Characterization of chronic active multiple sclerosis lesions with sodium (23Na) magnetic resonance imaging—preliminary observations

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Abstract

Background and purpose: There has been an increasing interest in chronic active multiple sclerosis (MS) lesions as a new magnetic resonance imaging (MRI) marker of disease progression. Chronic active lesions are characterized by progressive tissue matrix damage, axonal loss and chronic inflammation. Sodium (23Na) MRI provides a biochemical marker of cell integrity and tissue viability in a quantitative manner. The aim of this study was to investigate with 23Na MRI tissue abnormalities in chronic active lesions as indicators of tissue destruction.

Methods: To identify chronic active lesions, two 3D magnetization-prepared rapid acquisition gradient-echo datasets obtained 12 months apart were processed using the voxel-guided morphometry algorithm. Cross-sectional 23Na MRI was performed during the 12-month follow-up period. Total sodium concentration was calculated in chronic active lesions compared to shrinking, chronic stable and acute contrast-enhancing lesions.

Results: Overall, 70 MS lesions (21 chronic active, 10 shrinking, 29 chronic stable lesions, 10 acute contrast-enhancing lesions) in 12 patients were included. Total sodium concentration in chronic active lesions (49.57 ± 8.47 mM) was significantly higher than in shrinking (42.16 ± 3.9 mM; p = 0.03) and chronic stable lesions (39.92 ± 4.82 mM; p < 0.001). Chronic active lesions showed similar sodium values compared to acute contrast-enhancing lesions (48.06 ± 6.65 mM; p = 0.97). No differences between shrinking and chronic stable lesions were observed (p = 0.89).

Conclusion: High sodium values in chronic active MS lesions may be an indicator of ongoing inflammation and tissue damage.

Keywords: chronic active lesions, MRI, multiple sclerosis, sodium

INTRODUCTION

Sodium (23Na) magnetic resonance imaging (MRI) is a new marker of brain tissue integrity and several studies have demonstrated increased sodium levels in focal white matter multiple sclerosis (MS) lesions and normal-appearing brain tissue [1,2]. In a previous study acute inflammatory contrast-enhancing lesions have shown higher sodium values than non-enhancing lesions [1]. Recently, there has been a growing interest in “chronic enlarging” lesions that are likely to represent “smoldering” or “chronic activity” as they have been identified pathologically [3,4]. They are characterized by...
tissue matrix damage and axonal loss due to ongoing low-grade inflammation in the absence of contrast enhancement [3,4]. On susceptibility-weighted MRI they are frequently accompanied by hypointense rims and previous studies have suggested these lesions to be a new imaging biomarker of disease progression [3,4].

The aim of this study was to investigate with $^{23}$Na MRI tissue abnormalities in chronic active lesions as opposed to chronic stable and contrast-enhancing lesions.

METHODS

This was a retrospective analysis of a recently completed longitudinal MRI study investigating chronic active MS lesions. In the initial longitudinal study, two 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) datasets (echo time TE = 2.49 ms, repetition time TR = 1900 ms, inversion time TI = 900 ms, field-of-view 240 mm, spatial resolution $0.9 \times 0.9 \times 0.9$ mm$^3$) acquired at baseline and after 12-months follow-up on a 3 T MRI (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany, 12-channel head coil) were processed using the voxel-guided morphometry (VGM) algorithm. Using an automated combined linear and non-linear transformation process to register 3D datasets from two or more time points, VGM detects regional volume changes on a voxel-by-voxel basis in chronic MS lesions. A detailed protocol is described elsewhere [5]. Color-coded VGM maps were investigated by two experienced readers to identify chronic active lesions compared to shrinking and chronic stable lesions. To minimize partial volume effects only supratentorial lesions ≥5 mm in their long axis were included for further analysis.

For all patients included in the initial longitudinal study ($n = 67$), whether patients were also investigated with $^{23}$Na MRI during the 12-month follow-up period was retrospectively screened. The cross-sectional $^{23}$Na MRI was performed on a clinical 3 T whole-body scanner (MAGNETOM TIM Trio, Siemens). The standardized protocol included a $^{23}$Na sequence (dual-tuned $^{23}$Na/$^1$H birdcage head coil) with the parameters TR = 60 ms, TE = 0.22 ms, flip angle 80°, readout time 15 ms, 3.6 mm isotropic resolution and 12,000 projections (acquisition time 12 min), a 3D MPRAGE sequence (TE = 3.4 ms, TR = 1900 ms, TI = 900 ms, spatial resolution $0.9 \times 0.9 \times 0.9$ mm$^3$, 12-channel head coil) and post-contrast T1-weighted images (TR = 225 ms, TE = 2.5 ms). Reconstruction of the sodium 3D radial acquisition was performed with MATLAB; co-registration onto the 3D MPRAGE images was performed with statistical parametric mapping (SPM8) software for MATLAB (version 7.10.0(R2010a), The MathWorks Inc., Natick, MA, USA). A detailed protocol is described elsewhere [1].

After lesion identification and classification on the color-coded VGM maps, the corresponding lesions were identified on the MPRAGE sequence acquired at the time point of $^{23}$Na MRI. To obtain the total sodium concentration (TSC) for each lesion, a third reader blinded to the VGM analysis identified lesions with semi-automated assistance using the drawing tool of MRicroGL (https://www.mccauslandcenter.sc.edu/microgl/home). The resulting masks were applied to the quantitative sodium concentration maps; mean values were extracted and used for statistical assessment. Contrast-enhancing lesions were identified on post-contrast T1-weighted images.

Statistical analysis was performed with IBM SPSS Statistics version 25. Between-group comparisons of TSC were calculated using one-factorial analysis of variance (ANOVA) and Scheffé tests for post hoc group comparisons. The Scheffé test was chosen for post hoc group comparisons because of varying sample sizes, the Scheffé test’s robustness against violation of variance homogeneity and its being quite conservative regarding alpha-error adjustment.

This study was approved by the local ethics committee (Ethikkommission II, Medical Faculty Mannheim, University of Heidelberg, 2017-830R-MA); patient consent was waived due to the retrospective nature of the study and the lack of patient interaction.

RESULTS

Twelve relapsing–remitting MS patients (10 women; mean age 33 ± 11 years; mean disease duration 6.4 ± 9 years; median EDSS 1.5 ± 1.5; 10 patients on best individually selected immunomodulatory treatment) who were investigated with $^{23}$Na MRI during the 12-month follow-up period of the initial study were included. Overall, 70 MS lesions were identified. These included 21 chronic active, 10 shrinking, 29 chronic stable lesions and 10 acute contrast-enhancing lesions.

The total sodium concentration in chronic active lesions (49.57 ± 8.47 mM) was significantly higher than in shrinking (42.16 ± 3.9 mM; $p = 0.03$) and chronic stable lesions (39.92 ± 4.82 mM; $p < 0.001$; see Figure 1). Interestingly, chronic active lesions showed similar sodium values to acute contrast-enhancing lesions (48.06 ± 6.65 mM; $p = 0.97$). Furthermore no differences were observed between shrinking and chronic stable lesions ($p = 0.89$).

DISCUSSION

The Na$^+/K^+$ pump maintains a high gradient of sodium concentration between the intracellular and extracellular (15 vs. 145 mM) compartment that is responsible for the high sensitivity of $^{23}$Na MRI. Indeed, high sodium values can indicate extracellular edema as seen in contrast-enhancing lesions with blood–brain barrier breakdown or can be indicators of tissue matrix destruction associated with an increased extracellular space [1]. Previous studies demonstrated that chronic active MS lesions are characterized by progressive tissue matrix damage, axonal transection, neurodegeneration and chronic inflammation due to iron-laden activated microglia/macrophages and reactive astrocytes at the lesion edge [3,4]. These lesions have been suggested to be of particular importance as they may be indicators of clinical worsening and of disease progression [3,4].

Additional information is now provided on this type of lesion and interestingly the sodium concentration in chronic active lesions is as high as in acute inflammatory lesions that show contrast enhancement. In contrast, chronic stable and shrinking lesions show
comparatively lower sodium values. Higher lesion sodium may therefore be an indicator of ongoing inflammation and tissue damage.

The limitations of our study include the small sample size and the combination of multiple MRI datasets. Therefore, further studies in larger cohorts may investigate the differences observed in chronic active versus stable lesions. It is suggested that high sodium values in chronic active MS lesions may be an indicator of ongoing inflammation and tissue damage. However, our results should be regarded as preliminary observations.

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Philipp Eisele: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); writing original draft (equal). Matthias Kraemer: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (equal); writing review and editing (equal). Andreas Dabringhaus: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (equal); writing review and editing (equal). Claudia E. Weber: Data curation (supporting); formal analysis (supporting); investigation (supporting); validation (supporting); writing review and editing (equal). Anne D Ebert: Formal analysis (equal); investigation (supporting); methodology (supporting); software (equal); validation (supporting); writing review and editing (equal). Michael Platten: Formal analysis (supporting); investigation (supporting); validation (supporting); writing review and editing (equal). Lothar Schad: Data curation (supporting); investigation (supporting); methodology (equal); software (equal); validation (equal); writing review and editing (equal). Achim Gass: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing original draft (equal).

ETHICAL APPROVAL
The material is original research and has not been previously published or submitted for publication elsewhere. The study was approved by the local ethics committee; patient consent was waived due to the retrospective nature of the study and the lack of patient interaction.

DATA AVAILABILITY STATEMENT
The data supporting the results of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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