Physical Principles, Use of High b-Values And Clinical Applications of Diffusion-Weighted Imaging of Ischemic Stroke

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Abstract— Diffusion weighted imaging has been a highly sensitive technique and a great success in neuroimaging for the early detection of water diffusion in cerebral ischemia. A diffusion weighted image provides the contrast, based on microscopic molecular motion and shows the changes in MRI signal intensity that is not possible with conventional T1- weighted and T2-weighted images. The addition of two strong diffusion gradient pulses to the normal MRI pulse sequences, generate the images being water-motion sensitized in the direction of applied gradients. This process helps to determine the diffusion weighting of the images, characterized by gradient factor b. In images that are obtained with Fast Spin Echo Imaging (FSEI), Segmented Echo Planar Imaging (SEPI), Single Shot Echo Planar Imaging (SSEPI), like quick imaging modalities, bulk motion related artifact can be minimized. Consequently imaging time will be shortened and image quality would be better and much more enhanced. Conclusively, DWI is a non-invasive technique that provides exceptional information and the utility for monitoring and predicting response to treatment.

Index Terms—Acute, ADC, b-value, Diffusion, DWI, Hyperacute ,Ischemic Stroke

1. INTRODUCTION

Diffusion weighted imaging has been a highly sensitive technique and a great success in neuroimaging for the detection and management of Cerebrovascular events [1],[2] especially for the early detection of water diffusion in cerebral ischemia over the past decade [3],[4],[5]. DW-MR imaging has become more popular because of the recent advancement in the scanning hardware and development of echo planner imaging (EPI) and parallel imaging [6],[7],[8]. All these have extended the applications of DWI from cerebral to extracranial [9] and the whole body imaging [10],[11],[12]. DWI reflects the variations in the random thermal motion of water molecules in body tissues, by the use of high amplitude diffusion gradients [11],[13] it allows us to evaluate water diffusibility in brain [14],[15] as was initially described by Stejskal and Tanner [16]. A diffusion weighted image provides the contrast, based on microscopic molecular motion and shows the changes in MRI signal intensity that is not possible with conventional T1- weighted and T2-weighted images [17]. Ischemic strokes are associated with the restricted water diffusion, so can be detected as high-signal intensity areas or bright in DW images and conversely dark in ADC maps that shows the signal hypo intensities [18].

Conventional MRI takes hours in diagnosing of ischemic stroke in its acute phase but this can only be done within minutes by DW-MRI [19],[20]. DW-MRI also discriminates whether the stroke is chronic or acute as well as old or new [21],[22]. This article briefly provides the physical concepts, clinical significances and applications of DW-MR imaging in Ischemic Stroke. The purpose of this article is to shortly describe the basic mechanism underlying water diffusion changes in ischemic brain tissues, and to focus on the contribution of the clinical research to investigate the degree of signal intensity using high b-values. Use of Diffusion-Weighted images for accurate and early detection of Ischemic stroke, the image formation, current role of DW imaging and the possible future applications in a brief manner are also included.

2. CONCEPT AND PRINCIPLES OF DIFFUSION-WEIGHTED MR IMAGING

Molecules in a fluid (water) move in a complicated pattern, as they are agitated by the thermal energy. Molecular diffusion is a random and mass transport process which results in molecular or particle mixing without requiring bulk motion [23],[24]. Physical law explaining the phenomenon of diffusion is Fick's first law,

$J = -D\nabla C$ relating the diffusive flux (J) to any concentration difference(C) and the constant of proportionality D, the diffusive coefficient, an intrinsic property of the medium [23].

MR images generically displays differences in MR signal intensities [25]. Anatomic imaging and characterization of tissue needed the contrast that is produced by these differences in signal intensities [26]. T1-weighted, T2-weighted techniques use contrast in relaxation time, while fMRI uses the contrast that is blood-oxygen-level-dependent [27]. The contrast used in DW-MRI images is produced because of the changes in the rate of translational, temperature dependent and random water diffusion in biological tissues, namely intercellular, intracellular and

extra cellular [28]. Diffusion imaging is a micro structural probe to distinguish diffusion modes (free, hindered , restricted) in tissues.

These modes can further be divided into Isotropic and Anisotropic diffusion [28]. We can distinguish between the diffusion process by looking at the mean displacement and diffusion ratio [29]. There is a linear relation between diffusion time with diffusion coefficient and square root of the mean displacement, for free diffusion processes [28].

$$< x > = \sqrt{nDt}$$

The equation is known as Einstein's equation. Where

$< x >$ = mean displacement

D = diffusion coefficient

t = diffusion time

n = measurements dimensions (2 for 1D, 4 for 2D, 8 in 3D)

Contrary to this we characterized restricted diffusion by $< x >$ (which is constant) as a function of t.

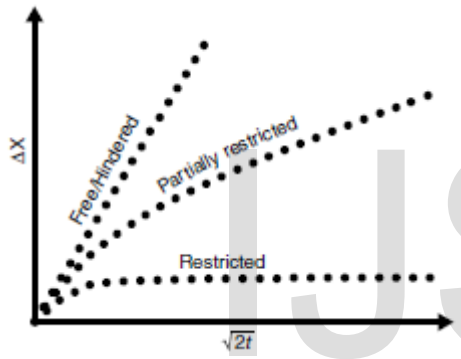

Fig.1. Possible diffusion processes in biological tissues. Free and hindered diffusion show a linear relation between mean displacement and square root of the diffusion time, partially restricted (or highly hindered) and restricted diffusion will show non-linear dependency.

The fact that DW imaging does not measure the actual diffusion coefficient, but measure the displacement of molecules in CNS, stems the motivation and urge to search for water diffusion process in Brain tissues.

3. Theory of Restricted Diffusion

A profound restriction in the normal water diffusion of Brain tissue occurs following the Ischemia [30], and this forms the basis of early detection of Ischemic Stroke with DWI [31]. The exact biophysical mechanism for these changes is still not clear. But there are experiments pointing towards the relative decrease in the intra-cellular diffusion [32],[33] supported by the studies on animals, that associates ischemic infraction with the reduction of NA+/K+ pump activity [34]. The idea of restricted water diffusion in intracellular compartment as compared to extracellular compartment is not universally supported as some studies refute the concept by giving importance to the water diffusion changes in extra-cellular space [35],[36]. Another important contributor is cytotoxic edema—the process of cell swelling associated with the altered distribution of Na+/K+ ions [34]. As studies show the decreased ADCs in early Ischemia in rat's Brain tissue [37],[38] and the reduction in Na+/K+ adenosine-triphosphate activity [34]. Small but significant ADC decrease, using (b > 1200 s/mm2), was observed in tissue areas in conjunction with brain activation in the cat visual cortex at 9.4 T [39].

It was found that diffusivity in white matter tissue is much slower, if diffusion measurements are perpendicular to the neuronal fiber orientation than in parallel. The hindrance or restrictions in water diffusion perpendicular to the fibers is most probably by the alignment of neuronal fibers and because of the thick myelin membrane they are covered with [40].

The above findings have led to the theory of restricted water diffusion in stroke.

There is a disruption of energy metabolism within minutes after the onset of Ischemia [41] and the failure of Na+/K+ pump leads to the loss of ionic gradients. From the extra-cellular to the intra-cellular compartment, [32] there is a net translocation of water.

A study on animal model suggests that in Ischemia there is increase tortuosity of extra-cellular pathways [42] and substantial reduction in ADCs that contributes to the restricted water diffusion [43].

In principle, identification of number of water molecules, experiencing restricted/hindered diffusion and their displacement that would be significantly smaller than that of free diffusion of water molecules, is very important. And this measure of sensitivity to diffusion or the degree of diffusion weighting is determined by the b-value. Diffusion attenuation factor or the b-value reflects the degree of diffusion weighting of a sequence [14].

Signal attenuation from diffusing protons gives the magnitude of b-value and is determined by the following physical factors [14].

$$b \equiv (\gamma \delta G)^2 (\Delta - \delta/3)$$

(γ) gyro magnetic ratio (G) gradient strength (δ) gradient duration (Δ) time interval between two pulses.

By using different combinations of these three factors, we can produce the same numerical value of b, but DWI results will be potentially different [28].Typical units of b-value are second per square millimeter (s/mm^2). Thoeny et al [44] divided the b values from 0 to 100 s/mm^2 as low and >500 s/mm^2 as high. The higher the b-value the greater the diffusion weighting would be.

B-value equals to zero (no diffusion weighting) uses no diffusion sensitizing gradients, delivers a T2-weighted EP image and serves as a reference for the calculation of an ADC.

From a voxel of tissue the signal intensity can be calculated as

$$SI = So \exp(-b^* ADC) \quad (1)$$

or $$SI = So \exp[-(\gamma \delta G)^2 (\Delta - \delta/3)^* ADC] \quad (2)$$

Where ADC stands for apparent diffusion coefficient.

Water molecules in biological tissues do not move freely and completely at random because this motion is restricted by the cell membrane and other molecules [31]. So in comparison to free water diffusion, the diffusion in a tissue is referred as apparent diffusion, hence the diffusion coefficient as apparent diffusion coefficient.

The above equation shows that the higher the diffusion coefficient the larger the signal loss is. The amount of signal loss depends upon Δ (time interval between two pulses). As there is more time for water diffusion and less perfect will be the refocusing of precessing protons. If the gradient pulses are stronger (G) and/or longer (δ), signal loss is also large

The relation between the signal intensity and b-value is

$$S(b) = So \exp(-b * ADC) \quad (3)$$

$$S(b)/So = \exp(-\gamma^2 G^2 \delta^2 (\Delta - \delta/3) D)$$

$$= \exp(-b * ADC) \quad (4)$$

So = signal intensity with no diffusion gradients
Sb = signal intensity with diffusion gradient

If the gradient pulses are applied in all three orthogonal directions, this would sensitize the water diffusion changes along all three x, y and z directions. Gradient applied along one particular axis, say x-axis will give information particularly along that direction which is useful in anisotropy of water diffusion [44].

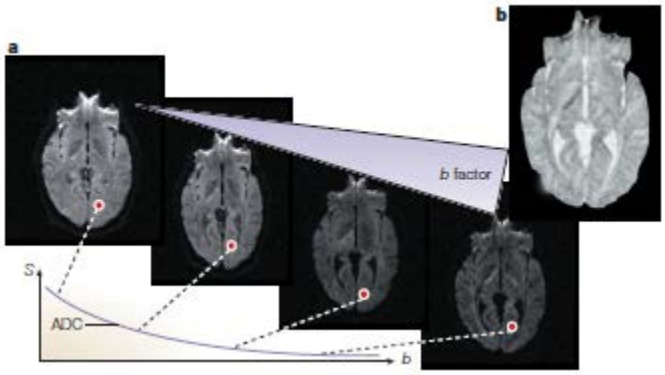

Fig.2. DW images of different degree are obtained using different b-factors. (a) Signal Intensity attenuation is due to the larger b-factor. The larger the value of b-factor the more the signal intensity attenuation is, and it is modulated by the diffusion coefficient. With increasing b, the signals in areas with fast diffusion decays rapidly, whereas decreases more slowly in tissues with slow diffusion. ADC can be obtained by fitting the signal decay as function of b [40].

4. Use of High b-values in Diffusion Weighted Imaging of Ischemic Stroke

Optimizing the b-value and the number of image averages to the tissue of interest, is essential for producing high-quality ADC maps [40],[45].

Table 2: Summary of Diffusion-Weighted MR imaging studies (2000-2012) of Ischemic Stroke in humans, using High b-values (≥1000s/mm^2).

1st author Year	Title	Patient [n]	Mean age [yrs]/ age range	Latency to DWI [hrs]	b-values s/mm^2	Conclusion
Joel R 2000[46]	High-b-value DW-MRI of Suspected Brain Infarction	12	67.7	Nm[1]	1000 2500 3000	High-b-value b=2500 s/mm2 when combined with b=1000 s/mm2 gave improved results in low signal lesions.
Delano MC 2000[18]	High-b-value diffusion-weighted MR imaging of adult brain: image contrast and apparent diffusion coefficient map features.	6	17 to 65	Nm	0 1000 2000 2500 3000 3500	The study provides the normative data for future investigations at high b values. Increased b values resulted in a progressive decrease in the gray to white matter signal intensity ratio and ADC values.
Ayeesha K 2002[47]	Quantitative DW-MRI in TIA	28	Nm	24	1000	Quantitative DW imaging may have better sensitivity in detecting TIA compared with conventional DW imaging.
Burdette JH 2002 [48]	Diffusion-weighted imaging of cerebral infarctions: are higher B values better?	26	66	6 h to 14 days	1000 3000	High -value (b= 3,000 s/ mm2) offers no apparent diagnostic advantages For the evaluation of late acute/subacute cerebral infarctions, and in terms of SNR and CNR significantly inferior.
Mehdizade A 2003 [49]	DW- MRI on a low-field open magnet Comparison with findings at 1.5T in 18 patients with cerebral ischemia	18	69	24hrs to 7dys	0 700 1000	High SI lesions were recorded. ADC was found decreased relatively to be between 0.8 and 1.2 on the open machine and 0.75 and 1.3 on the 1.5 system. DWI on a low-field scanner is an interesting approach to image patients with acute stroke syndrome.
Dorothee Saur2003 [50]	Sensitivity & Interrater agreement of CT and DW-MRI of Hyperacute Stroke	45	62.8	6	0 500 1000	DW imaging helped identify EIS with higher sensitivity than that of CT
K Rima 2003[51]	Role of DW-MR images in early	40	30 to 70	24	0 500	Abnormal signal intensity was found within 24 hours of

[1] not mentioned

	diagnosis of cerebral infarction				1000	symptom onset but there was a %age decrease with time and changes in signal intensity were rare after the onset of clinical symptoms.
Jessica E2004 [52]	(FLAIR) Preparation: not an Improvement over conventional DWI at 3T in Acute Ischemic Stroke	20	20 to 83	6	0 1500	Hyperacute strokes are better detected by DW images. B-values do not affect the degree of fluid suppression.
Kim HJ 2005[53]	High b-value DW- MRI of Hyperacute Ischemic Stroke at 1.5T	94	62 ± 8	6	0 1000 2000	DW images acquired with a b value of 2000 s/mm2 were better than DW images acquired with a b value of 1000 s/mm2.
Khin K 2005[54]	Early Detection of Global Cerebral Anoxia: Improved Accuracy by High-b-Value DWI with Long Echo Time	6	54.3	24	1000 3000	High-b-value DWI with long TE improved accuracy and early diagnosis.
Toyoda K 2007[55]	Usefulness of high-b-value DWI in acute cerebral infarction.	32		48	0 1000 2000 3000	High-b-value DWI provided better identification of lesion extension in the cerebral ischemia. Irreversible cytotoxic edema is more predictable on high-b-value(≥1000 s/mm2) DWI
Aidos Doskaliyev 2009[56]	Advantages of High b Value Diffusion-Weighted Imaging in the Diagnosis of Acute Stroke – A Case Report	1	73	6	1000 4000	DWI at b = 4,000 s/mm2 on the 3-T scanner was found superior for the ischemic lesions identification.
Francisco Purroy MD 2012[57]	Contribution of High-*b*-Value DWI in Determination of Brain Ischemia in TIA Patients	75		3.25 ± 1.5 days	0 1000 2000 3000	High-*b*-value DWI did not improve the conspicuity of the ischemic lesions and was unable to made lesion distinctions.

*Nm--not mentioned

Typically used b-values in DTI are from 700-1500 for probing diffusion distances of 5-10 µm but larger b-values (~ 8000- 15000) are required for probing restricted diffusion (as ischemia is associated with restricted diffusion) for minimum diffusion distance (about 1-2µm) and time range of 50-100 ms for diffusion [58].

Therefore, DW-MRI experiments for slow diffusion are also referred as high b-value imaging. With high b-value DWI, molecules experiencing restricted diffusion are probed, and at low b-value DWI, molecules experiencing hindered diffusion will dominate [59].

Use of high b-values for increased sensitivity is an emerging approach in DWI. Although this technique has some minor problems to cope with but will prove beneficial in near future. High b-value image acquisition is now possible due to the advancement in gradient strength and strategies to facilitate the imaging artifacts [60],[61],[62]. High b-values as 1000s/mm² is now being frequently used to produce contrast between lesion and the background tissues. Generally the degree of signal attenuation is greater at high b-values.

In the identification of lesions, DWI has the accuracy of 97% over conventional MRI that showed 64%. A recent study explores the sensitivity of high b values at 3T for diagnosing Hyperacute ischemic stroke, using the b values: 1000s/mm², 3000s/mm², and 5000s/mm², and high b-values were found helpful in diagnosing Hyperacute stroke [63], as they provide higher sensitivity and therefore more diffusion-weighting. However, SNR decreases exponentially at these high values. And thus signal attenuates greatly at high amount of phase shift. Long echo time required for high b-values further decreases the SNR, and accurate diagnostic benefit remains to be proven. Multiple excitations are needed at high b values, to overcome the decreased signal-to-noise ratio problem. [46],[64]. Signal decays with high b-values range up to 6,000 s/mm2 reveal a non-monoexponential decay behavior for both gray and white matter in human brain [65],[66].

Table 2 showed the summary of DW-MRI studies of ischemic stroke in humans where high b-values, from 1000 s/mm2 to 35000 s/mm2 were used .Only the studies of last decade (2000-2012) are considered. Although some studies considered the high b-value technique more accurate and demonstrate that DW images acquired with b-values of 2000 s/mm2 or higher, were better than 1000 s/mm2 [48],[53],[54],[64].

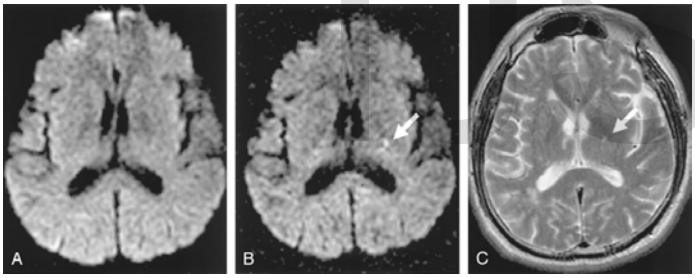

Fig.3. A–C, A 63-year-old man who had right hemiparesis for 6 hours. Abnormal hyperintensity is noted at left posterior limb of internal capsule on b =2000 image (B, white arrow) but it is not definite on b = 1000 image (A). Follow-up T2-weighted image obtained 2 days later shows a small hyper-intense lesion in the same location (C, white arrow). (Image used with permission from cgchoi) [2].

But some studies contradict this; with the results that high b-values 3000 s/mm2 had no impact on infarct diagnosis and did not improve the conspicuity and distinction of ischemic lesions. [46],[57]. One case of a 73 years old man where the scan were performed within 6 hours of the acute-onset, and DWI at b = 4000 s/mm2 at 3T scanner identified the ischemic lesions (that were missed at b = 1000 s/mm2) [56].

Meyer et al [46] used various b values for theoretical calculations of signal intensity differences in acute infarct and grey matter, and found the optimal values to lie between 1500 and 2000.After a comparison of DW images acquired with different values he has proved that as the b values increased the lesion contrast improved.

DW imaging at b = 2000 s/mm2 are theoretically considered better than DW imaging at b = 1000 s/mm2 for early detection of hyperacute ischemic strokes but experimental based studies are very less in number [53]. As still very rare work is performed on Diffusion studies of ischemic stroke in human with b values higher than1000 s/mm2 [46],[48],[87].

The problems of decreased SNR and increased imaging time must be solved. An optimal b value must be determined for the early assessment of ischemic stroke and to practically implement the technique in hospitals for diagnostic imaging with better and useful results.

B-values < 1000 s/mm2 also showed the improved results [17,67,68,69]. Sequences where low b-values are used give high SNR, but show increased sensitivity to perfusion and less to diffusion weighting [70],[71].

In comparison, on DW images the lesions will appear brighter because of the restricted diffusion, as they suffer with very little signal attenuation on high b- values than normal background tissues, whereas the signal is attenuated greatly because of the rapid diffusion and they appear dark on DW image. This increased contrast helps in lesion detection [53].

5. Data Display and Post Processing (ADC)

Typically data is filmed as image. At a given b-value an image shows the signal intensity. Data can also be presented as a trace-weighted image obtained by geometric averaging of all the three or more diffusion directional measurements, the trace-weighted map doesn't show the orientation of diffusion but only the strength of diffusion. In trace image the observed signal intensity depends on T2 relaxation time and water diffusion .Consequently, areas with very long T2 remain high signal on DWI and can be misunderstood for restricted diffusion. This pitfall of trace image is known as T2 shine through. This cannot be avoided easily but can be reduced by choosing short TE and large b-value. Figure 6 shows the T2 shine through effect.

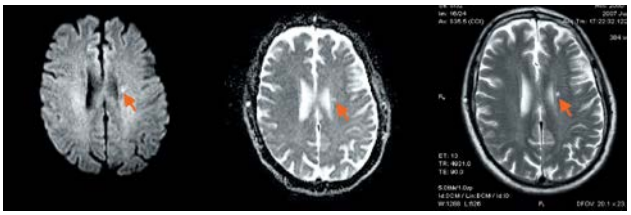

Fig. 4. "T2-shine-through effect". (A) On DW image small 'bright' lesion suggested acute ischemia. (B) On ADC map, the bright appearance clarified the lesion as weeks old." Bright" lesions on the DW-image (A) shows that signal intensity on DW-images reflects not only diffusion characteristics but also T2 properties of tissue. (C) T2-weighted image reflects the lesion "bright". The contribution of increasing T2-signal on the signal intensity

on DW-images has been termed "T2-shine through" effect [76],[77].

An alternative way and a solution of T2 shine through is the use of exponential image (with out a T2 component and is exponentially diffusion weighted) and the computation of apparent diffusion coefficient (ADC), that represents the proton's diffusibility through the tissue [78]. ADC map (linearly DW without T2 component) of water from DW images can be calculated (by acquiring more than one b-value) .ADC map is an image whose signal intensity is equal to the magnitude of the ADC [77].

We can calculate the ADC values for each pixel with the help of equation (1.1) , but these estimations of ADC are done automatically by the scanner software by measuring the amount of signal loss between the images made by using different b-values.

Different b-valued Diffusion-Weighted images are useful for quantitative analysis and are produced by the scanner. Another simplified way of visualizing this is the consideration of signal attenuation with increasing b-values for the same tissue and then plotting the graph. The slope of the line describes the ADC [79].

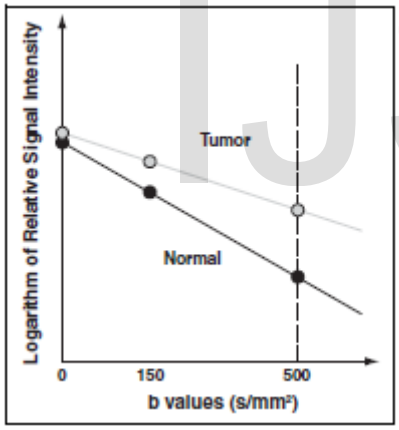

Fig.5. Simplified schematic shows derivation of ADC. Logarithm of relative signal intensity is plotted on y-axis against values on x-axis. Slope of line fitted through plots is ADC. In this example, slope of line (ADC) is smaller for tumor (gray line) than for normal liver (black line).

As ADC is independent of strength of magnetic field, thus allows more accurate and meaningful results, it also overcomes the T2 shine through effect .Contrast on an ADC image is entirely different from that of the Diffusion-Weighted image. Areas of high diffusion i.e. CSF appears hyper intense on ADC image because of high signal .Whereas CSF is markedly hypo intense on DW image. The lesion which is an area of restricted water diffusion (i.e. lowered ADC value) and appear hyper intense on a DW image, will have low signal loss and be hypo intense on ADC image [80].

After Ischemic stroke the observed hyperintensity of DW image reflects the decrease in ADC and is related with cytotoxic edema [81], developed within minutes of insult.

Restricted diffusion is associated with high cellularity and these high cellular areas show low ADC values because the diffusion is not free there. Comparatively less cellular areas return high ADC values, as the diffusion is not hindered there. The presence of organized anatomic structure in Brain, allows a quantitative diffusion technique, to be used to advantage name DTI.

Animal studies of stroke showed that ADC values are decreased shortly and then return to base line within 24-48 hours approximately [82,83]. In humans peak signal reduction is visible in ADC within 4 days and return to the base line in approximately 4-10 days [75,84-87].

A clear transition is evident in ADC values from decreasing to increasing in nonlacunar infarcts than lacunarinfarcts [88].

However, absolute ADC values are dependent on b-values used in different post-treatment work and greatly varied ,0 and 300 s/mm², higher than 1000 s/mm² and in some studies b = 0 s/mm² [44],[89],[90],[91],[92]. The variations in b-values make the calculation of ADC data bit problematic, as ADC represents diffusion as well as perfusion in micro vessels [70].

Table: 3 .Selected articles on Diffusion Weighted Imaging of the Brain ischemic stroke in humans.

Author	Title	Subjects	Overview
Warach S 1992[75]	Fast magnetic resonance diffusion-weighted imaging of acute human stroke	acute stroke	The study showed the potential role of DWI in early anatomic diagnosis of hyperacute, acute and chronic infarcts. The relative difference in ADC values of infracted and noninfarcted regions in the first 24 hours , has improved diagnostic accuracy
Warach S 1995[87]	Acute human stroke studied by whole brain echo planar diffusion-	acute cerebral ischemia	Potential role of DWI in human stroke pathophysiology and detection of early ischemic stroke within 3 hours after the onset of symptoms.

	weighted magnetic resonance imaging.		
Marks MP 1996[21]	Acute and chronic stroke: navigated spin-echo diffusion-weighted MR imaging	cerebral infarction	Phase-navigated SE DW motion-correction sequence helped to differentiate acute from chronic stroke and improved the early diagnosis.
Lutsep HL 1997[22]	Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke	Ischemic strokes	Detection of small changes in water diffusion t in ischemic brain tissues was most useful in detecting acute stroke within 48 hours of the ictus and proved DWI superior to T2W MRI, whereas both techniques helped in lesion age evaluation.
Karl-Olof Lo¨vblad 1998[1]	Clinical Experience with Diffusion-Weighted MR in Patients with Acute Stroke.	acute ischemic stroke	Positive DW-MRI studies in 133/151 cases showed the specificity and sensitivity of echo-planar DW-MRI for acute infarction.
Van Everdingen1 KJ 1998[104]	Diffusion-weighted magnetic resonance imaging in acute stroke	acute stroke patients and 15 control subjects	98% of ischemic lesions detected and their size was measured on DW image. ADC values were potential parameters for predicting clinical outcome.
Kidwell CS 1999[105]	Diffusion MRI in patients with transient ischemic attacks Stroke	Transient ischemic attack	Diffusion imaging results showed significant clinical utility, 20 out of 42 identifiable lesions were found on DWI.
David Lefkowitz 1999[106]	Hyperacute Ischemic Stroke Missed by Diffusion-Weighted Imaging	Hyperacute Ischemic Stroke	Failure of DWI to reveal ischemic stroke within 3 hours of symptom onset, demand the additional techniques necessary to identify tissues at risk more thoroughly.
Yoneda Y 1999[19]	Diffusion-weighted magnetic resonance imaging: detection of ischemic injury 39 minutes after onset in a stroke patient	Ischemic injury	DWI detected hyperacute ischemic injury within 39 minutes of symptom onset in human whereas; T1- and T2-weighted imaging gave failed to detect the change.
González RG 1999[107]	Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset	Stroke	DWI provides superior lesion contrast compared with that of CT and conventional MR imaging, within 6 hours of symptom onset and a b value of around 1,000 sec/cm2 was found optimal for sufficient diffusion weighting.
Takayama H	Usefulness of	transient	DWI clinically proved a useful technique for the

2000[108]	diffusion-weighted MRI in the diagnosis of transient ischemic attacks	ischemic attack	detection of responsible lesions in TIA.
Okuyama T 2000[109]	Diagnosis of acute cerebral infarction using diffusion-weighted imaging by low field (0.2 T) magnetic resonance image	acute cerebral infarction	Diffusion-weighted imaging is able to diagnose acute cerebral infarction by the use of low field (0.2 T) as well as high field MRI
Narisawa A 2001[110]	Diffusion-weighted magnetic resonance imaging (MRI) in acute brain stem infarction.	Acute brain stem	Negative findings of DWI in the acute stage do not exclude possibility of the brain stem infarction.
Hjort N 2005[111]	Ischemic injury detected by diffusion imaging 11 minutes after stroke	Ischemic injury	Diffusion-weighted images obtained 11 minutes after stroke showed tissue injury and abrupt diffusion changes in hypoperfused tissue, not found on initial images.
P L Tan, 2006[4]	Diffusion weighted magnetic resonance imaging for acute stroke: practical and popular	Suspected acute stroke	After the Clinicians' (general physicians, neurologists, and radiologists) perceptions, DWI significantly proved both feasible and sustainable improvement to stroke services.
T. Wessels 2006[112]	Contribution of Diffusion-Weighted Imaging in Determination of Stroke Etiology	Ischemic stroke	Single, scattered, or multiple lesions were classified with significant overall association of DWI lesion patterns and classification with stroke subtype.
Rahul Rathakrishnan 2006[111]	Diffusion-negative MRI in acute ischemic stroke	Acute ischemic stroke	The case of a 49-years old man performed after 12 hours of symptom onset was negative showing that in early stage DWI may not be100% sensitive but clinically, assessment still retains priority.
C. Rosso 2010[112]	Diffusion-weighted MRI in acute stroke within the first 6 hours 1.5 or 3.0 Tesla	Acute stroke patients and 34 controls	1.5-T diffusion-weighted MRI (DWI) proved more sensitive and specific than 3.0-T DWI for imaging of hyperacute stroke

6. Clinical applications of Diffusion-Weighted Imaging in Brain Ischemia

Although the diffusion weighted imaging of brain was started in mid 1980s, both in patients and normal subjects, But DW-MRI really took off not until the mid 1990s. Initially the acquisition times were (10-20 minutes) because of the specification of scanner and the large gradient pulses that were necessarily required for DWI and ultimately, the images suffered with motion artifacts [115]. Now with standard MRI scanner, well equipped with EPI, images are acquired in seconds or minutes [64],[73]The most successful results of DW-MRI have been in Brain Ischemia since 1990s [1],[5],[14],[15],[20],[22]. The patients with chronic infarction were treated readily with this technique [116],[117],[118].The important discovery was made by

Moseley. He demonstrated the significant decrease in water diffusion coefficient (by 30%-50%) in Brain tissues of Ischemic patient [119]. This occurs within minutes, and cannot be identified by conventional techniques as T2-Weighted SE-MRI. DW-MRI identified the changes in ADC of water, especially in cerebral ischemia [120],[121]. These findings were confirmed in clinical trials by several groups of researchers, using animal models and later in humans.

T2-weighted images, by contrast remain normal for several hours after the onset of stroke and increase in T2 occurs later, after the development of vasogenic edema. DWI allows a faster detection of ischemic stroke. Recent study of DW imaging of suspected acute stroke showed the prognostic superiority of DW imaging for scan obtained up to 12 hours after the emergency, when DW images were obtained up to 12 hours after the onset in consecutive 691 patients. Imaging performed within six hours, however showed greatest results [122].

The interpretation of decreased water diffusion coefficient, immediately after the arterial occlusion, is still incomplete. The relationship of decrease in water diffusion with the severity of ischemic injury and clinical outcome is still a subject of study [84],[123]. Regardless, in the management of stroke patients DW imaging has a great potential.

Various theoretical considerations and experimental studies show the role of diffusion weighting imaging in the predictability and staging of evaluation of cerebral infarction.

Table 2 shows the selected work that is being done on Ischemic stroke on different stages. Only those studies are selected specifically where DWI clinically proved best and a sensitive tool for early diagnosis (11 minutes in one case) of stroke. It showed significant results in detecting minor changes in water diffusion after the onset of sign and symptoms, in comparison to conventional T2 MRI. Phase navigated SE DW imaging technique and the use of 3.0 T magnetic field are the exciting advancements in this field and will be helpful in improving the existing modalities used in DWI. Although there are some cases where DWI was not 100% accurate in lesion detection in early stages, but it doesn't exclude the high sensitivity and clinical utility of DWI [21],[22],[104],[114].

Diffusion-Weighted imaging and Transient ischemic attack (TIA or mini stroke):

TIA or more accurately a warning attack is due to the blocked or reduced blood flow that leads to the deficiency of oxygen in part of brain and is usually resolved completely within 24 hours. Early (1999) studies on TIA patients, showed that about two third of patients with symptoms had lesions visible on DW images [105],[123],[124],[125]. TIA patients with lesions have high risk of stroke [126],[127].Whether DWI helps in early detection of TIA or improves the predictability of recurrent events, is still a subject of investigation.

The sensitivity for the detection of recent lesions in TIA patients can be improved by some modifications,

to minimize partial volume effect, by reducing the thickness of section.

to improve the SNR and angular resolution by increasing diffusion directions and signal intensity.

A comparison of standard and optimized DWI had proved the optimized DWI more positive in 36 TIA patients and showed more lesions (56 verses 42) than standard (19 verses 16). There was a decrease in the rate of false-negative DWI in TIA patients with optimized DWI [128].

Observations of four research groups showed that decreased ADC of ischemic lesion in patients who got recovered within 24 hours, it was less pronounced than in patients with a complete stroke. And the degree of ischemic compromises may seem less severe in patients with TIA than patients with stroke [105],[125],[127],[129].

Diffusion-Weighted imaging and Acute Ischemic Stroke: Stroke is defined as sudden loss of neurological function characterized by rapid or sudden onset of symptoms. Permanent neurological damage or disability can occur depending on the affected part of the Brain and the duration of the cerebrovascular disturbance. Approximately 85% of all strokes are Ischemic, and are the result of blockage or obstruction within the blood vessel to the Brain.15% of the strokes are hemorrhagic, and are caused by the breakage or leakage of blood vessel into the Brain [5].

DWI depict ischemic lesions more precisely and earlier than conventional (T1-weighted and T2-weighted) imaging or CT scans [130], or contrast enhanced images, so DW protocols are recommended for the acute and subacute cerebral patients.

DW-MRI has detected six lesions, which were not seen on T2-weighted images, in one study on a total of 103 images [22]. A significant decrease was found in abnormal diffusion studies, with time and the change in signal intensity were rare, if the scans were performed more than two weeks after the onset of insult. Whereas, the abnormal signal intensity was evident on all (11/11) DW-MR studies performed on 40 suspected patients of cerebral infarction [51]. Stroke subtypes were analyzed by the trial of ORG 10172 in acute stroke treatment. 95% patients of Ischemic stroke and 5% of TIA were investigated by DW imaging, lesions were classified and a strong relationship was found between stroke subtype lesion patterns on DW imaging [112].

Despite the fact that DWI is acknowledged as highly sensitive for stroke detection , there are diffusion-negative reports describing that DWI may not rule out infarction, as Hyperacute stroke was undetected by DWI [131]. But DWI cannot be excluded in diagnosis of a stroke on the base of DWI without visible lesions, as greater than 95% of ischemic lesions were visualized, in most series of DW imaging [1],[104],[107],[132],[133],[134],[135].

Although the software and hardware to perform DWI are available widely, the technique has not been efficiently and routinely applied in clinics, especially for extra cranial diseases. One possible reason is the lack of recognition of DWI as a radiological tool, and the lack of procedural

instructions for radiologists making this unique imaging method not as applicable as required for the better evaluation of infarction and other diseases.

Training and teaching of radiologists related to DWI and its protocols, would help in better understanding of the subject. Research in DWI applications in applying DWI and active engagement of radiologists would facilitate its practical adaptation to clinical practice.

7. Conclusion

Diffusion Weighted Imaging is truly a quantitative technique, through the observation of molecular movement i.e. random and translational; this method gives insight into microscopic physical properties of tissues. Experimental and theoretical analysis based on the facts regarding the effects of restricted diffusion, hindrance, membrane permeability and tissue inhomogeneity have carefully underlined the precautionary measures that must be taken to interpret data and accurately infer the information from the DW images, ADC images or map. As the DW images display primarily water dependent signal intensities. The addition of two strong diffusion gradient pulses to the normal MRI pulse sequences, generate the images being water-motion sensitized in the direction of applied gradients. This process helps to determine the diffusion weighting of the images, characterized by gradient factor b.

DW- imaging pulse sequence provide valuable and unique information on anatomy, function and physiologic state of Brain. DWI is particularly sensitive to, an accurate and early detection of Ischemic stroke, necessary to prevent any abnormality, for treatment success and for the differentiation of stroke in its stages.

A decrease in water diffusion in Brain tissues appears shortly after the onset of insult in rats. If the scans are obtained within 6h of onset of symptoms, DW is 93-100% sensitive for stroke detection clinically.

From different values of gradient factor b, the ADC map can be calculated which apparently displays the decrease in water diffusion and Ischemic lesion as dark areas. Whereas, T1-weighted, T2-weighted or proton density, has no contribution in this regard.

There are arguments about the high b-value DW imaging for the diagnostic advantages. Some researchers believed that, high b-values at DWI do not confer diagnostic advantages. An upgrade hardware is required for high b-value DWI because most MRI-units are not efficient enough of generating high gradient fields as 40mT/m.

There are experimental proofs, showing the advantage of high b-values. DWI at b = 3000 s/mm² than DWI at b = 1000 s/mm² is more useful in discriminating high grade Glioma and low grade glioma at 3 T. For the estimation of extent of water diffusion changes, DWI at b = 2000 s/mm² proved better than DWI at b = 1000 s/mm².

Studies and experiments demonstrate DW imaging a unique diagnostic tool, which has superiority over conventional imaging in detecting lesions and differentiation of old lesions from new lesions in Brain territory.

Diffusion-Weighted images that are obtained with Fast Spin Echo Imaging (FSEI), Segmented Echo Planar Imaging (SEPI), Single Shot Echo Planar Imaging (SSEPI), like quick imaging modalities , bulk motion related artefact can be minimized.

Consequently imaging time will be shortened and image quality would be better and much more enhanced. Conclusively, DWI is a non-invasive technique that provides exceptional information and the utility for monitoring and predicting response to treatment.

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