10] Thus, the longer image acquisition time resulting from imaging at low-field strength impairs quick decision making which is critical in acute stroke management and increases the chances of patient-induced motion artefact.^[15] In a study comparing single-shot-DWI at 1.5T and multishot-DWI at 0.3T, it was found that patient movement was the only factor militating against successful multishot-DWI acquisition on low-field units.^[17]

Diffusion-weighted MRI is particularly sensitive for the detection of acute stroke [Figure 2]. A few years ago, a study^[15] retrospectively compared 18 patients with clinical suspicion of acute stroke on a standard 1.5T unit and an open low-field MR scanner with DWI and apparent diffusion coefficient (ADC) mapping on both systems. The technique used was a rotating fast-spin echo T2 at low-field and an EPI sequence at 1.5T. They obtained the same results on DWI sequences on both systems, regarding high-intensity lesions on DWI. Chronic lesions were better-visualized at low than at high field. In their opinion, DWI on a low-field open MR scanner is a good technique to evaluate sub-acute stroke and was as reliable as when performed on a 1.5T MR system.^[15]

Diffusion Weighted Magnetic Resonance Imaging Sequence

The classical diffusion MRI sequence was introduced by Stejskal and Tanner (1965).^[8] This gradient pulsed spin echo sequence involves the application of at least two diffusion gradient pulses. The first gradient pulse “labels” the spins of water molecules according to their initial positions. The second gradient labels the spins according to the extent they have moved which is dependent on the magnitude and duration of the applied gradient. Spins of water molecules which move during application of the gradient produce low signal as they are inefficiently rephased by the rephasing pulse, unlike spins which did not move. However, because the initial gradient pulse labels the spins of water molecules

according to their initial positions, T2 effect is likely to predominate leading to the so-called “T2 shine through.” Thus, the greater the duration and strength of the applied gradient, the more likely the signal to be as a result of water diffusion.^[18]

Clinical Application of Diffusion-weighted Imaging in Acute Stroke

The advent of DWI along with PWI in the early 1990’s and the implementation of the hardware necessary to achieve echo-planar imaging in clinical MRI scanners later in the same year has added an improved dimension to the diagnostic imaging of stroke.^[3,10] Until recently, the sequence of choice for DWI has been echo-planar imaging. However, echo-planar imaging is not readily available on all MRI units. Diffusion imaging though requiring strong gradients is less dependent on field strength and thus can be performed at low-field strengths using sequences such as fast spin-echo.^[15]

By relying on the diffusivity of water, DWI is able to provide information about the morphology of the ischemic tissue^[5] such that acute focal regions characterized by cytotoxic edema and restricted diffusion^[3-5,18] appear hyperintense on DWI while sub-acute and chronic phases which set in after the first 4 days following an ischemic event appear normal to hypointense. Chronic stroke lesions which appear hyperintense on fluid-attenuated inversion recovery (FLAIR) and T2 sequences can also appear hyperintense on DWI because of the T2 shine through phenomenon. This is the relevance of obtaining ADC maps which correct for the T2 shine through effect thereby differentiating these falsely hyperintense chronic lesions from acute ischemia which also have an accentuated hyperintensity on DWI by maintaining the hyperintensity of the chronic lesion on the ADC map.^[5] The ADC also quantifies the diffusivity of water thereby refining the prediction of the ischemic tissue depicted on the DW image.^[3,19] The use of ADC thresholds may also help improve reproducibility of outcomes.^[20] In a cohort of 25 ischemic stroke patients imaged with DWI, the wide gap between the ADC decrease ($170 \times 10^{-6} \text{ mm}^2/\text{s}$) measured 1.3–5.4 h after symptom onset and ADC increase ($803 \times 10^{-6} \text{ mm}^2/\text{s}$) creates a strong contrast between the infarcted tissue and the unaffected brain tissue.^[3] While DWI can be reasonably applied clinically for evaluation of acute stroke on low-field scanners, the interpretation of ADC proves rather difficult. In a retrospective study, patients with high suspicion of acute stroke were examined on a 1.5T echo-planar system (Eclipse, Marconi) and later (within 1 h and 24 h), on a low-field 0.23T (Outlook, Marconi) scanner using a rotating fast-spin echo T2 weighted sequence. The images obtained on the two scanners were analyzed independently by two Neuroradiologists. Lesion intensity results were similar at both field strengths; however, ADC map interpretation proved difficult on the low-field system near the lateral ventricles. Although similar difficulty was experienced

on both low- and high-field systems in the cerebellum, temporal fossa and cortex situated near bone resulting from susceptibility artefacts.^[15] In this regard, low-field scanners have an advantage of the absence of image distortions and susceptibility artefacts which are more pronounced on images obtained on high-field strength scanners.^[15]

Diffusion-weighted imaging confirms the presence and location of the infarct with 73% sensitivity at a time <3 h to 92% at a time <12 h of onset of infarction.^[18] In contrast, the sensitivity of CT at these times is 12% and 16%, respectively.^[5] The sensitivity of DWI for the diagnosis of AIS is also higher than that of FLAIR (46%).^[3,5,6,11] Conventional MRI techniques are not very sensitive to changes associated with ischemia before 8–25 h.^[10] The superior sensitivity and specificity of DWI make it the MRI sequence of choice for diagnosing AIS.^[12]

Diffusion-weighted imaging is able to reproduce the evolution of the ischemic core and penumbra over time. In essence, it is dynamic.^[5] Information from clinical trial reveals that DWI lesions grow over time in the absence of any correction therapy due to increase in the extent of the infarcted core. Several studies suggest that the initial DWI lesion volume correlates well with the final infarct volume and neurological and functional outcomes and could, therefore, serve as an early prognostic tool.^[5]

Diffusion-weighted imaging lesion pattern can help define specific stroke subtypes for instance cardio embolism is associated with single cortico-subcortical lesions, multiple lesions in the anterior and posterior circulation and in multiple cerebral territories while large-artery atherosclerosis is associated with a watershed distribution of small lesions in one vascular territory and multiple lesions in the anterior and posterior circulation. Identifying stroke subtypes using lesion pattern on DWI may help in selecting the most appropriate method of prevention.^[5]

Diffusion-weighted imaging has provided a means of evaluating and managing patients with TIA. TIA lesions lasting >1 h are usually detected on DWI, and these individuals have a higher risk of stroke than individuals without acute abnormalities on MRI. This has led to a redefinition of TIA as a brief episode of neurological dysfunction caused by focal brain ischemia with symptoms lasting <1 h and without evidence of acute infarction.^[5,12]

Because DWI provides the most reliable estimate of infarct core,^[4] when used in combination with PWI, becomes an optimal technique for diagnosing acute stroke.^[3,5,6] PWI assessment of the infarct enables estimation of the tissue volume at risk (although it is not yet clear which PWI parameter gives the closest estimate of hypoperfusion) and the vascular distribution of the ischemic lesion.^[3,6] The difference in diffusion and perfusion values (or the diffusion/perfusion “mismatch”) reflects the difference

between the infarct core and the ischemic tissue which correlates with the ischemic penumbra thereby providing an idea of the tissue which has the potential of being salvaged.^[3,4,6,10] If there is no difference between DWI and PWI termed DWI/PWI match, this reflects a patient who has no penumbral tissue either due to the complete extension of the ischemic core or normalization of prior hypoperfusion.^[3] This mismatch model which was first proposed by Warach *et al.*^[19] however, does not take into consideration areas of oligemic reserve where brain tissue still remains functionally unaffected as this cannot be detected by PWI^[3,10] and that DWI abnormalities are not necessarily infarcts.^[3] But even with these criticisms, MRI DWI/PWI mismatch is the most widely used tool to identify ischemic tissue at risk in the early phases of acute stroke.^[10] The disadvantage of low-field systems in this regard is that the DWI-Perfusion mismatch cannot be delineated since perfusion-weighted MRI is not available on low-field systems.^[15]

Limitations of Diffusion Weighted Imaging

Despite the high sensitivity of DWI, however, some false negatives might occur with this technique. The chances of having a false negative increases with small infarcts, early imaging and brainstem location and is higher in patients having two or more of these predisposing factors compared to patients with one or none.^[5] Furthermore, DWI lesions are known to represent irreversibly damaged tissue, however, recent evidence points out that some DWI lesions can be reversible, at least to some extent.^[10,14,20] This feature has been well-established in animal models. Thus, the use of DWI and ADC maps to discriminate irreversibly from reversibly damaged tissues still remains a matter of controversy.^[20]

Experience with DWI in acute stroke management in Nigeria

In Nigeria, the availability and use of MRI remain comparatively low.^[8] Mostly due to the high cost of MRI examinations and the lack of adequate technical and power support for high-field strength magnets, hence the relatively high number of low-field strength MR scanners.^[21] The University College Hospital, Ibadan [Figure 3], one of the foremost tertiary hospitals in Nigeria established in 1952 and located in the largest city in West Africa with a capacity of 840 bed spaces and over 60 departments^[22,23] began operating its MRI unit, a Siemens 0.2T (Magnetom Concerto) in 2005. Between 2006 and 2010, the percentage of case referrals for cerebrovascular disease was 3.9%. However; no trials on DWI were performed.^[22] Recently, in 2013, a MINDRAY 0.36T (MagSense) Scanner was introduced and DWI pilot images obtained from the new system were found to be of diagnostic quality [Figure 4] with a potential to further enhance diagnostic accuracy.^[22] The late presentation of stroke patients and high cost of imaging remain a great challenge and limits use and application of the available MRI.

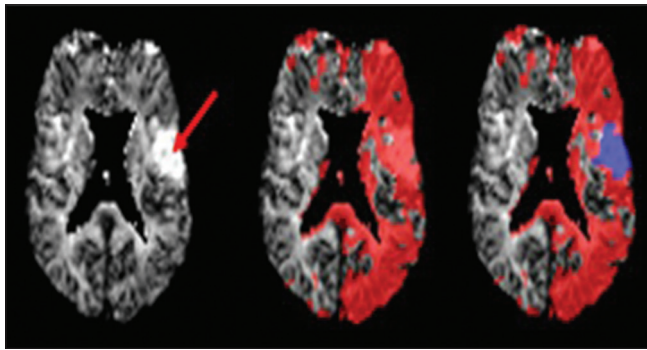


Figure 2: Left: An acute diffusion-weighted imaging (DWI) lesion depicted by the arrow. Middle: The red region represents perfusion deficit. Right: Subtraction of DWI from perfusion deficit reveals the penumbra^[14]



Figure 3: Front view of University College Hospital, Ibadan, Nigeria's premier tertiary hospital

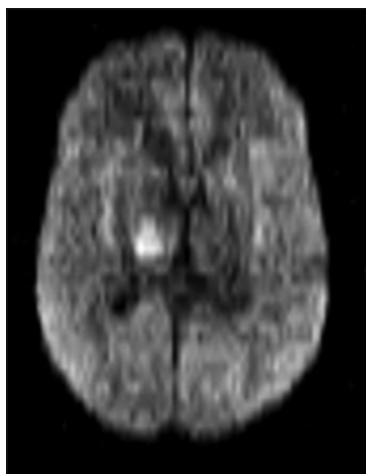


Figure 4: Diffusion-weighted image obtained from our 0.36T scanner at $b = 600 \text{ s/mm}^2$ showing an area of restricted diffusion as evidenced by the increased signal intensity in the right thalamus in a 59-year-old man

A prospective study carried out in University College Hospital, Ibadan found that acute stroke constituted about 1% of the total hospital admissions and 7.3% of medical deaths. The study which accessed patients who presented to the emergency department between August 2004 and March 2005 pointed

out that the common risk factors for ischemic stroke in that setting were systemic hypertension, obesity, alcohol/substance abuse, and diabetes mellitus.^[24] Maestroni *et al.*, reported that only a few patients are able to present early to the hospital following the onset of stroke even in industrialized countries.^[25] The high cost of MRI exam could be one among many factors militating against early presentation to the emergency department in developing countries like Nigeria. This might have an impact on mortality and morbidity rate of patients with ischemic stroke. To the best of our knowledge, no study has fully assessed the mean time of presentation for imaging of stroke patients and evaluated factors responsible for imaging delays in Nigeria. It is our intention to explore this area of research in Nigeria in the near future.

Conclusion

Diffusion-weighted imaging provides the earliest information about the physiology of AIS. It enables further classification of stroke and confirms the presence and location of infarcts with strong contrast and high sensitivity in comparison to CT and other MRI techniques. In addition, DWI can be used to accurately monitor the evolution of the ischemic core over time. When used with PWI, the diffusion/perfusion mismatch reveals the extent of tissue that has the potential of being salvaged. The limitations of DWI using a low-field MRI, relate to the difficulty with ADC map interpretation in certain locations of the brain. PWI is also not feasible with low-field MRI. Nevertheless, DW images acquired on low-field units are able to accurately demonstrate sub-acute ischemia comparable to high-field MRI scanners and the open MRI configuration of low-field systems provides a useful advantage of ease of access. This report of the preliminary use of DWI with a low-field strength scanner in a resource-poor clinical setting shows that use of low-field MRI in Nigeria in spite of daunting challenges holds great promise for improved and qualitative stroke imaging diagnosis.

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