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Diffusion Weighted Imaging Changes in Multiple Sclerosis Patients, Frequency and Correlation to Disease Activity

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Abstract

Introduction: Diffusion Weighted Images (DWI) is conventionally used to identify acute ischemic lesions. The role of DWI lesions in the evaluation of demyelinating lesions has not been well established.

Objective: To determine the prevalence and nature of DWI changes in MS and to assess the correlation between DWI changes and disease activity in MS.

Method: 100 RRMS patients were included in the study. The location and number of DWI lesions (Diffusion restriction and T2 shine through) and gadolinium enhancing lesions were visually located and calculated. Follow up MRI's were analyzed to monitor the resolution of existing DWI lesions and to detect new lesions.

Results: DWI changes were observed in 61% of the patients (49% T2 shine through; 12% Diffusion restriction). Gadolinium enhancement was observed in all lesions with diffusion restriction [p- value <0.001] and in 55% lesions with T2 shine through [p-value <0.001] activity. Location of enhancing lesions did not always correspond to the lesions showing restriction or T2 shine. All patients who presented with DWI restriction lesions were symptomatic and experienced an aggressive clinical course

Conclusion: Our study illustrated a high prevalence of DWI lesions in patients with RRMS. Diffusion restricted lesions predicted severe disease activity, both radiologically and clinically. DWI sequence revealed lesions not seen with other standard MRI sequences or with Gadolinium enhancement and may have a potential to serve as radiological biomarker of aggressive demyelinating disease.

Keywords: Multiple sclerosis; Diffusion weighted images; Magnetic resonance imaging; Autoimmune disease; Central nervous system

Abbreviations

MS: Multiple Sclerosis; CNS: Central Nervous System; DWI: Diffusion Weighted Images; FLAIR: Fluid Attenuated Inversion Recovery; MRI: Magnetic Resonance Imaging; EPI: Echo Planar Image

Introduction

Multiple Sclerosis (MS) is an inflammatory demyelinating disorder of the Central Nervous System (CNS). It represents the most common cause of acquired neurologic dysfunction in young patients. The most accepted etiology is autoimmune in addition with other factors including genetic and environmental. The incidence of MS in the United States is approximately 100 cases per 100,000 people per year [1]. It presents a socioeconomic problem due to the long duration of the disease, early onset and disability.

MRI is an essential tool in the evaluation and diagnosis of MS. Characteristically MS plaques are multiple, hyper intense in T2 Weighted Images (WI) and in Fluid Attenuated Inversion Recovery (FLAIR). Hypo intense lesions in T1- WI ("black holes") are associated with areas of myelin loss. Contrast enhancing lesions suggest blood brain barrier disruption due to acute inflammation; enhancement may persist for 2 to 6 weeks if untreated with steroids [2].

MRI also demonstrates silent lesions and it is estimated that the disease activity seen on MRI imaging is 5 to 10 times higher than what is clinically recognized [3].

Diffuse Weighted Image (DWI) allows measurement of the Apparent Diffusion Coefficient (ADC) of water in the brain. Water diffusion in the brain is restricted by cellular boundaries, and the ADC increases with any breakdown in cellular structure [4].

Diffusion characterizes the random translational motion of molecules driven by their internal thermal energy [5]. With the advance of MR measurable diffusion effects, it is possible to derive information about the structural organization of tissues far beyond the spatial resolution of conventional MR imaging techniques. DWI employ spin echo-based sequences that are sensitized to diffusion by strong magnetic field gradient pulses [6].

Even though not all restrictive diffusions are due to stroke [7,8] in

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Table 1: Sample characteristics (n=100).

	Female (n=69)	Male (n=31)	p
Age (years), M (SD)	45.3 (11.8)	37.9 (10.1)	0.003
Age at diagnosis (years), M (SD)	36.8 (11.9)	33.1 (9.2)	0.13
Years since diagnosed, M (SD)	8.5 (8.2)	4.8 (5.3)	0.024
Previous treatment, n (%)	35 (50.7)	12 (38.7)	0.266
Current treatment, n (%)	61 (89.7)	29 (93.6)	0.537

Note: p value was calculated using t-test for continuous variables and chi-squared test for categorical variables.

Table 2: Presence of DWI and active gadolinium enhancing lesions (%) in the sample (n=100).

	n	% (95% CI)
DWI lesion	62	62 (51.9–71.1)
ADC representation	12	12 (6.9–20.1)
T2 shine	59	59 (49.0–68.3)
Both (T2 + ACD)	9	9 (4.7–16.6)
Enhancing lesion	41	41 (31.7–51.0)

clinical practice DWI neuro imaging is primarily used in the detection of acute brain ischemia. Water diffusion drops to half of its normal value at the early stages of ischemia causing them to appear as areas of marked hyper intensity on DWI scans. DWI allows a relatively accurate and early delineation of the area of ischemia and along with perfusion imaging is now an integral part of the evaluation of acute strokes. Even though the DWI appears to have greater resolution of micro structural components of the cells than conventional MRI sequences, few studies have investigated the use of DWI imaging in specific disease states other than acute stroke.

The experience with DWI in MS to date is limited to a few case reports of MS patients who present with DWI signal and reduced ADC. To our knowledge, our study is the first one to evaluate the frequency and correlation to clinical presentation in a wide number of patients [9].

In our study we evaluated over 200 brains MRI of 100 patients with RRMS for presence of DWI changes and the radiographic correlation of these DWI changes with disease activity. We also evaluated the radiographic correlation of DWI findings with gadolinium enhancing lesions.

Study Design and Methods

This was a retrospective study conducted at Texas Tech University Health Sciences Center (TTUHSC) between 2015 – 2017. Approval by the institutional review board was obtained prior to conducting the study. Patients were selected from a list of 280 active MS patients from TTUHSC neurology clinic. These patients received comprehensive care for multiple sclerosis at our institution between 2013- 2017.

A total of 100 patients with Relapsing Remitting MS (RRMS) according to McDonalds 2010 revised criteria were included. Time of diagnosis, treatment history and other epidemiologic data were documented. Brain MRI from these patients was evaluated for the presence of DWI changes in association to hyper or hypo intensity in ADC sequence. Clinical correlation and follow up MRI was evaluated and documented.

MRI scans were performed on a 1.5 Tesla MRI scanner. Brain MRI sequences included T1 and T2 weighted axial, FLAIR axial and sagittal, diffusion weighted axial, and gadolinium enhanced axial views (5 minute delay for gadolinium enhanced sequences) in all patient. FLAIR and T2-weighted images were obtained with a pixel size of 0.98 × 0.98 mm, slice thickness 5 mm, interslice gap 0.5 mm. A diffusion weighted scan was also performed with a spin Echo Echo Planar Image (EPI) sequence with diffusion gradients applied in three orthogonal directions.

Patient Inclusion and Exclusion

Patients were retrospectively selected from a list of 280 active MS patients in our center. Medical records were screened randomly. Patients with RRMS for whom there was MR of the brain were included in study.

Patients with other forms of MS and patients for whom there were no MRI images were excluded from the study.

Disease duration was defined as time of onset of first symptoms to now.

Burden of disease was defined as the total number of white matter lesions.

Aggressive clinical course was considered if there was precipitous accumulation of neurological deficits associated with multiple enhancing white matter lesions in MRI.

Disease activity was defined as the presence of enhancing lesions in the MRI.

Electronic medical and brain MRI scans were analyzed by the same investigator in order to ensure consistency in data interpretation.

Statistical analysis

We calculated descriptive statistics as Mean (Standard Deviation) or n (%), to report the sample characteristics by gender in age, age at diagnosis, treatment received and MRI findings. Difference between groups was assessed using t-test or chi-squared (χ^2) as appropriate. Presence of lesions at MRI was reported as percentage and 95% confidence interval (with logit transformation to compute the limits) for DWI changes in MS, ADC representation, T2 shine, and presence of active gadolinium enhancing lesions. We used Odds Ratios (OR) to report the association between active enhancing lesions and positive in DWI lesions, ADC representation and T2 shine. Logistic regression was used to estimate the OR adjusted for MS current treatment, age, gender and duration of disease. Association between age at diagnosis and lesions at MRI was assessed using Spearman's correlation. In the event of significant associations are found between these outcomes, the relation with previous and current treatment, and age at diagnosis will also be checked. The significance level will be set at p=0.05. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX).

Results

Data from 100 patients diagnosed with multiple sclerosis by the McDonald 2010 criteria were analyzed. Age ranged 23-65 years (mean=43 years, SD=11.7), 69 were female and 31 male, and

Table 3: Unadjusted association between DWI lesions and contrast enhancing active lesions.

	(%) Active lesions		Unadjusted odds	Adjusted odds	
	Yes	No	ratio and 95% CI	ratio and 95% CI	p-value
DWI lesion	62.9	5.26	30.5 (6.57–275)	26.3 (5.64–122)	<0.001
ADC representation	100	0	—	—	<0.001
T2 shine	87.8	12.2	11.3 (3.59–41.1)	9.7 (3.24–29.1)	<0.001

Note: Adjusted for MS current treatment, age, gender and duration of disease; Odds Ratio and exact confidence levels not calculated for ADC representation due to perfect prediction.

Table 4: Location of lesion by DWI diagnosis.

		DWI lesion				
	No lesion	T2 only	ADC only	T2 + ADC	χ^2	p
	(n=38)	(n=4)	(n=49)	(n=9)		
Periventricular, n (%)	36 (94.7)	4 (100.0)	48 (98.0)	9 (100.0)	1.23	0.747
Subcortical, n (%)	34 (89.5)	4 (100.0)	46 (93.9)	9 (100.0)	1.76	0.623
Cortical, n (%)	7 (18.4)	1 (25.0)	17 (34.7)	6 (66.7)	8.54	0.036
Brainstem, n (%)	4 (10.5)	1 (25.0)	16 (32.6)	8 (88.9)	22.32	<0.001

diagnosis was made on average 7.3 years before last MRI of the head. Full sample characteristics by gender are shown in (Table 1). Female patients in this sample were significantly older than male patients, t (98)=3.03, p=0.003. However, no significant differences were found in age at diagnosis (t[98]=1.53, p=0.130), having been treated for MS (χ2(1)=1.24, p=0.266), or being currently in treatment (χ^2(1)=0.38, p=0.537).

DWI lesions were found in 62% of the patients (Table 2). In our sample, 49% of the patients had T2 shine through only and 12% had restriction on ADC. As shown in (Tables 3 & 4), the odd of having active enhancing lesions was significantly higher if in cases with DWI.

Enhancing lesions were present in 100% of the patients who had DWI restriction [p- value <0.001] and in 55% of the patient with T2 shine through lesions [p-value <0.001]. Although some enhancing lesions also showed DWI restriction and T2 shine through, there were many cases where lesions with DWI restriction and T2 shine through did not enhance with contrast. All patients who presented with DWI restriction lesions were symptomatic and the clinical histories suggested a clinical aggressive course.

Age of diagnosis was neither associated to DWI lesions (rho=-0.04, p=0.716), nor ACD representation (rho=0.1, p=0.327), nor T2 shine (rho=-0.07, p=0.471).

Location of the lesions in the periventricular or subcortical white matter did not predict the risk for the presence of DWI lesions. However, significantly differences in presence of cortical (χ^2=8.54, p=0.036) and brainstem (χ2=22.32, p<0.001) lesions were found.

Discussion

MRI is a crucial tool in the diagnosis and assessment of treatment efficacy of Multiple sclerosis. T2 weighted sequences demonstrate the evolution of MS lesions but do not reflect the age of the lesion. This sequence also fails to differentiate specific changes in the histopathologic substrate or the subtle abnormalities in the so called "normal appearing white mater". Currently used MRI measures do not strongly correlate with clinical disability measures.

Diffusion-Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) sequences in MRI are an important tool in the management of acute CNS ischemia but its role has not been established in MS. There is evidence that, unlike the restricted ADC values found in acute infarction, which reflect the presence of cytotoxic edema, DWI abnormalities in MS plaques may also have elevated ADC values. Diffusion-weighted imaging (DWI) allows measurement of the Apparent Diffusion Coefficient (ADC) of water in the brain. Water diffusion in the brain is restricted by cellular boundaries, and the ADC increases with any breakdown in cellular structure [10].

Preliminary studies showed that the diffusion coefficient is higher in macroscopic MS lesions than in normal appearing white matter.

MS lesions evolve differently during early versus chronic phase of the disease. Within each phase, different plaque types and plaques in different stages of demyelinating activity are evident. Histologically, several basic processes drive the formation of plaques, including inflammation, myelin breakdown, astrogliosis, oligodendrocyte injury and neuro degeneration. Considering the diversity of processes, it is reasonable to assume that different MRI parameters capture different aspects of this complex process.

This study demonstrates a correlation between disease activity and the presence of DWI changes. DWI occurred independently of contrast enhancement and probably reflects something other than the breakdown of the blood brain barrier. All patients with DWI restriction showed evidence of disease activity and had an aggressive course of disease.

Conclusion

Our study demonstrates that the MRI of the head of patients with RRMS will frequently show changes in the DWI sequence. Some DWI restricted lesions can enhance after administration of contrast while others do not. The DWI and contrast enhancement probably reflect different pathological substrates i.e. break down of blood brain barrier). Although our numbers are relatively small, our findings also suggest that the presence of DWI changes on the head MRI of patients

with RMMS may be a marker for more aggressive disease activity.

In summary, DWI sequence appears to be an overlooked diagnostic tool for patients with MS that is already available for general use. Further studies will be needed to confirm whether DWI provides information not given by other MRI sequences and whether these findings indeed have important implications for the management and prognosis of patients with RRMS.

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