Characterizing contrast-enhancing and re-enhancing lesions in multiple sclerosis

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ABSTRACT

Objectives: In multiple sclerosis (MS), contrast-enhancing lesions (CELs) in T1-weighted postcontrast MRI are considered markers of blood-brain barrier breakdown. It remains unknown if re-enhancement can be considered a radiologic indicator of different pathology in CELs. We investigated 1) the incidence of re-enhancing lesions (re-CELs) from chronic lesions; 2) differences in size, magnetization transfer ratio (MTR), and likelihood to appear as acute black holes (aBHs) between new lesions (n-CELs) and re-CELs; and 3) associations between re-CELs and features indicating more advanced disease.

Methods: In this retrospective natural history study, we examined 264 monthly MRI scans performed at month 1 (M1), month 2 (M2), and month 3 (M3) for 88 patients with MS. CELs were defined as n-CELs if not present in the M1 T2W MRI and re-CELs if present in the M1 T2W MRI.

Results: A total of 311 (82.7%) n-CELs and 65 (17.3%) re-CELs were identified. Of the 88 patients, 54 presented only n-CELs, 8 presented only re-CELs, and 26 presented both CEL types. Patients with both lesion types presented more CELs than those presenting only one type ($p = 0.01$). Re-CELs were larger ($z = 2.72, p = 0.007$) and had lower MTR ($z = -2.80, p = 0.005$) than n-CELs but the estimated proportion of aBHs from n-CELs was similar ($z = -0.09, p = 0.1$) from the proportion of aBHs from re-CELs.

Conclusions: Nearly 20% of CELs represent the reoccurrence of enhancement in chronic plaques. Re-CELs represent larger areas of inflammation, not necessarily associated with larger areas of edema. *Neurology*® 2012;78:1493-1499

GLOSSARY

aBH = acute black hole; **BBB** = blood-brain barrier; **CEL** = contrast-enhancing lesion; **EDSS** = Expanded Disability Status Scale; **FLAIR** = fluid-attenuated inversion recovery; **Gd** = gadolinium; **GEE** = generalized estimating equation; **MS** = multiple sclerosis; **MTR** = magnetization transfer ratio; **n-CEL** = new contrast-enhancing lesion; **NIB** = Neuroimmunology Branch; **NINDS** = National Institute of Neurological Disorders and Stroke; **re-CEL** = re-enhancing lesion; **SE** = spin echo.

The use of MRI has revolutionized the diagnosis and follow-up of patients with multiple sclerosis (MS). Several MRI techniques are presently available to visualize, quantify, and characterize to some extent the MS disease status and stage in vivo.¹ Conventional MRI, which includes 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.² While T1W precontrast and T2W SE images provide accurate tools for measuring chronic disease, T1W SE imaging obtained upon the administration of Gd-DTPA allows visualization of acute lesions referred to as contrast-enhancing lesions (CELs). Due to its physical and chemical properties, Gd-DTPA cannot cross an intact blood-brain barrier (BBB). Therefore, CELs are considered markers of inflammation linked to the leakage of the BBB.³⁻⁵

Heterogeneity in radiologic characteristics of CELs has been identified and seen to be associated with the varying evolution of CELs over time. Re-enhancement is a distinguishing feature of CELs. Short-term longitudinal studies have shown that in MS, from <10%^{3,6-8} to

Supplemental data at
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Supplemental Data

From the Neuroimmunology Branch (NIB) (Z.C., D.S., K.D., J.J., M.D., C.P., J.O., N.R.) and Office of the Clinical Director (S.A.), National Institute of Neurological Disorders and Stroke (F.B.), NIH; and Frank Laboratory (J.A.F.), Radiology and Imaging Sciences Clinical Center, Bethesda, MD.

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35%⁹ of CELs may be visible at multiple times during the course of short-term time periods of observation. In previous studies it has also been described that active CELs may arise in the site of chronic lesions^{3,10,11} visible as hyperintensities in T2W SE images. Nevertheless, the frequency of occurrence of re-enhancing CELs (re-CELs), the radiologic characteristics of new CELs (n-CELs) and re-CELs in patients, and their clinical implications have never been systematically investigated. Conversely, since early pathologic studies¹² indicated that the continuous breach of the BBB in the same area might lead to more severe demyelination, identifying how this is reflected in vivo is important. Ultimately, re-CELs could serve as markers of more severe inflammation sustaining demyelination. Re-CELs may be used to help better understand individual disease evolution, and may be used as indicators of differential drug effects in clinical trial design.

Motivated by this notion, we performed our investigation in a cohort of 88 patients followed with monthly MRIs during a short natural history time course. Using an automated overlay procedure over 3 monthly MRIs, we systematically analyzed the proportion of CELs arising from preexisting chronic lesions visible as hyperintensities in T2W SE images. Differences in size, magnetization transfer ratio (MTR), and appearance as an acute black hole (aBH) between n-CELs and re-CELs were assessed. The goals of the present study are 1) to assess whether in vivo findings confirm that the re-enhancement event may be considered an indirect hallmark of differing and more severe inflammatory pathology; and 2) to investigate the clinical characteristics of patients presenting with re-CELs.

METHODS Patients and study design. The work is based on the retrospective evaluation of clinical scores (i.e., the Expanded Disability Status Scale [EDSS] score¹³) and MRIs obtained from 88 patients with MS over 3 months (month 1 [M1], month 2 [M2], and month 3 [M3]) of the natural history phase. None of the patients were undergoing any effective disease-modifying therapy during the course of the study or at any time prior to the study. All patients were ensured to have had 1) a diagnosis of MS according to Poser criteria¹⁴; 2) 3 monthly MRIs inclusive of precontrast and postcontrast T1W SE images, dual echo proton density (PD)-weighted and T2W SE, and T2 fluid-attenuated inversion recovery (FLAIR) images; (3) ≥ 1 CEL in either M2 or M3 postcontrast MRI that was not enhancing in

the M1 scan; and 4) neither relapses nor steroid administrations during the study, beginning from the month prior to the M1 scan and lasting throughout the course of the study period (M1, M2, M3).

Setting. The present study was performed in the Neuroimmunology Branch (NIB) at the NIH in Bethesda, MD. Our database was searched from 1996 (when the T2-FLAIR sequence was introduced in the NIB protocol) to 2008 (time of the study start).

Standard protocol approvals, registrations, and patient consents. Prior approval from the Institutional Review Board of the National Institute of Neurological Diseases and Stroke (NINDS) was obtained. Each study participant signed an informed written consent.

Image acquisition. At each timepoint, a 1.5-Tesla MRI with a standard quadrature head coil (General Electric Medical Systems, Milwaukee, WI) was used for imaging as described previously¹⁵ and in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

Image analyses. Image analyses were performed on hard copies and electronic copies were saved in DICOM format on Linux workstations (Redhot 8 System). Each investigator (D.S., D.K., J.J., Z.C., C.P., M.D., F.B., and N.R.) involved in image analysis was blind with respect to the clinical measures of the patients at the time the analyses were performed.

Details on the image postprocessing are reported in appendix e-1.

CEL definition. CELs identified on M2 scan (either continuing to enhance at M3 or actively enhancing only at M2) and seen not to enhance at M1 as well as CELs identified at M3 scans and not enhancing at M1 and M2 were considered as new CELs and included in the analysis. These newly identified CELs either on M2 or M3 scan were classified into re-CELs and n-CELs based on their relationship to preexisting visible lesions on the proton density-weighted and FLAIR images of the M1 scan. n-CELs were characterized as new lesions arising from areas of normal-appearing white matter or sharing a border but not overlapping a lesion area on the proton density-weighted and T2-FLAIR image. Re-CELs were characterized as emerging entirely or partially from a lesion on proton density-weighted and T2-FLAIR image. Figures 1 and 2 illustrate an example of n-CELs and re-CELs.

Statistical analysis. Group differences in continuous variables (but EDSS scores) were computed using an analysis of variance. Chi-square tests were used to investigate group differences in categorical variables. Group differences in EDSS score were investigated using the nonparametric Mann-Whitney test. All above-mentioned analyses were conducted with the use of SPSS (version 17.0).

In patients presenting both n-CELs and re-CELs ($n = 26$), generalized estimating equation (GEE) methods were used to examine the effect of different CEL type on CEL-LV, MTR, and likelihood of being aBH. CEL-LV was transformed using a natural log function because its distribution was skewed right. We assumed that distributions of log-transformed lesion size and MTR follow a normal distribution, and occurrence of aBHs follows a binomial distribution. For all GEE methods, working correlation matrix for measurements per subject was assumed as exchangeable correlation structure in order to take into account the correlations of multiple measurements on the same individual. Estimates of parameters were produced with empirical standard error estimates, and z statistics were computed to assess statistical significance. The distributions of the original lesion

Figure 1 New contrast-enhancing lesions (n-CELs)

T1-weighted spin echo postcontrast image shows a n-CEL (A) distant from previous lesions seen in the proton density-weighted (B) and fluid-attenuated inversion recovery images (C) of the previous month. White arrows indicate lesions.

size and MTR for each of the 2 lesion types are described using medians and 25th and 75th quantiles. All statistical tests were 2-sided and conducted with an α of 0.05. GEE was implemented in the GENMOD procedure of SAS version 9.1.3 (SAS Institutes Inc., Cary, NC).

RESULTS Study cohort. A total of 92 patients were identified meeting the study criteria from the NIB-
NIH database. Of those 92 patients, MRIs of 3 patients were eliminated because of image artifacts (2 cases) and technical problems with the image registration process (1 case). A fourth patient presented with 105 CELs over M2 scan and M3 scan and was eliminated to avoid biases linked to outlier values in CEL number. The cohort ultimately included 88 patients with 264 analyzed MRIs.

Demographic and clinical characteristics of the patients at the time of the M1 MRI are provided in the table.

n-CEL and re-CEL occurrence in patients and differences between patients with different CEL types. Of the 88 examined patients, 54 (61.4%) presented with

only n-CELs, 8 (9.1%) showed only re-CELs, and 26 (29.5%) presented with both CEL types at M2 or M3. Figures 1 and 2 illustrate an example of each of those CEL types. Patients with both types of lesions ($n = 26$) had on average a higher number of total CELs than patients with either n-CELs ($n = 54$, $p < 0.0001$) or re-CELs ($n = 8$, $p = 0.01$). There were otherwise no group differences in terms of demographic (age and sex), clinical (years of MS, EDSS score, MS type), or imaging (cBHs, T2-LV, brain parenchyma fraction) characteristics (table).

Of the sample of the 88 patients with MS, there was a total of 376 CELs identified for the first time at either M2 or M3. Of the 376 identified CELs, 311 (82.7%) were n-CELs and 65 (17.3%) were re-CELs. Of the 311 n-CELs, 22 (5.8% of the 376 total) were touching but not overlapping previous chronic lesions, and 289 (76.9% of the 376 total) were distant from previously identified T2 lesions. Of the 65 re-CELs, 43 (11.5% of the 376 total) were partially re-CELs and 22 (5.8% of the 376 total) completely re-CELs.

Differences in mean size, MTR, and aBH occurrence between n-CELs and re-CELs. Differences in radiologic characteristics between n-CELs and re-CELs were investigated only in the subgroup of patients ($n = 26$) presenting with both lesion types during the study. The analysis was restricted to this subgroup of patients to avoid biases due to interpatient variability and to obtain only paired within-patient comparisons. At the same time, on the notion that within-person association in lesion biology may exist, the GEE models were employed for their flexibility of analysis of variance while accounting for within-person correlation.

In this group of patients, a total of 202 CELs were identified. Of those, 159 (78.7%) were n-CELs and 43 (21.3%) were re-CELs.

Log-transformed lesion size was larger ($z = 2.72$, p value = 0.007) in re-CELs compared to n-CELs (figure 3A). The median lesion size (mm cubic) of re-CELs was 76.46 (25th quantile = 36.91; 75th quantile = 295.31) compared to 60.64 (25th quantile = 26.37; 75th quantile = 116.02) of n-CELs.

Mean lesion MTR was lower ($z = -2.80$, p value = 0.005) in re-CELs (mean = 0.32, SD = 0.0488) compared to nCELs (mean = 0.35, SD = 0.051) (figure 3B).

The estimated proportion of aBHs arising from re-CELs (estimated proportion = 0.31) was not different ($z = -0.09$, p value = 0.93) from the proportion of aBHs arising from n-CELs (estimated proportion = 0.32).

DISCUSSION The main novel findings of the present work with respect to the previous literature are as follows: 1) over a 2-month period nearly 20% of

Figure 2 Re-enhancing lesions (re-CELs)

T1-weighted spin echo postcontrast image shows a re-CEL (A) entirely overlapping previous lesions seen in the proton density-weighted image (B) and fluid-attenuated inversion recovery image (C) of the previous month.

Table Demographic, clinical, and MRI characteristics of all patients and those with and without re-CELs^a

Variable	All patients (n = 88)	Patients with only re-CELs (n = 8)	Patients with only n-CELs (n = 54)	Patients with both CEL types (n = 26)
Age, y	39.5 ± 9.9	43.5 ± 12.4	39.2 ± 9.3	38.9 ± 10.4
F/M	55/33	4/4	35/19	16/10
MS type, RR/SP/PP	77/8/3	7/1/0	48/3/3	22/4/0
Years since MS onset	5.8 ± 7.8	8.7 ± 9.0	6.5 ± 8.8	3.4 ± 4.2
EDSS	1.75 (0–7.0)	1.5 (1.0–3.0)	1.75 (0–7.0)	1.5 (0–6.0)
CEL-LL	4.3 ± 5.1	3.0 ± 5.3	2.7 ± 2.3	8.0 ± 7.2
T2 LN	58.9 ± 22.8	58.3 ± 26.3	57.5 ± 22.2	62.9 ± 23.8
T2 LV, cm ³	18.1 ± 16.2	22.5 ± 21.1	17.0 ± 15.6 (2.4–60.8)	19.0 ± 17.0
cBH-LN	8.3 ± 9.6	11.0 ± 12.8	7.2 ± 9.6	10.0 ± 8.2
BPF	0.85 ± 0.03	0.85 ± 0.05	0.85 ± 0.03	0.86 ± 0.03

Abbreviations: BPF = brain parenchyma fraction; CEL = contrast-enhancing lesion; EDSS = Expanded Disability Status Scale, expressed in median (minimum–maximum value); MS = multiple sclerosis; n-CEL = new contrast-enhancing lesion; PP = primary progressive; re-CEL = re-enhancing lesion; RR = relapsing remitting; SP = secondary progressive.

^a Data reported as mean ± SD unless otherwise indicated. Group differences were seen only in the mean number of CELs. See text for details.

CELs originate from a preexisting area of chronic WM pathology seen as T2 lesion in about 40% of the patients; 2) patients with higher level of inflammatory activity tend to have both n-CELs and re-CELs; and 3) re-CELs tend to have larger sizes and lower MTRs compared to n-CELs, but yet are not more likely to be associated with aBHs than n-CELs. In the examined dataset, 18% of CELs originated from a preexisting lesion area. The results are consistent with previous imaging findings^{3,10,11} sustaining the temporal reoccurrence of active lesions in sites of stable and previous lesions. Our findings are also in agreement with previous pathologic evidence, which showed that acute lesions may occur in previously affected areas, where in some instances acute lesions are likely centered on the same vessel.¹⁶

Why re-CELs occur in MS is an intriguing question and several arguments may be addressed. First, we can postulate that the immunologic milieu residual in some of the chronic MS lesions is still embedded of antigenic triggers potentially leading to the reoccurrence of inflammatory events. Second, it is conceivable that re-CELs represent only the overt phase of enhancement of areas of chronic lesions where subtle inflammation and leakage of the BBB is chronically present¹⁷ but not captured by standard-dose Gd-enhanced T1W MRI. Early pathologic studies have indeed shown that the BBB may extend in chronically inactive plaques beyond classically considered inflammatory lesions.¹⁸ The BBB was also found to be permanently damaged in several old plaques and demonstrated to be not always sufficient to induce active demyelination.¹² Subsequent imaging studies using quantitative MRI measurements, such as signal intensity changes^{19,20} and T1 map-

ping,²¹ have confirmed that subtle BBB leakage is a consistent feature in lesions that do not enhance even upon the injection of triple dose of Gd-DTPA.²²

When looking at differences in clinical and imaging disease parameters between patients with and without re-CELs, we observed patients with very active MS associated with high inflammatory activity having both lesion types. It is highly likely that the differences observed reflect only a mathematical phenomenon. Or in other words, the higher number of CELs also increases the likelihood of encountering both CEL types at the same time. Conversely, the likelihood to present with re-CELs, either alone or in combination with n-CELs, was not associated with a larger chronic lesion burden in T1W images as one could a priori hypothesize. The findings indirectly suggest that some qualitative factors of the already formed WM pathology, more than its quantitative factors, predispose patients to present with re-CELs. At the same time, however, the findings need to put in perspective that, although not in a statistically significant manner, patients with re-CELs presented with larger volume of cBHs and T2 lesions and lower brain parenchyma fraction compared to those without re-CELs. The results support the hypothesis that re-CELs could be a feature of more advanced MS.

The analysis of differences in radiologic characteristics between n-CELs and re-CELs provided interesting results. When compared to n-CELs, re-CELs appeared to have larger sizes and lower MTRs. However, re-CELs were not more likely to be present as aBHs. These 2 findings are not necessarily contradictory. aBHs are a common finding associated with up to 80% of CELs.^{7,22,23} aBHs are characteristically considered to represent a phase of transient edema in

Figure 3 New contrast-enhancing lesion (n-CEL) and re-enhancing lesion (re-CEL) size

The figure depicts the box plots of the CELs size (A) and magnetization transfer ratio (MTR) (B) component of n-CELs ($n = 159$) and re-CELs ($n = 43$), in the 26 patients presenting with both lesion types. Log-transformed data were used to create graphs for CEL size and raw data for MTR. The central line within the box indicates the median value. The box plots report the median value and marks the 25th and 75th percentiles. The lower and upper lines correspond to the values between the 10th and 90th percentiles. Differences between lesion types were all significant. See text for details.

the majority of the cases and are not necessarily associated with a worse outcome over time, as instead known to be for some of the cBHs. Conversely, larger CELs are considered to indirectly express more severe pathology as they are more likely to evolve into cBHs.^{22,24} As observed in the present study, the analysis of CELs with nonconventional MRI techniques such as MT imaging²⁵ has also shown that larger CELs, which tend to occur more frequently in patients with secondary progressive MS, have lower MTRs than smaller CELs.²⁶

Therefore, we hypothesize that in comparison to n-CELs, the inflammation sustained in re-CELs is

more aggressive and is characterized by higher degree of demyelination, which may not necessarily translate into larger edema accumulation. As previously hypothesized,¹² the continuous exposure of demyelinated axons and glia to cytokines, antibodies, and other factors chronically present in circulation resulting from breach of the BBB might lead to more severe demyelination during reactivation of enhancing lesions and prevent oligodendrocyte regeneration.

Some intrinsic study design limitations need to be addressed before drawing conclusions. As mentioned earlier, the sample size and the limited time window affected the results by narrowing the spectrum of possible analyses. Both factors hinder addressing the question of whether re-CELs indeed occur in every patient over time or if some patients never encounter the re-enhancement phenomenon.

In addition, it should be noted that our results pertain to CELs at their first appearance. It is likely that some CELs change radiologic features over the course of their visibility, and uncertainty remains as to whether an estimate of the used parameters was obtained across the different months of visibility, therefore allowing different conclusions. Third, although an attempt was made to classify re-CELs as partially and totally re-enhancing and to group n-CELs based on distance from old plaques, the number of CELs in each category did not allow sufficient statistical power for subsequent analyses. Had such a categorization been possible, informative details regarding lesion diversity would have most certainly emerged.

To ensure that no effect of steroids could interfere with the output of the analysis, the occurrence of a clinical relapse within a month prior to the study start was an exclusion criterion. As a result, lesions subtending clinical attack warranting therapy were excluded from the analysis. Because of this exclusion criterion, information regarding difference between n-CELs and re-CELs in the proportions that were symptomatic is also lacking. Also due to the same reason, we cannot unambiguously rule out the possibility that had this group of CELs been included in the analysis, differences in reported results would emerge.

Two important additional observations need to be highlighted in this study. The first observation involves the method by which n-CELs were classified. In our work we used an imaging-based method of classification where CELs touching without invading previous chronic lesions were classified and defined as n-CELs. But from a biological standpoint, it is likely these n-CELs are rather more similar to re-CELs and that a separate grouping would have permitted different results. The second observation

relates to the lower MTR data reported for re-CELS. We believe that the occurrence of lower MTRs in re-CELS is likely attributed to a combination of previous demyelination and possible neurodegeneration within preexisting lesions, and active inflammation within the reoccurring lesions. While the concomitant and indiscernible presence of these 2 factors may be perceived as a drawback to the study, the data may actually more accurately reflect the true biology of disease, highlighting the reality that lesion classification may in some instances be arbitrary and still driven by methods of detection rather than biology.

Notwithstanding the above considerations, our evidence provides a solid confirmation that areas of chronic MS-induced disease may still go through periods of visible BBB breakdown and inflammation, and when this occurs, larger areas of inflammation are present. Before drawing certain conclusions and generalizing the results we advocate for future studies. Analyses in a larger sample of patients, followed for longer periods of time and with the additional use of nonconventional quantitative techniques, should provide clarifying insights into the role of re-CELS as distinguishing markers of neuroinflammation in MS and as an indicator of subtle chronic BBB leakage. In addition, the use of MRI at higher resolution will aid in identifying larger chronic-lesion areas,²⁷ perhaps proposing a more accurate classification of re-CELS vs n-CELS hence defining this interesting topic more precisely.

AUTHOR CONTRIBUTIONS

Each author contributed to acquisition and interpretation of the different parts of the data as well as drafting the manuscript.

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DISCLOSURE

Dr. Bagnato works as a consultant for reading and interpretation of scans in a 6-month MRI initiative project with Biogen Idec. Dr. Richert is employed by Biogen Idec as a Neurology fellow since April 2010. Dr. Campbell, Mr. Sahm, Ms. Donohue, Mr. Jamison, Mr. Davis, Dr. Pelligano, Dr. Auh, Ms. Ohayon, and Dr. Frank report no disclosures. **Go to Neurology.org for full disclosures.**

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AAN Publishes New Guidelines on Migraine Prevention

Research shows that many treatments can help prevent migraine in certain people, yet few people with migraine who are candidates for these preventive treatments actually use them, according to two new guidelines issued by the American Academy of Neurology. The guidelines were published in the April 24, 2012, issue of *Neurology*®.

To read the guidelines and access PDF summaries for clinicians and patients, a slide presentation, and a clinical example, visit www.aan.com/go/practice/guidelines. For more information, contact Julie Cox at jcox@aan.com or (612) 928-6069.

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