Increased contrast enhancing lesion activity in relapsing–remitting multiple sclerosis migraine patients

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Background and objectives: While the literature supports the idea that multiple sclerosis (MS) and migraine are related, the exact mechanism(s) of this association is not well understood. Observations of increased contrast enhancing (CE) lesion activity in individual MS patients suffering from migraine prompted us to determine a relationship between migraine and MRI outcomes in a large cohort of MS patients.

Methods: We included 509 MS and 64 clinically isolated syndrome (CIS) patients and 251 age- and sex-matched healthy individuals (HIs) who obtained 3 T MRI and were assessed for history of migraine. Number and volume of T2, T1 and CE lesions and brain volume measures were determined. The MRI findings were analyzed adjusting for key covariates and correcting for multiple comparisons.

Results: More MS (22.2%) and CIS (17.2%) patients had migraine, compared to HIs (14.6%, p = 0.067). More MS patients with migraine presented with CE lesions compared to those without (35.4% vs. 23.7%, p = 0.013). MS migraine patients had significantly increased number (p = 0.019) and volume (p = 0.022) of CE lesions compared to those without. In the regression analysis, MS migraine patients had an increased number of CE lesions (B = 1.242, p = 0.001), specifically those with relapsing–remitting disease course (B = 1.377, p = 0.001). No significant association of other MRI measures and migraine was found in MS and CIS patients or in HIs.

Conclusions: Our findings suggest an increased inflammatory pathology in MS patients with migraine headaches requiring possibly more frequent MRIs and also more efficient anti-inflammatory treatment.

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that the migraine frequency is increased in patients with relapsing-remitting (RR) MS, whereas the tension-type headache is more frequent in patients with chronic progressive MS (D’Amico et al., 2004; Ergun et al., 2009; Moisett et al., 2013; Villani et al., 2008). A recent case report illustrated a young woman whose initial presentation was that of status migrainosus, after which she developed MS within 2 years (Alroughani et al., 2015). The term radiologically isolated syndrome (RIS) has been recently proposed to describe patients with atypical symptoms of MS who present with MRI features suggestive of underlying demyelinating pathology (Okuda et al., 2009). One of the most common complaints in RIS subjects which led to performance of the MRI examination was migraine type headache (Lebrun et al., 2008; Okuda et al., 2009). This suggests that migraine can be prominent symptom at early onset of the disease, in addition to have increased comorbidity frequency in RRMS patients.

It has been recently reported in a case study that a patient who had a history of migraine, experienced worsening of migraine headache symptoms as the initial manifestation of MS, and showed concomitant asymptomatic contrast enhancing (CE) lesions on T1-weighted MRI after gadolinium (Gd) contrast injection (Lin et al., 2013). This case report raises question, as to the role of CE lesions in the presentation of migraine in MS patients. Our own clinical routine observations prompted us to investigate whether the number and volume of CE lesions are associated to increased frequency of migraine in MS patients. In addition, we aimed to determine if there is relationship between migraine and the presence of other lesion and global and tissue specific brain volume measures in patients with MS.

2. Methods

2.1. Subjects

This study used data from an ongoing prospective study of cardiovascular, genetic and environmental risk factors in MS that enrolled over 1000 patients with clinically isolated syndrome (CIS), MS, other neurological diseases and HIs (Kappus et al., 2015; O’Connor et al., 2012; Zivadinov et al., 2011). The inclusion criteria for this sub-study of migraine in MS were as follows: a) age 18–75 years old, b) having CIS or MS, or being HI and c) MRI examination performed at the time of the clinical visit (±30 days) with standardized 3 T MRI protocol. The exclusion criteria were as follows: a) the presence of a relapse or steroid treatment within 30 days preceding study entry for MS and disease group or MS disease subtype, as the grouping measure and migraine status, age, gender and DMT status as the independent variables. Regression analysis was applied to both the ANCOVA, MRI outcomes were input as the dependent variables, using chi-square test, Mann-Whitney rank sum test and analysis of variance (ANOVA), as appropriate. In the analysis of covariance (ANCOVA), MRI outcomes were input as the dependent variables, and disease group or MS disease subtype, as the grouping measure with age, gender and DMT status selected as covariates. Given the correlation between age and disease duration, the latter was not used as covariate.

Additionally, the data were also analyzed using a negative binomial regression given the non-normally distributed lesion data. The inputs into the model included the number of CELs as the dependent measure and migraine status, age, gender and DMT status as the independent variables. Regression analysis was applied to both the disease groups and MS subtypes. The Benjamini–Hochberg correction was used to control the false discovery rate and p-values < 0.05 were considered significant using two-tailed testing (Benjamini et al., 2001).

3. Results

3.1. Demographic and clinical characteristics

A total of 826 subjects who fulfilled inclusion and exclusion criteria were selected for this substudy of migraine and MRI. These included 320 patients with RRMS, 124 patients with secondary-progressive (SP) MS, 36 patients with primary-progressive (PP) MS, 64 patients with CIS and 251 HIs. As expected MS patients had higher age, longer disease duration and more advanced disability compared to CIS patients.
were considered significantly more females with migraine (p = 0.01). The age of the MS patients with migraine was younger (p = 0.015), while the PPMS patients with migraine were younger (p = 0.032) and had lower disease duration (p = 0.039). The CIS patients with migraine were younger compared to those without migraine (p = 0.001).

### Table 2

**Characteristics of subjects with and without migraine in patients with relapsing-remitting, secondary-progressive and primary-progressive multiple sclerosis.**

|                | RRMS (n = 320) | SPMS (n = 124) | PPMS (n = 36) |
|----------------|----------------|----------------|---------------|
|                | Migraine (n = 241) | Migraine (n = 79) | Migraine (n = 20) | Migraine (n = 30) | Migraine (n = 6) | p-Value |
| Female, n (%)  | 159 (78.8) | 68 (86.1) | 0.001 | 77 (74) | 18 (90) | 0.122 | 17 (56.7) | 3 (50) | 0.764 |
| Age in years, mean (SD) | 44.6 (10.3) | 42.2 (11.4) | 0.081 | 54.7 (7.5) | 49.9 (10.6) | 0.015 | 56.0 (6.9) | 49.3 (4.7) | 0.032 |
| Age at onset in years, mean (SD) | 32.3 (9.2) | 30.4 (9.4) | 0.062 | 32.4 (11.1) | 29.2 (9.9) | 0.22 | 37.9 (10.8) | 42.4 (6) | 0.374 |
| Disease duration in years, mean (SD) | 12.4 (8.9) | 11.4 (8.7) | 0.401 | 22.4 (10.9) | 20.7 (9.8) | 0.527 | 18.1 (11.5) | 6.8 (4.5) | 0.039 |
| Presence of DMT, n (%) | 27.5 (5.6) | 27.0 (6) | 0.555 | 25.8 (5) | 24.7 (5.7) | 0.376 | 26.1 (4.2) | 26.0 (5.6) | 0.954 |
| EDSS, mean (IQR) | 204 (84.6) | 60 (75.9) | 0.579 | 72 (69.2) | 15 (75) | 0.831 | 13 (43.3) | 3 (50) | 0.85 |

**MS**—multiple sclerosis; **RRMS**—relapsing-remitting; **SPMS**—secondary-progressive; **PPMS**—primary-progressive; **SD**—standard deviation; **EDSS**—Expanded Disability Status Scale; **DMT**—disease modifying therapy; **NA**—not available; **BMI**—body mass index; **IQR**—interquartile range.

The comparison between the migraine and non-migraine groups was performed using chi-square test, Mann–Whitney rank sum test and one-way analysis of variance. p-Values < 0.05 were considered significant (highlighted in bold).
3.2. Frequency of migraine

Hundred and thirteen (22.2%) MS patients, 11 (17.2%) of CIS patients and 37 (14.7%) of Hs had migraine (p = 0.067). In the MS disease subtype analyses, patients with RRMS had the highest rate of migraine (24.7%), followed by PPMS (16.7%) and SPMS (16.1%) (p = 0.108).

3.3. MRI differences in subjects with and without migraine

Table 3 and Fig. 1 show within disease group differences in subjects with and without migraine. More MS patients with migraine presented with CE lesions compared to those without (35.4% vs. 23.7%, p = 0.013). The mean number of CE lesions in MS patients with migraine was increased respect to those without (0.91 vs. 0.21, p = 0.019). The mean CE-LV was also increased in subjects with migraine respect to those without (0.91 vs. 0.21, p = 0.019). No other MRI lesion and brain volume MRI outcome differences were found in subjects with and without migraine within specific disease groups.

Table 4 shows within MS disease subtype study MRI outcome differences in subjects with and without migraine. More RRMS patients with migraine presented with CE lesions compared to those without (41.8% vs. 28.2%, p = 0.035). RRMS patients with migraine had increased mean number of CE lesions (1.19 vs. 0.27, p = 0.023) and CE-LV (164.4 vs. 41.1 mm³, p = 0.02) compared to those without. No other MRI lesion and brain volume outcome difference were found in subjects with and without migraine within MS disease subtypes.

3.4. Regression analysis

Given the non-normally distributed lesion data, we used negative binomial regression to validate the ANCOVA results. MS patients with migraine had increased number of CE lesions (B = 1.242, p = 0.001), but not CE-LV (B = 1.320, p = 0.133) compared to those without migraine. RRMS patients with migraine had increased number of CE lesions (B = 1.377, p = 0.001), but not CE-LV (B = 1.490, p = 0.098) compared to those without migraine.

4. Discussion

This is the largest case–control study to date that investigated the association between migraine and MRI outcomes in MS patients. We found that there is an increased frequency of CE lesions in MS patients with migraine, specifically within the RRMS disease subtype. Given that our clinical/MRI assessments were performed on MS patients with a stable clinical status and in absence of acute headache attack prior to MRI examination, the current findings suggest that having migraine comorbidity may increase level of blood–brain–barrier (BBB) disruption in RRMS patients.

Presence of CE lesions is an indicator of inflammation and breakdown of the BBB, and MRI hallmark for diagnosis and monitoring of MS. Migraine is a disorder characterized by a strong vascular component in which vasoconstriction is followed by vasodilation, mediated by underlying inflammatory cytokines and/or neurotransmitters (Silberstein, 2004). On the other hand, cardiovascular risk factors, including smoking, hypertension, hyperlipidemia, overweight/obesity, diabetes and heart disease are associated with MS (Kappus et al., 2015; Karmon et al., 2012). The pathophysiology of migraine is complex and variety of mediating mechanisms have been proposed including changes in levels of magnesium, calcium and glutamate, as well 5-HT, which stimulates the release of substance P and calcitonin gene-related peptide (Silberstein, 2004). While our study did not assess any of these factors, our findings do suggest that alterations of the BBB may compromise the microenvironmental vascular regulation. Indeed, previous studies suggested that the pathogenesis of migraine includes an inflammatory component (Longoni and Ferrari, 2006). The inflammation of the meninges is an accepted component of the migraine process with release of vasogenic substances such as calcitonin gene-related peptide, substance P, neurokinin A, vasoactive intestinal peptide, and nitric oxide (Buzzi et al., 1991). In the last decade, it has been established that highly inflammatory cortical demyelination is also present and common in early MS, topographically associated with prominent meningeal inflammation and may even precede the appearance of classic WM plaques in some MS patients (Lucchinetti et al., 2011). Therefore, future work should explore the association between meningeal inflammation and BBB in MS patients with and without migraine.

In line with previous studies, we found that migraine is present at higher rates in patients with RRMS, compared to those with chronic progressive MS disease subtype (D’Amico et al., 2004; Ergun et al., 2009; Moisset et al., 2013; Villani et al., 2008). These findings are of interest in the context of our results that showed that only RRMS patients had increased number and volume of CE lesions. This may suggest that increased inflammatory component of the disease, usually present in earlier disease stages, may contribute to the development of migraine.

### Table 3

Within group MRI comparisons between subjects with and without migraine.

|                    | Hs (n = 251) | Migraine (n = 509) | p-Value | CIS (n = 64) |
|--------------------|-------------|--------------------|---------|-------------|
| Presence of CE lesions | NA          | NA                 |         | NA          |
| Number of CE lesions | NA          | NA                 |         | NA          |
| CE-LV               | 164.4       | 41.1               | 0.023   | 65.8        |
| Number of T2 lesions | 2.7         | 0.2               | 0.022   | 22.2        |
| Number of T1 lesions | 11.2       | 11.5               | 0.41    | 4.14        |
| T1-LV               | 3021.6      | 5528.6             | 0.032   | 423.6       |
| NBV                 | 1533.8      | 1551.9             | 0.089   | 1483.9      |
| NGMV                | 780.2       | 789.9              | 0.191   | 747.4       |
| NWMV                | 753.6       | 762.1              | 0.015   | 737.5       |
| NCV                 | 636.1       | 644.3              | 0.231   | 607.1       |
| Number of T1 lesions | 11.2        | 11.5               | 0.41    | 4.14        |
| Presence of CE lesions | NA          | NA                 |         | NA          |
| Number of CE lesions | NA          | NA                 |         | NA          |
| CE-LV               | 31.2        | 125.3              | 0.019   | 65.8        |
| Number of T2 lesions | 0.91        | 0.2               | 0.013   | 22.2        |
| Number of T1 lesions | 0.91       | 0.2               | 0.013   | 22.2        |
| T1-LV               | 3021.6      | 5528.6             | 0.032   | 423.6       |
| NBV                 | 1533.8      | 1551.9             | 0.089   | 1483.9      |
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| NCV                 | 636.1       | 644.3              | 0.231   | 607.1       |

Hs—healthy individuals; MS—multiple sclerosis; CIS—clinically isolated syndrome; CE—contrast enhancing; LV— lesion volume; NA—not available; NBV—normalized brain volume; NGMV—normalized gray matter volume; NWMV—normalized white matter volume; NLV—normalized lateral ventricular volume; NCV—normalized neocortical volume.

All data are presented as mean and standard deviations. The presence of CE is reported as the number and percentage. Volumetric measures are presented in cubic millimeters (mm³) for LV and in cubic centimeters (cm³) for brain volumes.

The comparison between Hs, MS and CIS groups was performed using analysis of covariance with age, gender and disease-modifying treatment, as covariates. p-Values < 0.05 were considered significant (highlighted in bold) after correction for multiple comparisons.
However, the present study was not designed to collect information on the temporal relationship between onset of migraine and MS onset. The fact that no association of CE lesions and migraine was found in CIS patients and that frequency of migraine was higher in RRMS vs. CIS in the present study, indicates that migraine may be, at least in part, a comorbidity of MS disease process which is related to more severe BBB damage. A meta-analysis study demonstrated that the number of CE lesions over the first 6 months of follow-up increased the relative risk of relapse occurrence in the subsequent year (Kappos et al., 1999). It has been shown that patients in the relapsing phase have significantly more migraine attacks than those in the remitting phase (Ergun et al., 2009). Indeed, there were no differences in CE lesions in patients with SP and PPMS with and without migraine in the present study. However, it has to be underlined that PPMS patient did not present any CE lesions. While the present study was cross-sectional in design, it will be interesting to monitor the occurrence of CE lesions and migraine attacks in future longitudinal prospective studies using serial MRI.

Several previous MRI studies aimed to establish whether a specific locations of lesions in MS patients is associated with the presence of migraine. One study showed that MS patients with migraine had more lesions in red nucleus, substantia nigra and periaqueductal GM compared to MS patients without migraine (Tortorella et al., 2006). Another study confirmed that MS patients who have midbrain plaques, in close proximity to the periaqueductal GM have a four-fold increase in migraines compared to MS patients without plaques (Gee et al., 2005). These studies aimed to explain the onset of migraine symptoms by interruption of circuits involved in modulating pain pathways. As CE lesions rarely form in those brain areas, the present study poses an alternative hypothesis.

**Fig. 1.** Representative MRI images of a 32 years old female relapsing-remitting multiple sclerosis patient with disease duration of 11 and 9 years history of migraine. On the left are displayed T1-weighted spin echo post-contrast images (after 5 min delay), in the middle are shown T1-weighted spin echo pre-contrast images and on the right are displayed representative fluid attenuation inversion recovery images. There are 3 visible contrast enhancing lesions (white arrows) in different brain lobes and hemispheres.
as to the presence of migraine in MS, by demonstrating that the under-
lying widespread inflammatory process may be also an initial trigger in
some of the MS patients. It is also possible that these findings are not
mutually exclusive, and that both the lesion location and the inflamma-
tory process contribute to pain and migraine onset. In line with a previ-
ous study (Kamson et al., 2012), we did not find that MS patients or HIs
with and without migraine differed significantly in T2 or T1 lesion bur-
den, although the RRMS patients with migraine in the present study
showed somewhat greater T2- and T1-LVs despite shorter disease dura-
tion compared to those without migraine.

Past studies have suggested that migraine is associated with GM pa-
thology (Rocca et al., 2006), although these findings were based on a
small number of subjects and there were other studies showing con-
flicting results (Muthur et al., 2003). It has been demonstrated that mi-
gaine subjects do not present with cortical lesions (Absinta et al.,
2012). Brain volumetry findings from the current study suggest that
there is no significant difference in the GM and WM in HIs, MS and
CIS groups between migraine and non-migraine subjects. Furthermore
we did not find a significant difference in GM volumes by MS disease
subtype. In terms of overall impact on MS severity, previous studies
have found no significant correlation between level of disability and
the presence of headache (D’Amico et al., 2004), which was confirmed
in the current study.

It has been shown that treatment of MS with interferon-beta is asso-
ciated with higher rate of migraine, but this increase is mainly due to the
exacerbation of preexisting migraine and is less commonly associated
with the presence of CE. The presence of CE is reported as the number
and percentage. Volumetric calculations are presented in cubic millimeters
(mm³) for NCV.

In a recent study, 32% of the MS patients who presented both with
migraine and neuropathic pain, had more severe pain and lower
health-related quality of life than MS patients with either migraine or
neuropathic pain alone (Moisset et al., 2013). The pain intensity in
MS patients with migraine was higher (6.0 ± 0.1) than that of neu-
ropathic pain (4.9 ± 0.1). Moreover, in agreement with the present
study, the migraine MS patients were younger and had more likely
RRMS. This indicates that neuropathic pain and migraine pain may be
mediated by different mechanisms and that optimal treatment for man-
agement of the migraine pain needs more attention at individual patient
level.

There are several limitations to this study which warrant consider-
ation. Firstly, the timeline between the presentation of migraine and im-
aging was not well established, therefore it was not possible to assess
the correlation between MRI outcomes and frequency of migraine at-
acks or migraine onset. This study utilized data from an ongoing pro-
longative process contribute to pain and migraine onset. In line with a previ-
ous study (Kamson et al., 2012), we did not find that MS patients or HIs
with and without migraine differed significantly in T2 or T1 lesion bur-
den, although the RRMS patients with migraine in the present study
showed somewhat greater T2- and T1-LVs despite shorter disease dura-
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thology (Rocca et al., 2006), although these findings were based on a
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RRMS. This indicates that neuropathic pain and migraine pain may be
mediated by different mechanisms and that optimal treatment for man-
agement of the migraine pain needs more attention at individual patient
level.

Table 4

| RRMS          | SPMS (n = 124) | PPMS (n = 36) |
|---------------|---------------|---------------|
| Presence of CE lesions | 68 (28.2) 33 (41.8) 0.035 26 (25) 7 (35) 0.354 0 (0) 0 (0) NA | 41.1 (144.4) 6.1 (28.6) 0.02 6.1 (28.6) 0 (0) 0.324 1.6 (8.5) 0 (0) 0.806 |
| Number of CE lesions | 0.3 (0.84) 0.21 (4.9) 0.023 0.07 (3.3) 0 (0) 0.224 0 (0) 0 (0) 0.806 | 27.1 (19.3) 33.8 (19.7) 0.951 29.4 (24.1) 24.1 (14.1) 0.241 31.8 (24.4) 15.3 (11.7) 0.061 |
| Number of T2 lesions | 11,421.3 (14,030.7) 12,163.3 (14,300) 0.722 19,357.2 (17,541.4) 19,850.3 (20,378.2) 0.701 17,256.3 (19,859.5) 10,457.4 (12,508.5) 0.413 |
| Number of T1 lesions | 10.1 (10.8) 9.7 (11.9) 0.658 15.1 (12.3) 12.4 (14.1) 0.352 11.6 (12.7) 11.3 (10.4) 0.98 |
| T1-LV | 2424.2 (4769.6) 3020.2 (8106.5) 0.417 5050.6 (7378.7) 4338.9 (6419.1) 0.580 2236.3 (2554.0) 2015.9 (2725.2) 0.850 |
| NBV | 1492.8 (88.5) 1488.8 (96.5) 0.187 1414.7 (77.4) 1482.5 (70.7) 0.832 1430.9 (93.9) 1485.9 (60.8) 0.688 |
| NCMV | 742.5 (66.3) 748.9 (64.7) 0.747 697.5 (58.9) 710 (54.5) 0.59 715.7 (48.4) 732.3 (57.5) 0.521 |
| NWMV | 750.3 (60.9) 740 (67.2) 0.144 717.2 (71.6) 718.6 (61.2) 0.825 715.3 (71.3) 753.6 (76.2) 0.423 |
| NCV | 45.8 (20.1) 45.6 (22.8) 0.402 60.3 (22.7) 54.2 (23.6) 0.353 57 (26.8) 43 (8.8) 0.494 |

MS—multiple sclerosis; RRMS—relapsing-remitting; SPMS—secondary-progressive; PPMS—primary-progressive; SD—standard deviation; CE—contrast enhancing; LV—lesion volume; NA—not available; NBV—normalized brain volume; NCMV—normalized gray matter volume; NWMV—normalized white matter volume; NCV—normalized lateral ventricular volume.

All data are presented as mean and standard deviations. The presence of CE is reported as the number and percentage. Volumetric calculations are presented in cubic millimeters (mm³) for LV and in cubic centimeters (cm³) for brain volumes.

The comparison between RRMS, SPMS and PPMS groups was performed using analysis of covariance with age, gender and disease-modifying treatment, as covariates. p-Values < 0.05 were considered significant (highlighted in bold) after correction for multiple comparisons.
migraine symptoms by location of CE lesions and future studies should investigate this topic. In conclusion, MS patients with migraine had a greater CE lesion activity and this was specifically manifested in RRMS patients. Our findings suggest an increased inflammatory pathology in MS patients with migraine headaches requiring possibly more frequent MRIs and also more efficient anti-inflammatory treatment.

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