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Follow-Up Assessment of Multiple Sclerosis Active Plaques Clinical Disability and MRI Study

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) has diverse modalities, among which gadolinium-enhanced DTPA (Gd-DTPA) visualizes acute lesions referred to as contrast-enhancing lesions (CELs) in multiple sclerosis (MS). In this regard, the current study aims to assess the neuroimaging characteristics of MS-related CELs in a 12-month follow-up study.

Material and Methods: This prospective cohort study was conducted on 41 patients with relapsing-remitting MS (RRMS) in 2019-21. The participants' demographic characteristics and Expanding Disability Status Scale (EDSS) were recorded. Gd-DTPA MRI was performed once, repeated within the next year, and interpreted by a panel of an expert neurologist and two skilled neuroradiologists.

Results: The MR assessments of the patients revealed 139 active plaques, among which 52 (37.5%), 49 (35.2%), and 38 (27.3%) had nodular, heterogeneous, and ring & arch pattern of enhancement, respectively. Eighteen plaques remained activated within the next year with heterogenous (11.2%), ring & arch (44.4%), and nodular (44.4%) enhancement patterns. The inactivated ones turned into gliosis (84.6%) and black hole (15.4%). EDSS was statistically less in nodular plaques than both ring & arch (P-value = 0.009) and heterogeneous patterns (P-value = 0.028).

Conclusion: The current study found that most of the plaques get inactivated during one year and changes to gliosis. Patients with a predominant nodular enhancement pattern had a lower increase in EDSS during one year follow up, in contrast who had the predominant ring & arch pattern experienced the highest. Additionally, the nodular pattern causes fewer disabilities in comparison to other types based on EDSS.

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1.INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease affecting the central nervous system with the potentiality of multiple relapsing and remission courses, which can cause a significant disability over time and impairs the quality of life (1). Particularly, accurate neuroimaging, magnetic resonance imaging (MRI) can help precise diagnosis and management of the disease to reduce the relapsing courses and slow down the disease progression to disabilities (2).

Numerous MRI techniques have been deployed to visualize and characterize the plaques and the course of MS disease. Conventional MRI neuroimaging, including T1- and T2-weighted (T2W) spin-echo (SE) images, the former obtained before and after the injection of gadolinium-DTPA (Gd-DTPA), is a preeminent diagnostic means in MS (3, 4). Chronic disease can be accurately investigated using T1W pre-contrast and T2W SE images, while T1W SE imaging obtained upon the administration of Gd-DTPA visualizes acute lesions referred to as contrast-enhancing lesions (CELs) (5). According to chemical properties, Gd-DTPA is not able to cross an intact blood-brain barrier (BBB). Therefore, any enhanced lesion represents an inflammatory process in BBB leading to Gd-DTPA leakage (6).

Heterogeneity has been notified in CELs and observed to be associated with the varying evolution of CELs over time. Moreover, CELs may re-enhance in short-term longitudinal investigations and arise in the site of chronic lesions, as well (7, 8). Nevertheless, a paucity of knowledge is available regarding the frequency of re-enhancing CELs, the pattern of the lesions, and new enhanced lesions in follow-up neuroimaging investigations. However, it has been proposed that persistent enhancement in a particular area can be contributed to a more severe demyelinating process; identifying how this is reflected in vivo is essential (9).

Accordingly, it can be estimated that repeated evaluation of CELs may provide a comprehensive understanding of individual disease evolution. Besides, it can be administered to assess the efficacy of different drugs in trials (9). In this regard, the current study aims to assess the neuroimaging characteristics of MS-related CELs in a 12-month follow-up study.

2. METHODS

2.1. Study population

This is a cohort study conducted on 41 patients with relapsing-remitting MS (RRMS) referring to outpatient MS clinic of Kashani Hospital, referral center of MS affiliated with Isfahan University of Medical Sciences, from October 2019 to August 2021.

The study protocol that met the Helsinki declaration criteria was primarily proposed for the Ethics Committee of Isfahan University of Medical. Then, the study was explained to the patients; they were reassured of the confidentiality of their personal information and requested to sign written consent.

The patients with documented RRMS diagnosis who experienced a recent relapsing course within the previous two weeks regardless of the clinical manifestations and had enhanced active plaque(s) in contrast-enhanced MRI were included in the study.

Any contraindication for taking MRI or gadolinium administration, corticosteroid use within the recent two weeks, any other pathology in the brain, and any other plaques with different enhancement patterns were considered the exclusion criteria.

The studied patients were recruited through convenience sampling until achieving the desired numbers of participants. A panel performed all the examinations, and neuroimaging interpretations consisted of an expert neurologist and two skilled neuroradiologists to minimize the probable biases.

2.2. Study protocol

The participants' demographic information, including age and gender, were primarily entered into a checklist. The neurologist comprehensively examined them, and their disability severity was determined using Expanding Disability Status Scale (EDSS) (10).

Afterward, neuroimaging was performed for the patients by a 1.5 Tesla MRI based on MS centers consensus 2019 guidelines. Accordingly, gadolinium-based contrast (287 mg/ml) with the dosage of 0.1 mmol/kg was administered intravenously for 30 seconds, and the imaging was performed within the next 15 minutes (11).

The study panel interpreted the MRIs. The numbers of the plaques, their location (periventricular, subcortical and juxtacortical, centrum semiovale, corpus callosum, cerebellum, brain stem, and cervical cord), and the pattern of enhancement (heterogeneous, nodular, and ring & arch) were entered into the study checklist.

The patients were followed for a year, they were telephoned to be revisited by the neurologist, and another MRI was performed. Similar data including, EDSS and neuroimaging findings, were re-evaluated.

2.3. Statistical analysis

The recruited data was entered into the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23. Descriptive data were presented in mean, standard deviation, percentages, and absolute numbers. The Smirnov-Kolmogorov test was employed to determine the normality of data distribution. For analytic data, Wilcoxon and Kruskal-Wallis tests were employed. Bon Ferroni post hoc test was applied to compare the data tow-by-two. P-value of less than 0.05 was considered as a significant level.

3. RESULTS

Data of 41 patients with MS were analyzed in the current study. The studied population was predominantly consisted of females (n=25, 61%) and had the mean age of 31.33±8.95 years old (age range of 18-48 years old). The mean period of MS diagnosis was 3.18±2.16 years (range: 1-10 years).

The mean EDSS of the patients was 1.57±1.61 (range: 0-6) and 2.19±2.01 (range: 0-6.5) at study initiation and within the next year, respectively. According to the Wilcoxon test, EDSS was significantly different comparing the primary and follow-up assessments (P-value<0.001).

The MR assessments of the patients revealed 139 active plaques, among which 52 (37.5%), 49 (35.2%), and 38 (27.3%) had nodular, heterogeneous, and ring & arch pattern of enhancement, respectively. The follow-up evaluations within the next year showed that 30 (21.60%), 18 (12.94%), and 91 (65.45%) plaques were disappeared, activated, and inactivated, respectively. However, those 18 plaques that continue to enhancement after one year mat be deactivated and reactivated within a year. The remained 18 active plaques had enhancement patterns of heterogenous (11.2%), ring & arch (44.4%), and nodular (44.4%). Besides, the inactivated plaques had turned into gliosis (84.6%) and black hole (15.4%). Detailed information is presented in Table 1 and 2.

Table 1. The patterns of enhancement in MR assessment of MS plaques (Base line)

Number of acvtive plaques	patterns of enhancement					
	Heterogeneous		Ring and arch		Nodular	
139	49	35.2%	38	27.3%	52	37.4%

Table 2: The patterns of enhancement in MR assessment of MS plaques (One year later)

Active plaques				Deactive plaques			Disappear
Total	Heterogeneous	Ring and arch	nodular	Total	Gliosis	Black hole	
18(12.9%)	2 (11.2 %)	8(44.4 %)	8(44.4 %)	91(65.4%)	77(84.6%)	14(15.4%)	30 (21%)

Table 3 presents the association of EDSS with the patterns of enhancement. Accordingly, the highest EDSS was noted in ring & arch and the least in nodular enhancement patterns. The baseline assessments showed no association between EDSS and the patterns of plaques enhancement (P-value = 0.245), while a significant difference was noted in the follow-up MRs (P-value = 0.003). Bonferroni post hoc test revealed that EDSS was statistically less in the nodular enhancement pattern than both ring & arch (P-value = 0.009) and heterogeneous patterns (P-value = 0.028)

Table 3. The association between plaques enhancement pattern and EDSS

Predominant pattern of enhancement	Number of patients	Baseline		Follow-up	
		Mean	Standard deviation	Mean	Standard deviation
Heterogeneous	13	1.84	1.98	2.92	2.22
Ring & arch	7	2.28	1.97	3.57	1.90
Nodular	19	0.97	0.85	1.05	1.07
P-value		0.245		0.003	

The location of the plaques in MRs and their type of enhancement regardless of the time of assessment is demonstrated in Table 4. The plaques were primarily located in the periventricular (27.5%) and centrum semiovale (22.5%) area. Nodular plaques were the most common types in periventricular (44.2%), subcortical and juxtacortical (46.4%), corpus callosum (100%), and cerebellum (75%) areas, while heterogeneous enhancement was notified in 37.1%, 55.6%, and 46.4% of the plaques in centrum semiovale, brainstem and cervical cord, respectively.

Table 4. The distribution of plaques location and type of enhancement

Location of active plaques	Heterogeneous		Ring & arch		Nodular		Total	Percentage
	Number	Percentage	Number	Percentage	Number	Percentage		
Periventricular	7	16.3	17	39.5	19	44.2	43	27.5
Subcortical & juxta cortical	7	25	8	28.6	13	46.4	28	18.2
Centrum semiovale	13	37.1	12	34.3	10	28.6	35	22.5
Corpus Callosum	0	0	0	0	1	100	1	0.7
cerebellum	1	25	0	0	3	75	4	2.8
Brainstem	10	55.6	5	27.8	3	16.7	18	11.5
Cervical cord	13	46.4	4	14.3	13	39.3	26	16.8
Total	51	32.5	46	29.3	60	28.2	157	100

Among 49 plaques with the heterogeneous pattern of enhancement at baseline, 2 (4.1%) ones remained heterogeneous, while 1 (2%) and 6 (12.2%) ones turned to ring & arch and nodular patterns, respectively. Most heterogeneous plaques get inactivated with gliosis (63.3%) or black holes (4.1%). Besides, 14.3% of the plaques disappeared. Most of the ring & arch plaques at baseline inactivated in the follow-up investigation with gliosis (44.7%) or black hole (34.2%) patterns. Only seven remained ones turned to ring & arch pattern (18.4%), and a plaque (2.6%) disappeared. Nodular pattern enhanced plaques were 52 ones that disappeared in 42.3%, inactivated with the black hole (1.9%) or gliosis (51.9%) patterns or remained nodular (3.8%) in the follow-up investigations. 43.3% of nodular enhancing plaques disappeared after one year, while just 2.6 % of ring &arch and 14% of heterogeneous enhancing plaques had such a fate (Table 5).

Table 5. The changes in the pattern of plaques enhancement within a year follow-up

At base line	After one year					
	Active			Deactive		Disappeared
	Heterogeneous (n=2)	Ring & Arch (n=8)	Nodular (n=8)	Gliosis (n=75)	Black hole (n=16)	Number (n=30)
Heterogeneous (n=49)	2 (4.1%)	1 (2%)	6 (12.2%)	31 (63.3%)	2 (4.1%)	7 (14.3%)
Ring & arch (n=38)	0 (0%)	7 (18.4%)	0 (0%)	17 (44.7%)	13 (34.2%)	1 (2.6%)
Nodular (n=52)	0 (0%)	0 (0%)	2 (3.8%)	27 (51.9%)	1 (1.9%)	22 (42.3%)

4. DISCUSSION

According to our investigation, the most common pattern of plaque enhancement in MRI was nodular, followed by heterogeneous and ring & arch, respectively. Besides, nodular enhanced plaques were associated with the least severe disabilities assessed by EDSS, while the worst condition was notified in ring & arch ones.

In addistion, patients with a predominant pattern of nodular enhancement had a lower increase in EDSS than the other two groups during one year follow up, and patients with a predominant ring & arch pattern experienced the highest increase in EDSS.

Davis and colleagues conducted a follow-up study in which the patients were followed through monthly MRIs. Similarly, nodular CELs were more frequent than the ring ones. Besides, the ring plaques were accompanied by larger volumes than the nodular ones.

Nevertheless, they found no association between the severity of MS course of disease with the pattern of plaque enhancement(12). However, the study by Hashemi et al. on 62 MS patients presented a ring pattern of enhancement as the most frequent type (4). Further investigations have presented consistent outcomes regarding the abundance of nodular enhanced plaques in primary MRIs of the MS patients; however, the association between the enhancement pattern and the severity of disease course is a matter of debate yet (1, 13-15).

Our follow-up assessment revealed that 65.4% of the plaques get inactivated within a year follow-up, among which gliosis was the most common pattern of MRI presentation, while among the remained active ones, nodular and ring & arch enhancement was found in 44.4% for both.

Besides 43.3% of nodular enhancing plaques disappeared after one year, while just 2.6 % of ring &arch enhancing plaques had such a fate.Therefore, it considered better outcome for nodular plaques.

It has been well-elucidated that many plaques may change to gliosis by the subside of the inflammatory process; however, numerous MRIs of the MS patients have presented gliosis as the primary manifestation (16). The alteration of an active central nervous system plaque to gliosis has been noted since a long time ago; however, it has remained a question that the plaques gliosis formation either shows a change in the underlying disease process or reflects a chronic process of ongoing disease in a previously damaged part of the nervous system (17). Another destiny of the inactivated plaques is turning into the black hole seen in 15.4% of the plaques. Davis et al. found an insignificant association between the pattern of lesion enhancement and the plaque volume. Therefore, they concluded that the type of enhancement or its alteration by the time is not related to the course of MS disease (12).

Several patterns of ring-enhancing lesion development and resolution over weeks to months have been proposed in the assessment of active plaques (18). Qian and colleagues followed several MRIs of MS patients and presented that preceding ring formation may lead to a nodule appearance which will later become the non-enhanced region in the ring's center. Different patterns of ring resolution may suggest heterogeneity in the subsequent cascade of immunologic events. A ring will often fade over the months, turn into a nodule, or develop again after nodule resolution (19). This trend of alteration in enhancement pattern is in line with Gaitán's suggestion of expanding wave of inflammation recruiting additional vessels, with subsequent closure of the blood-brain barrier (BBB) within the lesion center (18).

Generally, periventricules, centrum semiovale, subcortical & juxtacortical, and cervical cord were the most common locations involved with MS plaques. Nodular followed by heterogeneous and ring and arch enhancement patterns were detected in 38.2%, 32.5%, and 29.3% of the active plaques regardless of assessment time. These findings are consistent with the literature in which nodular enhancement has been considered (20, 21).

Most of the plaques in any brain area were enhanced with nodular pattern except for centrum semiovale, brainstem and cervical cord, in which heterogeneous pattern was the most common. Moreover, one-year follow-up assessments showed that regardless of gliosis that was the most frequent MRI finding due to plaques inactivation, the active plaques with ring & arch or nodular enhancement presented a similar pattern in the follow-up assessments. In contrast, the heterogeneous ones mostly turned into a nodular pattern.

Surfing the literature illustrated an associative correlation between the pattern of enhancement and the site of MS lesions; however, it has been notified that the elapsed time between contrast injection and MRI acquisition is a crucial factor for the enhancement pattern presentation (22). Nevertheless, it seems that the pathophysiology of an inflammatory process in an area is related to enhancement patterns. For instance, open ring plaques are typically seen in grey matter or ventricular lesions, or centrifugal enhancement clearly supports the centrality of perivenular pathogenic events at lesion onset. Therefore, it is hypothesized that any pattern is representative of a wound-healing inflammatory reaction of the CNS parenchyma to focal demyelination (22, 23).

5. LIMITATIONS

The short follow-up period and limited numbers of obtained MRIs in the study interval are the significant limitations of our investigation. Furthermore, numerous confounders, including the medications, the duration of MS, and the patients' age, have not been examined; however, these variables have a considerable impact on EDSS and may have affected the assessed lesions, as well.However,all of our patients were under the supervision of a common neurologist,with the goal of kepping their medication as similar as possible. Therefore, some biases may have influenced our outcomes, and further detailed studies are highly recommended.

6. CONCLUSION

Due to the paucity of knowledge regarding the impact of MS plaques enhancement pattern on the course of the disease and their destiny after a relapsing course subside, the current study was performed and concluded that most of the plaques get inactivated during one year and changes to gliosis. Patients with a predominant nodular enhancement pattern had a lower increase in EDSS during one year follow up, in contrast who had the predominant ring & arch pattern experienced the highest increase in EDSS.Additionally, the nodular enhancing pattern causes fewer disabilities in comparison to other types based on EDSS.

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CONFLICT OF INTERESTS

The authors have no conflict of interests regarding this paper

Criteria for inclusion in the authors'/ contributors' list

Study concept and design: N. C., G. J. A.H. and V.S.; analysis and interpretation of data: N. C., A.H., V.S. and G. J.; drafting of the manuscript: N. C and P.H.; critical revision of the manuscript for important intellectual content: V. S., P. H., and G. J.; statistical analysis: N. C.

REFERENCES

Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019;142(7):1858-75.

Yaghoobi M, Harirchian MH, Firouznia K, Behzadi S, Hashemi H, Ghanaati H, et al. The relationship between enhanced plaques with Gadovist and Magnevist contrast brain magnetic resonance imaging and the neurological deficit in the acute phase of relapsing-remitting multiple sclerosis. Iranian journal of neurology. 2012;11(2):42.

Fechner A, Savatovsky J, El Methni J, Sadik J, Gout O, Deschamps R, et al. A 3T phase-sensitive inversion recovery MRI sequence improves detection of cervical spinal cord lesions and shows active lesions in patients with multiple sclerosis. American Journal of Neuroradiology. 2019;40(2):370-5.

Hashemi H, Behzadi S, Ghanaati H, Harirchian MH, Yaghoobi M, Shakiba M, et al. Evaluation of plaque detection and optimum time of enhancement in acute attack multiple sclerosis after contrast injection. Acta Radiologica. 2014;55(2):218-24.

Caruana G, Pessini LM, Cannella R, Salvaggio G, de Barros A, Salerno A, et al. Texture analysis in susceptibility-weighted imaging may be useful to differentiate acute from chronic multiple sclerosis lesions. European Radiology. 2020;30(11):6348-56.

Saade C, Bou-Fakhredin R, Yousem DM, Asmar K, Naffaa L, El-Merhi F. Gadolinium and multiple sclerosis: vessels, barriers of the brain, and glymphatics. American Journal of Neuroradiology. 2018;39(12):2168-76.

Filippi M, Rovaris M, Rocca M, Sormani M, Wolinsky J, Comi G. Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes". Neurology. 2001;57(4):731-3.

Barkhof F, Scheltens P, Frequin S, Nauta J, Tas M, Valk J, et al. Relapsing-remitting multiple sclerosis: sequential enhanced MR imaging vs. clinical findings in determining disease activity. AJR American journal of roentgenology. 1992;159(5):1041-7.

Campbell Z, Sahm D, Donohue K, Jamison J, Davis M, Pellicano C, et al. Characterizing contrast-enhancing and re-enhancing lesions in multiple sclerosis. Neurology. 2012;78(19):1493-9.

Meyer-Moock S, Feng Y-S, Maeurer M, Dippel F-W, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC neurology. 2014;14(1):1-10.

Arevalo O, Riascos R, Rabiei P, Kamali A, Nelson F. Standardizing magnetic resonance imaging protocols, requisitions, and reports in multiple sclerosis: an update for radiologist based on 2017 Magnetic Resonance Imaging in Multiple Sclerosis and 2018 Consortium of Multiple Sclerosis Centers Consensus Guidelines. Journal of computer assisted tomography. 2019;43(1):1-12.

Davis M, Auh S, Riva M, Richert N, Frank J, McFarland H, et al. Ring and nodular multiple sclerosis lesions: a retrospective natural history study. Neurology. 2010;74(10):851-6.

Absinta M, Vuolo L, Rao A, Nair G, Sati P, Cortese IC, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. Neurology. 2015;85(1):18-28.

Harrison DM, Wang KY, Fiol J, Naunton K, Royal III W, Hua J, et al. Leptomeningeal enhancement at 7T in multiple sclerosis: frequency, morphology, and relationship to cortical volume. Journal of Neuroimaging. 2017;27(5):461-8.

Jonas SN, Izbudak I, Frazier AA, Harrison DM. Longitudinal persistence of meningeal enhancement on postcontrast 7T 3D-FLAIR MRI in multiple sclerosis. American Journal of Neuroradiology. 2018;39(10):1799-805.

Cook SD, Dhib-Jalbut S, Dowling P, Durelli L, Ford C, Giovannoni G, et al. Use of magnetic resonance imaging as well as clinical disease activity in the clinical classification of multiple sclerosis and assessment of its course: a report from an international CMSC Consensus Conference, March 5–7, 2010. International Journal of MS care. 2012;14(3):105-14.

Willoughby E, Grochowski E, Li D, Oger J, Kastrukoff L, Paty D. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. Annals of neurology. 1989;25(1):43-9.

Cadavid D, Wolansky L, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFNß-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009;72(23):1976-83.

Qian P, Cadavid D, Wolansky LJ, Cook SD, Naismith RT. Heterogeneity in Longitudinal Evolution of Ring-Enhancing MS Lesions: In response to: Gaitán MI, Shea CD, Dphil IEE, et al. Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions. Annals of Neurology 2011: n/an/a. Annals of neurology. 2011;70(4):668.

Algin O, Hakyemez B, Taşkapilioğlu O, Parlak M, Turan F. Imaging of active multiple sclerosis plaques: efficiency of contrast-enhanced magnetization transfer subtraction technique. Diagn Interv Radiol. 2010;16(2):106-11.

Traboulsee A, Li D, Tam R, Zhao G, Riddehough A, Fang J, et al. Subcutaneous interferon ß-1a three times weekly and the natural evolution of gadolinium-enhancing lesions into chronic black holes in relapsing and progressive multiple sclerosis: Analysis of PRISMS and SPECTRIMS trials. Multiple Sclerosis Journal–Experimental, Translational and Clinical. 2017;3(4):2055217317745340.

Absinta M, Sati P, Gaitán MI, Maggi P, Cortese IC, Filippi M, et al. Seven-tesla phase imaging of acute multiple sclerosis lesions: a new window into the inflammatory process. Annals of neurology. 2013;74(5):669-78.

Absinta M, Sati P, Reich DS. Advanced MRI and staging of multiple sclerosis lesions. Nature Reviews Neurology. 2016;12(6):358-68.