MRI phase changes in multiple sclerosis vs neuromyelitis optica lesions at 7T

ABSTRACT

Objective: To characterize paramagnetic MRI phase signal abnormalities in neuromyelitis optica spectrum disorder (NMOSD) vs multiple sclerosis (MS) lesions in a cross-sectional study.

Methods: Ten patients with NMOSD and 10 patients with relapsing-remitting MS underwent 7-tesla brain MRI including supratentorial T2*-weighted imaging and supratentorial susceptibility weighted imaging. Next, we analyzed intra- and perilesional paramagnetic phase changes on susceptibility weighted imaging filtered magnetic resonance phase images.

Results: We frequently observed paramagnetic rim-like (75 of 232 lesions, 32%) or nodular (32 of 232 lesions, 14%) phase changes in MS lesions, but only rarely in NMOSD lesions (rim-like phase changes: 2 of 112 lesions, 2%, p = 0.001; nodular phase changes: 2 of 112 lesions, 2%, p < 0.001).

Conclusions: Rim-like or nodular paramagnetic MRI phase changes are characteristic for MS lesions and not frequently detectable in NMOSD. Future prospective studies should ask whether these imaging findings can be used as a biomarker to distinguish between NMOSD- and MS-related brain lesions.

Neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS) are distinct autoimmune CNS diseases with sometimes overlapping clinical phenotypes. Since treatment options for these 2 CNS diseases differ considerably, the distinction between NMOSD and MS is of high clinical relevance. Recently, new international consensus diagnostic criteria were proposed for NMOSD emphasizing the role of MRI and aquaporin-4 immunoglobulin G antibody testing. Notwithstanding this success, the distinction of NMOSD vs MS can still be challenging in current clinical practice. Ultra-high field MRI at 7 tesla (T) has improved the detection and morphologic characterization of brain lesions by visualizing a central intralesional vein and a T2*-weighted (T2*w) hypointense rim around many MS lesions. Contrarily, these imaging features are only rarely depictable in NMOSD lesions. At 3T, susceptibility-induced MRI phase signal changes were reported to be specific for MS in contrast to other neurologic disorders such as migraine, antiphospholipid syndrome, and Parkinson disease. Inspired by these findings, we rescanned previously reported patients with NMOSD at 7T and included additional NMOSD cases to describe MRI phase signal changes in NMOSD vs MS lesions in a cross-sectional study.
METHODS Study participants. Ten patients with NMOSD underwent ultra-high field MRI at 7T. Inclusion criteria were diagnosis of NMOSD as defined by the current international consensus diagnostic criteria for NMOSD,2 age of at least 18 years, and no contraindications to 7T MRI. Four of these patients have been previously reported in a 7T MRI study on T2*w lesion morphology3 and were rescaned. Nine patients with NMOSD were seropositive for aquaporin-4 immunoglobulin G. Ten patients with relapsing-remitting MS underwent ultra-high field MRI at 7T. Inclusion criteria were optimal characterization of the lesion morphology. T2*w lesions outside of the field of view of SWI-phase images were excluded from further analyses.

Next, each existing T2*w lesion was marked on phase images in a side-by-side analysis.

By contrast, the vast majority of NMOSD lesions were neither characterized by nodular (2 of 112 lesions) nor rim-like in appearance, (3) lesions without any intraleisonal phase changes, and (4) other lesions with intraleisonal phase changes not meeting these criteria. The latter were termed “lesions with unspecific phase changes” (figure). Since our scanner uses a left-handed system, a paramagnetic (positive) phase shift corresponds to a hyperintense or “bright” area on phase images. Phase changes that were clearly related to a blood vessel were excluded.

In addition, a lesion with a central vessel within the inner third of the lesion on axial T2*w images was classified as a perivascular lesion by an expert reader regarding the 3-dimensional shape of the lesion and the vessels.

Statistical analysis and interrater reliability. All analyses were performed using IBM SPSS Statistics (version 20; IBM, Armonk, NY). The p values <0.05 were considered significant. Because of the exploratory nature of the study, no adjustments for multiple comparisons were made. Group differences in age, disease duration, existence of a central vein, and intraleisonal phase changes between NMOSD and MS were assessed using a nonparametric Mann–Whitney U test. Pearson χ² was used to assess sex differences, and Student t-test was used to investigate group differences in the Expanded Disability Status Scale. In addition, 10 randomly selected patients with MS or NMOSD were reanalyzed by a second blinded investigator (K.M.) to assess interrater reliability. For this reason, intraclass correlation (ICC) was calculated as a 2-way mixed test of average measures using the consistency model.

RESULTS In total, we detected 112 brain lesions in patients with NMOSD, and 232 brain lesions were visualized in patients with MS on supratentorial T2*w images.

Next, rim-like or nodular paramagnetic (positive) intraleisonal phase changes were analyzed (figure). In MS, 32 of 232 lesions (14%) in 7 out of 10 patients were characterized by a nodular paramagnetic (positive) phase shift and thus appeared “hyperintense” on magnetic resonance (MR) phase images corresponding to a hypointense signal on T2*w and/or SWIs (lesion category I; figure, A).

Furthermore, a distinct rim-like paramagnetic (positive) phase shift was visible in 75 of 232 MS lesions (32%) in all but one patient with MS (lesion category II; figure, B).

Contrarily, the vast majority of NMOSD lesions were neither characterized by nodular (2 of 112 lesions, 2%, p < 0.001) nor rim-like intraleisonal phase changes (2 of 112 lesions, 2%, p < 0.001; table 2).

Table 1 Demographic details

<table>
<thead>
<tr>
<th></th>
<th>NMOSD</th>
<th>RRMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Female, n</td>
<td>10</td>
<td>5a</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>47 ± 12</td>
<td>40 ± 7h</td>
</tr>
<tr>
<td>Range</td>
<td>30–69</td>
<td>26–49</td>
</tr>
<tr>
<td>Disease duration,c y, mean ± SD</td>
<td>8 ± 7</td>
<td>6 ± 4d</td>
</tr>
<tr>
<td>Range</td>
<td>1–29</td>
<td>0–12</td>
</tr>
<tr>
<td>EDSS score, median</td>
<td>3.75</td>
<td>1.5a</td>
</tr>
<tr>
<td>Range</td>
<td>1.5–6.0</td>
<td>0–2.5</td>
</tr>
<tr>
<td>NMOSD, n</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>NMO, n</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>ON</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>LETM</td>
<td>7</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS = Expanded Disability Status Scale; LETM = longitudinally extensive transverse myelitis; NA = not applicable; NMO = neuromyelitis optica; NMOSD = NMO spectrum disorder; ON = optic neuritis; RRMS = relapsing remitting multiple sclerosis.

*p < 0.01, Pearson χ² test to assess differences in sex between patients with NMOSD and RRMS.

*p = 0.043, Mann–Whitney U test to assess differences in age between patients with NMOSD and RRMS.

*p = 0.853, Mann–Whitney U test to assess differences in disease duration between patients with NMOSD and RRMS.

*p = 0.001, Student t test to assess differences in the EDSS between patients with NMOSD and RRMS.
A significant proportion of lesions in patients with NMOSD (107 of 112 lesions, 96%) or MS (116 of 232 lesions, 50%) did not show any MRI phase changes (lesion category III; figure, C), and a total number of 9 MS and 1 NMOSD lesions presented with rather unspecific MRI phase changes (lesion category IV; figure, D).

In addition, the existence of an intralesional central vein was analyzed on T2*w images. As reported previously,3,4 a central vein was typically visible in the inner third of MS lesions (193 of 232 lesions, 83%) but only rarely existent in NMOSD lesions (28 of 112 lesions, 25%, \( p < 0.001 \)). The morphology of NMOSD and MS lesions is detailed in table 2.

**Interrater reliability.** Interrater reliability was assessed in a subgroup of 10 randomly selected patients. ICC was >0.8 for lesion count (ICC = 0.90), the number of lesions with a central vein (ICC = 0.95), and the number of lesions with rim-like (ICC = 0.96) or nodular (ICC = 0.84) phase changes indicating good interrater reliability of these parameters.

**DISCUSSION** In this study, we compared the morphology of NMOSD vs MS lesions on high spatial resolution SWI-filtered phase images and observed distinct lesion characteristics that were nearly exclusively found in MS but not in NMOSD lesions. Thus, this work adds to the ongoing discussion5 on the diagnostic value of phase white matter signal abnormalities in differentiating MS from other diseases.

In MS, the source of the phase contrast in or around lesions remains speculative, but iron-rich
portion of MS lesions as reported previously.9 Sequence of, e.g., dying iron-rich oligodendrocytes,10 is discussed to be caused by iron deposits as a consequence of, e.g., dying iron-rich oligodendrocytes,10 perivascular hemoglobin leakage,11 or a loss of diamagnetic myelin.12

In NMOSD, such nodular or rim-like paramagnetic phase changes were virtually absent. These differences may represent variant patterns of lesion evolution or iron metabolism between MS and NMOSD.13 In MS, evidence has emerged that brain iron metabolism is altered since iron accumulates, e.g., in the basal ganglia.14 In alignment with a previous study that failed to identify abnormal iron deposits in the basal ganglia of patients with NMOSD,15 our data suggest that NMOSD is not associated with alteration in brain iron metabolism, but histopathologic confirmation is needed.

Some limitations of this study of a small sample size need to be addressed. The NMOSD group was older than the MS group, which may have influenced our results since the magnetic susceptibility of (MS) brain lesions decreases with aging of the lesion.16 Most important, lesions within the brainstem, spinal cord, and optic nerves could not be analyzed, and brain lesions typical for NMOSD17 were not present in our NMOSD cohort. Thus, the existence of any MRI phase changes in these lesions remains unknown. From a technical point of view, signal inhomogeneities were present on 7T T2*w images, and automated procedures to determine the total lesion volume were thus not performed. Finally, we cannot exclude that differences in lesion count or volume between the subgroups may have influenced our results.

In conclusion, paramagnetic intralesional phase changes were virtually absent in NMOSD but frequently detectable in MS. Future work should address the question of whether these imaging findings in or around lesions can indeed be used as a biomarker to better distinguish MS from NMOSD.

Table 2 Lesion morphology on gradient echo images

<table>
<thead>
<tr>
<th></th>
<th>Lesion counta</th>
<th>Lesions with nodular positive phase changes</th>
<th>Lesions with rim-like positive phase changes</th>
<th>Lesions without phase alterations</th>
<th>Lesions with unspecific phase alterations</th>
<th>Perivascularb</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMOSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>112</td>
<td>2</td>
<td>2</td>
<td>107</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11 ± 13</td>
<td>0.2 ± 0.4</td>
<td>0.2 ± 0.4</td>
<td>11 ± 13</td>
<td>0.1 ± 0.3</td>
<td>3 ± 4</td>
</tr>
<tr>
<td>Range</td>
<td>1-35</td>
<td>0-1</td>
<td>0-1</td>
<td>1-35</td>
<td>0-1</td>
<td>0-11</td>
</tr>
<tr>
<td>RRMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>232</td>
<td>32</td>
<td>75</td>
<td>116</td>
<td>9</td>
<td>193</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23 ± 15</td>
<td>3 ± 3</td>
<td>8 ± 10</td>
<td>12 ± 12</td>
<td>1 ± 2</td>
<td>19 ± 13</td>
</tr>
<tr>
<td>Range</td>
<td>2-50</td>
<td>0-8</td>
<td>0-33</td>
<td>0-40</td>
<td>0-6</td>
<td>2-41</td>
</tr>
<tr>
<td>p</td>
<td>0.063</td>
<td>0.015</td>
<td>&lt;0.001</td>
<td>0.481</td>
<td>0.247</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: NMOSD = neuromyelitis optica spectrum disorder; RRMS = relapsing remitting multiple sclerosis.

*Lesion count = total number of lesions detectable on T2*-weighted images.

bPerivascular = visibility of a small central vein within the lesion center.

In conclusion, paramagnetically detectable rim-like phase changes are virtually absent in NMOSD but frequently detectable in MS. Future work should address the question of whether these imaging findings in or around lesions can indeed be used as a biomarker to better distinguish MS from NMOSD.

AUTHOR CONTRIBUTIONS

ACKNOWLEDGMENT
This work was supported by the Guthy-Jackson Charitable Foundation, the German Research Foundation (DFG Exc 257 to F.P.), and the German Ministry for Education and Research (Competence Network Multiple Sclerosis) to F.P. and K.R. Our technicians and study nurses Anjje Els, Susan Pikol, Cynthia Kraut, and Gritt Stoffels gave invaluable support.

STUDY FUNDING
This work was supported by the Guthy-Jackson Charitable Foundation, the German Research Foundation (DFG Exc 257), and the Competence Network Multiple Sclerosis.

DISCLOSURE
T. Sinnecker received travel funding from Bayer, Teva, Novartis, Genzyme. S. Schumacher and K. Mueller report no disclosures. F. Pache received travel funding from Genzyme, Bayer, Biogen Idec, ECTRIMS, received research support from Charité–Universitätsmedizin Berlin, Berlin Institute of Health, KRNMS–Bundesministerium für Bildung und Forschung, Novartis. P. Dušek received research support from the Ministry of Health of the Czech Republic. L. Harms served on the scientific advisory boards for Novartis, Sanofi/Genzyme, Roche, Biogen, received travel funding and/or speaker honoraria from Novartis, Biogen Idec, Merck Serono, Bayer HealthCare, Grifols, Teva. K. Ruprecht served on the scientific advisory board for Sanofi-Aventis/Genzyme, Novartis,
REFERENCES


© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.
MRI phase changes in multiple sclerosis vs neuromyelitis optica lesions at 7T
Neurol Neuroimmunol Neuroinflamm 2016;3;
DOI 10.1212/NXI.0000000000000259

This information is current as of July 22, 2016

Updated Information & Services
including high resolution figures, can be found at:
http://nn.neurology.org/content/3/4/e259.full.html

References
This article cites 17 articles, 2 of which you can access for free at:
http://nn.neurology.org/content/3/4/e259.full.html##ref-list-1

Citations
This article has been cited by 2 HighWire-hosted articles:
http://nn.neurology.org/content/3/4/e259.full.html##otherarticles

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Autoimmune diseases
http://nn.neurology.org/cgi/collection/autoimmune_diseases
Devic's syndrome
http://nn.neurology.org/cgi/collection/devics_syndrome
MRI
http://nn.neurology.org/cgi/collection/mri
Multiple sclerosis
http://nn.neurology.org/cgi/collection/multiple_sclerosis

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://nn.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology.
Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright © 2016 American Academy of Neurology. All rights reserved. Online ISSN: 2332-7812.