The Evaluation of MRI Diffusion Values of Active Demyelinating Lesions in Multiple Sclerosis

Mohammad Abdoli[1], Santanu Chakraborty[2], Heather J. MacLean[3], Mark S. Freedman[4]

[1] Multiple Sclerosis Clinic, Department of Medicine, Ottawa Hospital Research Institute, [2] Division of Neuro-imaging, Department of Medical Imaging, University of Ottawa
[3] Division of Neurology, Department of Medicine Ottawa, Ontario, Canada, [4] The Ottawa Hospital Research Institute and the University of Ottawa

INTRODUCTION

The detection of new MRI activity in early disease, during the course of disease and in monitoring the response to treatment of Multiple Sclerosis (MS) is key in disease management. Whereas the detection of new T2 lesions requires a solid reference scan and meticulous slice by slice analysis of a comparative new scan, the appearance of Gadolinium (Gd) enhancing lesions leaves little doubt that lesions are in fact recent, new or active. However, the administration of Gd is expensive, more labour intensive and has potential safety issues. It was observed that Gd-enhancing lesions often show restricted diffusion on Diffusion Weighted Imaging (DWI) studies, suggesting that DWI might supplant the use of Gd for detection of new MRI activity. DWI sequences are short, adding little to MRI scan time and do not require any infusion of dye.

The purpose of this study was to investigate how consistently Gd-enhancing lesions correlated with DWI restricted diffusion in MS patients.

PATIENTS AND METHODS

This is a retrospective cohort study of registered patients in the Ottawa Hospital Multiple Sclerosis clinic who had undergone MRI with both Gd and DWI sequencing.

The images were evaluated first for the presence of Gd+ enhancing lesions and then evaluated for whether these same lesions also showed restricted diffusion on DWI. DWI was acquired with a single-shot echo planar sequence in three orthogonal directions with diffusion gradients b-value of 0, 500 and 1000 sec/mm2. Apparent diffusion coefficient (ADC) maps were automatically generated. ADC values were measured on Gd+ lesions and all lesions showing restricted diffusion as well as 2 Gd- lesions along with 1 area of normal appearing white matter (NAWM) in all patients. Comparisons of the ADC values of the Gd+, Gd− lesions and NAWM were performed. The predictive value of the restriction on ADC map for the presence of Gd-enhancement of lesions was calculated.

Figure 1-Method used for screening of lesions and measurement of ADC values in ADC map

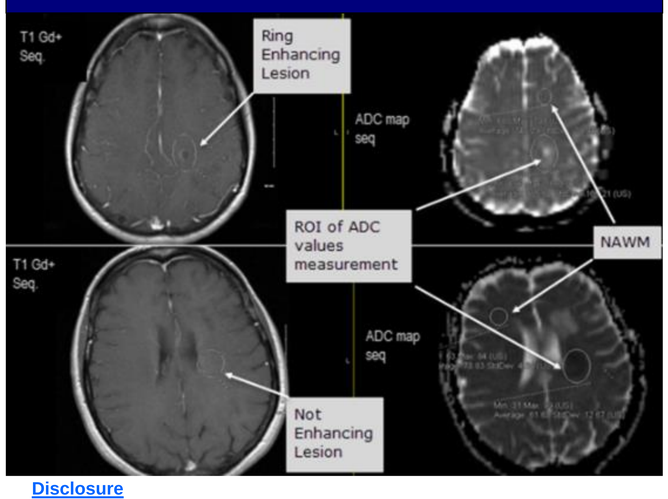


Figure 2-ADC minimum of Gd enhancing lesions vs. NAWM and Non-enhancing lesions

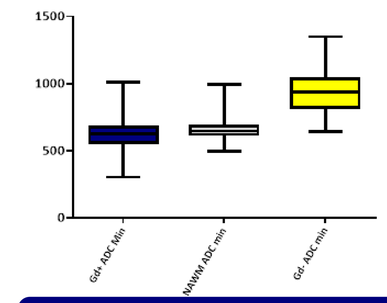
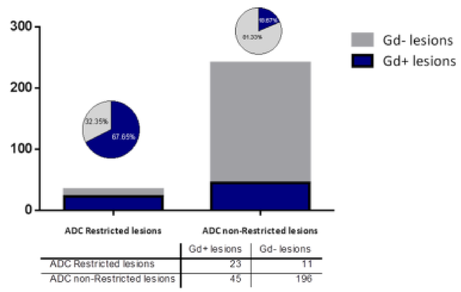


Figure 3-ADC Restricted lesions in visual apparent ADC map and enhancement pattern



	Gd+ lesions	Gd- lesions
ADC Restricted lesions	23	11
ADC non-Restricted lesions	45	196

Figure 4-ADC max &SD of Gad enhancing lesions vs. NAWM and Non-enhancing lesions

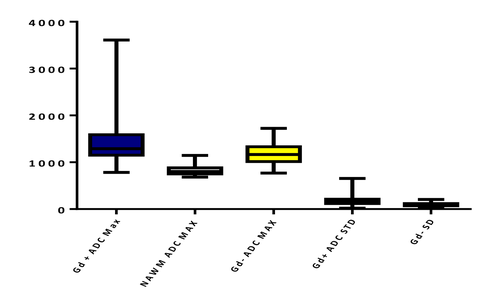


Table 1 -Sensitivity and specificity of Restriction in ADC map for Gd enhancement

	Gd+	Gd-
ADC Restricted lesions	23	11
ADC non-Restricted lesions	≥45	≥196
Total	≥68	≥207
Sensitivity and specificity	*Fisher's test(p<0.05)*	
Sensitivity	≤0.3382	
Specificity	≥0.9469	
Positive Predictive Value	0.6765	
Negative Predictive Value	≥0.8133	
Relative Risk	≥3.623	
Odds ratio	≥9.107	

Table 2- Analysis of ADC Metrics of Different Types of Lesions

(Mann- Whitney)/ Median of Diff (Wilcoxon Test)		Median 1/IQR ($\times 10^{-6}$ mm^2/s)	Median2/IQR ($\times 10^{-6}$ mm^2/s)	Actual Dif.	P value
Gd+ vs. NAWM	ADC min	626/109	646.5/60	-20.50/20.50	0.02/0.01
	ADC max	1293/439	800/130.3	493/483.5	<0.0001/ <0.0001
Gd- vs. NAWM	ADC min	936/213	646.5/60	289.5/268.5	<0.0001/ <0.0001
	ADC max	1167/315	800/130.3	365.5/382	<0.0001/ <0.0001
Gd+ vs. Gd-	**ADC min**	**626/109**	**936/213**	**-310/-291.5**	**<0.0001/ <0.0001**
	ADC max	1293/439	1167/315	126.5/169.5	0.0020/ 0.0012
	ADC SD	150/92.8	80/47.75	70/62.50	<0.0001/ <0.0001

Table 3 - Analysis of ADC Values of Sympt. vs. Asympt. lesions in enhancing lesions

	Median Sym./IQR ($\times 10^{-6}$ mm2/s)	Median Asym./IQR ($\times 10^{-6}$ mm2/s)	Actual Diff (Mann-Whitney)	P value
ADC min	**578.5/87.5**	**630/100**	**-51**	**0.0421**
ADC max	1235/665.5	1224/509	10.50	ns
ADC avg	837.5/206.5	871/207	-34	ns

Figure 5-Symptomatic vs Asymptomatic enhancing lesions ADC values

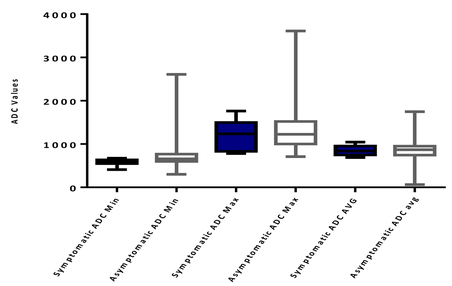
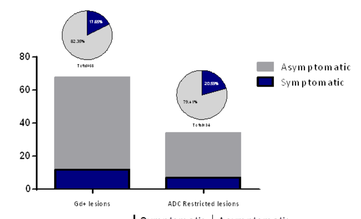


Figure 6- Symptomatic vs Asymptomatic lesions in Gd enhancing or restricted lesions



	Symptomatic	Asymptomatic
Gd+ lesions	12	56
ADC Restricted lesions	7	27

RESULTS

• DWI values were measured on 275 T2 lesions that included 68 Gd+ lesions and 207 Gd- lesions, as well as 104 corresponding NAWM area in each MRI.

•34 lesions showed restricted diffusion on DWI. The median ADC minimum of enhancing lesions was significantly lower than NAWM and even lower than the Gd- lesions. Most DWI restricted lesions showed Gd enhancement (specificity ≥94%), but many Gd+ lesions did not show detectable restriction on DWI (sensitivity ≤ 34%). Most of the Gd+ or restricted lesions were asymptomatic, but the median ADC minimum of symptomatic lesions was lower than asymptomatic lesions, suggesting that greater restriction might correlate with symptomatic lesions .

DISCUSSION

•Despite the hope that DWI sequences and the presence of restricted diffusion might substitute for the use of Gd to detect new MRI activity in MS, our data suggests that **it cannot**.
•Most Gd-enhancing lesions demonstrate heterogeneity in restricted diffusion, with generally a lower ADC minimum compared to Gd-lesions; however, many had no visually appreciable restriction in diffusion images, indicating that DWI would be insensitive an index for detecting MRI activity in most new lesions.
•Lesions that are felt to be symptomatic were more likely to be associated with restricted diffusion than those that were asymptomatic, whereas the same was not true of Gd+ lesions. This suggests that measuring restricted diffusion in lesions might offer insight as to the functional significance of these lesions.

References

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol.
2. Freedman M, Selchen D, Arnold D, et al. Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. Can J Neurol Sci. 2013;40(3):307-323.
3. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology. .
4. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology. 2015;275(3):772-782.
5. Kanal E, Shellock FG, Talagala L. Safety considerations in MR imaging. Radiology. 1990;176(3):593-606
6. Manual on Contrast Media v9 - American College of Radiology. http://www.acr.org/quality-safety/resources/contrast-manual.
7. Droogan AG, Clark CA, Werring DJ, Barker GJ, McDonald WI, Miller DH. Comparison of multiple sclerosis clinical subgroups using navigated spin echo diffusion-weighted imaging. Magn Reson Imaging. 1999;17(5):653-661.
8. Roychowdhury S, Maldjian JA, Grossman RI. Multiple Sclerosis: Comparison of Trace Apparent Diffusion Coefficients with MR Enhancement Pattern of Lesions. Am J Neuroradiol. 2000;21(5):869-874.
9. Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology. 1999;52(8):1626-1632.
10. Bammer R, Augustin M, Strasser-Fuchs S, et al. Magnetic resonance diffusion tensor imaging for characterizing diffuse and focal white matter abnormalities in multiple sclerosis. Magn Reson Med Off J Soc Magn Reson Med Soc Magn Reson Med. 2000;44(4):583-591.
11. Filippi M, Iannucci G, Cercignani M, Assunta Rocca M, Pratesi A, Comi G. A quantitative study of water diffusion in multiple sclerosis lesions and normal-appearing white matter using echo-planar imaging. Arch Neurol. 2000;57(7):1017-1021.
15. Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G. Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology.

Disclosure

Dr. Mohammad Abdoli: Participated in clinical MS research trials with Biogen, Novartis, Genzyme, Opexa, Sanofi-Aventis, Bayer and Roche; Receipt of educational grants: Genzyme Canada; Merck Serrano; Receipt of honoraria or consultation fees: CMSC, Merck Serrano, Genzyme Canada, MS Society of Canada

Dr. Santanu Chakraborty: Grant from GE and Bayer. Speaker/Consultant for Novartis

Dr. Heather MacLean: Participated in clinical MS research trials with Biogen, Novartis, Genzyme, Opexa, Sanofi-Aventis, Bayer and Roche, has done consultancy/lecturing for Biogen, Novartis, Genzyme and Teva.

Dr. Mark S. Freedman(from 2016 covering last 2 years) : Receipt of honoraria or consultation fees: Actelion, BayerHealthcare, BiogenIdec, Chugai, EMD Canada, Genzyme, Merck Serono, Novartis, Hoffman La-Roche, Sanofi-Aventis, Teva Canada Innovation ;Member of a company advisory board, board of directors or other similar group: Actelion, Bayer Health care, Biogen Idec, Hoffman La-Roche, Merck Serono, Novartis, Opexa, Sanofi-Aventis;Participation in a company sponsored speaker's bureau: Genzyme