Reduced myelin in patients with isolated hippocampal sclerosis as assessed by SyMRI

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Abstract

Purpose Synthetic MRI (SyMRI) enables to quantify brain tissue and morphometry. We aimed to investigate the WM and myelin alterations in patients with unilateral hippocampal sclerosis (HS) with SyMRI.

Methods Adult patients with isolated unilateral HS and age-matched control subjects (CSs) were included in this study. The SyMRI sequence QRAPMASTER in the coronal plane perpendicular to the hippocampi was obtained from the whole brain. Automatic segmentation of the whole brain was processed by SyMRI Diagnostic software (Version 11.2). Two neuroradiologists also performed quantitative analyses independently from symmetrical 14 ROIs placed in temporal and extratemporal WM, hippocampi, and amygdalae in both hemispheres.

Results Sixteen patients (F/M = 6/10, mean age = 32.5 ± 11.3 years; right/left HS: 8/8) and 10 CSs (F/M = 5/5, mean age = 30.7 ± 7 years) were included. Left HS patients had significantly lower myelin and WM volumes than CSs (p < .05). Myelin was reduced significantly in the ipsilateral temporal lobe of patients than CSs, greater in left HS (p < .05). Histopathological examination including luxol fast blue stain also revealed myelin pallor in all of 6 patients who were operated. Ipsilateral temporal pole and sub-insular WM had significantly reduced myelin than the corresponding contralateral regions in patients (p < .05). No significant difference was found in WM values. GM values were significantly lower in hippocampi in patients than CSs (p < .05).

Conclusion SyMRI revealed myelin reduction in the ipsilateral temporal lobe and sub-insular WM of patients with HS. Whether this finding correlates with electrophysiological features and SyMRI could serve as lateralization of temporal lobe epilepsy need to be investigated.

Keywords Synthetic MRI · Hippocampal sclerosis · Myelin · Epilepsy

Abbreviations

BPV | Brain parenchymal volume
BPF | Brain parenchymal fraction (BPV/ICV)
CS | Control subject
FA | Fractional anisotropy
GMFvol | The mean amount of GM within a single voxel
HS | Hippocampal sclerosis
ICC | Intra-class correlation coefficient
ICV | Intracranial volume
MD | Mean diffusivity
MY | Myelin
MYF | Myelin fraction (MY/BPV)
MyFvol | Myelin-correlated fraction volume within a single voxel
MyV | Myelin-correlated volume
NoN | Non-GM/WM/CSF

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**PD**
- Proton density

**QRAPMASTER**
- Quantification of relaxation times and proton density by multi-echo acquisition of a saturation-recovery using turbo spin-echo readout

**R1**
- Longitudinal relaxation rate

**R2**
- Transverse relaxation rate

**SyMRI**
- Synthetic MRI (synthesized)

**TLE**
- Temporal lobe epilepsy

**WMFvol**
- The mean amount of WM within a single voxel

### Introduction

Hippocampal sclerosis (HS) is the most common cause of refractory temporal lobe epilepsy (TLE) in adults [1] and consists of neuronal loss with glial tissue proliferation histopathologically. Magnetic resonance imaging (MRI) has a sensitivity of 91% for detecting focal epileptogenic lesions [2] and 93% and 83% for detecting hippocampal and amygdala abnormalities, respectively [3]. The imaging findings of HS on MRI include the following: increased T2/FLAIR signal intensity in the hippocampus, loss of internal structure of the hippocampus, reduced hippocampal size and related ipsilateral atrophy of the hippocampal collateral WM, enlarged temporal horn of lateral ventricle, diminished gray-white matter demarcation in the temporal pole, and decreased temporal lobe volume [3–6]. Atrophy of the ipsilateral mammillary body, fornix, and thalamus can also be seen [7]. Ipsilateral temporal pole signal abnormality in HS is another frequently associated finding on MRI [8, 9].

Synthetic MRI (SyMRI) is an FDA-approved unique faster MRI technique that is a compilation pulse sequence (multi-slice, multi-echo, multi-saturation delay acquisition) and enables the creation of multiple sequences based on the relaxation time of the tissue properties from a single acquisition. It can also automatically create intracranial tissue segmentation [10]. SyMRI was previously examined in several studies in patients with cognitive impairment [11], Sturge-Weber [12], multiple sclerosis [13–15], and brain metastases [16–18]. Diagnostic software Version 11.2 of SyMRI also allows quantification of WM, GM, and myelin-correlated volume (MyV) in the ROIs (https://synthetickr.com/products/symri-neuro/).

We hypothesized that SyMRI quantitatively would reveal myelin alterations in temporal and extratemporal structures of patients with unilateral TLE-HS.

### Methods

This study was approved by our institutional review board and informed patient consents were obtained.

### Patient selection

Patients diagnosed with HS between November 2019 and December 2020 were enrolled in the study prospectively (n = 20). All patients had brain MRIs applying epilepsy-dedicated protocol including T2W imaging obtained perpendicular to the hippocampi. These scans were reviewed, and the final diagnosis was confirmed independently by two neuroradiologists (KKO with 20 and GC with 8 years experience in epilepsy imaging).

The patients were invited to participate in the study if they met the inclusion criteria which were (i) clinical diagnosis and electroencephalography (EEG) findings supporting TLE, (ii) age > 18 years, and (iii) MRI demonstrating unilateral HS (increased T2/FLAIR signal intensity in the hippocampus, loss of internal structure of the hippocampus, reduced hippocampal size). Exclusion criteria were (i) bilateral HS on MRI, (ii) presence of any other structural lesion, and (iii) history of seizure within 1 week.

A total of 16 adult patients with unilateral isolated HS were included in this study. Control subjects (CSs) were chosen from age-matched patients who were referred to our department with headache, vertigo, or peripheral facial paralysis (n = 10) with normal brain MRI findings.

### MR image acquisition

All MR scans were acquired with a 1.5 T scanner (Magnetom, Aera, Siemens), equipped with a 20-channel standard head coil. Coronal T2W TSE (FOV: 199 × 220 mm; TR/TE: 6560/95 ms; FA: 150°; ST: 3 mm; NEX: 3) and FLAIR (FOV: 186 × 230 mm; TR/TE/TI: 7000/78/2229 ms; FA: 180°; ST: 4 mm; NEX: 1) were added as conventional MRI to use as reference images for visual assessment. The SyMRI sequence (QRAPMASTER: quantification of relaxation times and proton density by multi-echo acquisition of a saturation-recovery using turbo spin-echo readout) (FOV: 230 × 230 mm; voxel size: 1.5 × 1.5 mm; TE/TR/TI: 14, 28, 42, 56, 70 ms/7000/0.0974, 0.5846, 1.8511, 4.0919 ms; FA: 150°; ST: 4 mm, slice gap = 1 mm, acquisition time = 6.05 min) was obtained covering the whole brain on the coronal plane perpendicular to the hippocampi. No contrast material was used.

### SyMRI technique

SyMRI (Synthetic MR AB, Linköping, Sweden) enables variable contrast-weighted images after quantifying the longitudinal relaxation rate (R1), the transverse relaxation rate...
(R2), and the proton density (PD) and can create intracranial volume (ICV), GM, WM, CSF, non-GM/WM/CSF (NoN), myelin (MY), and myelin fraction volume (MYF) quantification of the whole brain [10].

The myelin, free water, cellular, and excess parenchymal water contribute to the MRI acquisition voxel [19]. Because each compartment has different relaxation properties, myelin volume can be estimated. The total volume of myelin in addition to WM, GM, CSF, and NoN can be calculated by multiplying the summed volume fractions for each tissue type based on predefined tissue characteristics. Among these, NoN represents the tissue not classified as GM, WM, and CSF [19–21].

Colored maps of WM, GM, CSF, and MyV can be automatically created, and the MyV map was demonstrated to have a high correlation with the partial volume of myelin in each voxel (https://syntheticmr.com/products/symri-neuro/). Normal appearing myelin-correlated compound on MyV map appears bright fluorescent yellow and green colors (yellow > green) (https://syntheticmr.com/wp/custom/uploads/2021/02/SyMRI-NEURO.pdf). Normal GM and WM are coded as green and pink colors, respectively.

Quantitative values consisting of R1, R2, PD, GM, WM, MyV, and volume (mean amount of a single voxel) of GM (GMVvol), WM (WMVvol), and MyV (MyVvol), were also automatically provided for selected ROIs by Diagnostic software Version 11.2.

Image analysis

The QRAPMASTER sequences were evaluated to identify artifacts before uploading to the software. Whole brain automatic segmentation yielded MY, BPV, BPF, ICV, MYF, GM, and nonWM/GM/CSF volumes in all subjects. The automatic segmentation yielded MY, BPV, BPF, ICV, MYF, GM, WM, CSF, and non-GM/WM/CSF volumes in all subjects. The colored myelin, GM, and WM maps were displayed. The segmented tissue properties were overlaid on the synthetic T1W sequence.

The quantitative analyses of myelin, WM, and GM maps were performed independently and individually by two neuroradiologists (SP and GC).

Region of interest (ROI) sizes ranged as follows allowing a sensitive sampling depending on the region: (1) bilateral temporal poles, temporal stem, posterior temporal and sub-insular region, and corpus callosum (genu, corpus, splenium) (20–22 ml); (2) superior and inferior frontal, parietal, and occipital WM and on the thalamus, on the myelin, and WM maps (40–42 ml) (Supplementary illustrated Fig. 1); and (3) bilateral hippocampi and amygdalae on the GM maps (20–22 ml).

The MyV, MyVvol, WM, WMVvol, GM, GMVvol, R1, and R2 relaxation rates and PD values were noted for each measurement. With the mirror copy option available in this version, ROIs drawn on an image set were copied to the contralateral side. The program also allowed that when an ROI was drawn on a single set, the other imaging sets also displayed the same ROI. These features let us avoid any misalignment while collecting data from different hemispheres or different maps.

Clinical evaluation

The age of onset and duration of epilepsy, presence of predisposing or risk factors for epilepsy (history of febrile convolution, meningitis/encephalitis, trauma, or perinatal brain injury), and presence of secondary generalized seizures or status epilepticus were recorded.

Histopathological evaluation

To observe myelin under light microscopy, luxol fast blue stain was added to routinely performed H&E and immunohistochemical stains. Histopathologic evaluation was done by a neuropathologist (FS) with an experience of > 30 years. The reduction in myelin was assessed visually by luxol fast blue (LFB) staining in comparison with autopsy sections obtained from patients without neurological disease. The evaluation was performed in a blinded fashion.

Statistical analysis

Quantitative variables were evaluated with the Kolmogorov–Smirnov test to reveal the presence of normal distribution. Descriptive statistics were expressed as mean ± standard deviation if variables were normally distributed or median (min–max) if variables did not show normal distribution. Independent sample t-test was used to compare normally distributed variables; otherwise, the Mann–Whitney U test was used. Paired sample t-test was used to compare the myelin amount of the different hemispheres in HS patients. If the data did not meet the normal distribution condition, two paired sample comparisons were performed using the Wilcoxon test. Comparison of left- and right-sided HS subgroups with side-matched hemispheres of CSs was assessed by independent sample t-test or Mann–Whitney U test. The relationship between quantitative values and clinical features was examined with the Pearson correlation or Spearman Rho correlation coefficient.

For comparisons of continuous variables, the adjusted p value was obtained using the Benjamini–Hochberg method. For the assessment of inter-observer agreement, intra-class correlation coefficient (ICC) was calculated. p < 0.05 was used as a reference setpoint for statistical significance.
IBM SPSS 21.0 Windows program was used for all statistical analyses.

**Results**

There was no statistical significance in terms of gender \((p = 0.689)\) and age \((p = 0.384)\) between the patients \((F/M = 6/10, \text{mean age} = 32.5 \pm 11.3 \text{ (range 19–48 years)})\) and CSs \((F/M = 5/5, \text{mean age} = 30.7 \pm 7 \text{ years (range 26–40 years)})\). All patients and CSs were right-handed.

Based on the MRI findings, 8 patients had HS on the right and left side. Clinical and EEG findings were compatible with MRI. Demographic and clinical features of patients were summarized in Table 1.

None of the patients had dual pathology.

**SyMRI analysis results**

**Automated whole brain segmentation**

Left-sided HS patients \((\text{MY} = 101.83 \pm 23.12; \text{WM} = 373.36 \pm 58.87)\) had significantly lower MY and WM volumes compared to CSs \((\text{MY} = 132.55 \pm 14.62; \text{WM} = 477.82 \pm 45.25)\) \((p < 0.003 \text{ and } 0.001, \text{ respectively})\). Although there was a trend that right-sided HS patients had lower MY and WM volumes compared to CSs, it did not reach a significant difference \((\text{MY}: 119.4 \pm 14.23; \text{WM}: 430.51 \pm 49.58)\) \((p; 0.073 \text{ and } 0.051, \text{ respectively})\). GM, CSF, or NoN volumes did not show differences between patients and CSs.

**Quantification of SyMRI maps**

In patients with HS, the MyFvol, MyV, and R1 values were significantly lower, and PD value was significantly higher in the ipsilateral temporal pole and sub-insular WM than contralateral regions for both observers \(< 0.05, \text{ Table 2, Figs. 1 and 2})\). R2 value showed no difference.

The observers noticed that the expected fluorescent yellow/green color was turned into pale green in the areas with lower MyV, especially in the ipsilateral temporal pole in HS (Fig. 1).

When compared to CSs, the MyV value was significantly decreased, and PD value was significantly increased in the ipsilateral side of temporal poles and temporal stems in both HS subgroups for both observers \((p < 0.05, \text{ Supplementary Table 1})\).

Left-sided HS patients showed lower mean MyV and R1 values and higher mean PD value in the ipsilateral posterior temporal lobe and sub-insular region in comparison

![Fig.1 Coronal myelin maps derived from SyMRI of a 32-year-old male patient with right HS, suffering temporal lobe epilepsy for 4 years. Increased T2 signal intensity in the hippocampus, loss of internal structure of the hippocampus, and reduced hippocampal size are seen on T2WI (A, arrow). Although there was no apparent gray matter-white matter demarcation loss (B), prominent myelin reduction in the right temporal pole (coded as pale green > yellow) compared to the contralateral side (bright fluorescent yellow > green) is seen on colored myelin map (C, arrows). Luxol fast blue–H&E stain of the white matter of the anterior temporal lobectomy section (D) shows myelin pallor easily observed by visual assessment compared to an autopsy control (E). The myelin fibers appear blue and neuropil appears pink.](image-url)
to corresponding regions of the CSs for both observers ($p<0.05$, Supplementary Table 1).

There was no statistical significance between the contralateral hemispheres of the HS subgroups and side-matched hemispheres of the CSs in any region.

Intra-class correlation for statistically significant results is given in Supplementary Table 2.

There was no significant difference in terms of WM and WMFvol in ipsilateral and contralateral hemispheric regions in HS patients or between patients and CSs.

Comparisons of hippocampi yielded lower GM, GMFvol, R1, and R2 values in both right and left HS patients than CSs ($p<0.05$, for both observers, ICC: 0.779–0.900, Table 3). The PD value showed an increasing trend in patients without significance. No significant difference was found in the amygdala.

No significant correlation was found between quantitative values and none of the investigated clinical features ($p > 0.05$).

### Histopathological results

Six patients (five right-sided HS and one left-sided HS) in this study underwent surgery consisting of hippocampectomy, amygdalactomy, and temporal lobectomy for refractory seizures ($n=6$). Neuropathological evaluations revealed severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions. Luxol fast blue stain combined with H&E revealed pale blue staining in the WM, thus was interpreted as myelin pallor in the anterior temporal lobectomy sections (Fig. 1 B and C). No significant pathology was observed in the amygdala sections included in the specimen.

### Discussion

This study has investigated the quantification in HS patients using SyMRI. With significantly lower MyFvol, MyV, and R1 and high PD values extensively in the temporal lobe WM and sub-insular regions in HS patients, alterations in
the myelin in HS patients have been shown by SyMRI. The interobserver correlation was high on myelin maps, which showed the reliability of the SyMRI in practical life.

Loss of the GM-WM differentiation, decreased T1, and increased T2 signal intensity in the ipsilateral anterior temporal lobe in patients with TLE ranging between 58 and 75% in studies vary depending on clinical profile of the patients [8, 9]. Histopathological investigations showed a decreased amount of myelinated axons in HS patients with temporal pole signal abnormalities on MRI when compared to HS patients without signal abnormalities [6, 22] compatible with experimental studies [23]. Our results with SyMRI are also in line with these studies showing extensive myelin loss. Furthermore, in this study, myelin loss was qualitatively assessed by pallor staining on LFB in temporal lobe ipsilateral to HS from histopathological specimens of six patients supporting SyMRI results. A semi-automated quantitative image analysis of myelin, as previously described in pathological specimens of a patient population of tuberous sclerosis, would reveal quantitative correlations with myelin assessment by SyMRI [24].

The validity of measurement of myelin by SyMRI was supported by previous studies. Quantitative results depicted the normal developmental pattern of myelination in pediatric patients in studies based on the normative quantitative segmentation of intracranial tissue [25] and acquired myelin partial volume values in different regions [26] on SyMRI. Also, measurement of myelin with SyMRI was correlated with Magnetization Transfer Saturation Index [27] and with postmortem brain studies using myelin sensitive luxol fast blue [28]. Underlying myelin and/or axonal abnormality of the WM by SyMRI was also shown in neurological diseases

Fig. 2 Consecutive coronal T2W images (A–C) of a 23-year-old male patient with right HS, suffering epilepsy for 15 years. Increased T2 signal intensity in the hippocampus, loss of internal structure of the hippocampus, and reduced hippocampal size are seen on T2W images (B, C). Coronal white matter (D) and myelin maps (E&F) derived from SyMRI of same patient. The MyFvol, MyV, and R1 values were decreased, and PD value was increased in the right temporal pole and sub-insular WM than contralateral regions on the myelin map without any color change in WM maps or any apparent gray-white matter demarcation loss. Myelin reduction in the right temporal lobe can easily be observed by visual assessment (arrows)
including demyelinating diseases, Sturge-Weber syndrome, and cognitive dysfunction in both normal and abnormal WM [11, 12, 29–31].

The role in lateralizing epileptic focus and the impact of TLE on the organization of cerebral networks were assessed with quantitative measurements on DTI. In HS, widespread increased mean diffusivity (MD) and decreased fractional anisotropy (FA) more prominent in the ipsilateral hemisphere were reported in a meta-analysis study [32]. These changes showed variable alterations in terms of spatial pattern and degree in left and right HS patients across the studies, and it is not certain if right or left HS shows wider abnormality [33–36]. Additionally, Oguz et al. reported that decreased FA was more extensive in men with left HS and in women with right HS compared to sex-matched controls [37]. SyMRI findings representing myelin loss were more extensive in patients with left HS in our study. This may be related to the effect of patients’ gender and male dominance in the left HS group.

Sclerosis of the hippocampus with gliosis and neuronal loss at various degrees is identified at histopathologic examinations of HS [38]. Our findings of decreased GM and GMFvol in the ipsilateral hippocampus with SyMRI reflect the neuronal loss observed in the histopathological specimens. However, in contradiction to previously reported changes frequently involving the amygdala in HS [39], we found no significant radiological and pathological abnormality in the amygdalae.

Neither we found a statistical abnormality in the thalami. Nonetheless, atrophy of medial dorsal thalamus and diffusion properties were shown by volumetric MRI [40] and DTI [41] studies, respectively, reflecting neuronal loss and gliosis in experimental [42], and postmortem histological studies in HS [43, 44]. Our failure of finding significant changes in the thalami using SyMRI may result from ROI placement method and the relatively small number of study populations.

Long-lasting pandemic conditions of COVID-19 apparently affected us as elsewhere in the world. Consequently, our study group and furthermore the number of patients undergoing temporal lobectomy were limited. Myelin alterations revealed by SyMRI in these patients also need to be investigated by other myelin imaging techniques on MRI especially on higher field scanners. One other limitation is that we could not assess all the structures belonging to the Papez circuit and other areas related to mesolimbic structures due to their small volumes. Despite normal brain MRI findings, subtle microscopic abnormalities cannot be completely excluded in subjects with a history of headache, vertigo, or peripheral facial paralysis, which constituted our control group.

### Conclusion

SyMRI is a potential imaging tool for the investigation of myelin abnormality in patients with HS. This study has shown reduced myelin in the ipsilateral temporal lobe and sub-insular WM in HS patients with SyMRI. Whether this finding correlates with electrophysiological features and SyMRI could serve as lateralization of TLE need to be investigated.

### Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00234-021-02824-6.

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Data availability Restrictions apply to the availability of the data which were used under licence for the current study and thus are not publicly available.

Code availability This study was performed using special complimentary transitional licence by SyMRI and code availability is not applicable.

Declarations

Ethical approval Institutional review board approval was obtained (Hacettepe University Institutional Review Board).

Consent to participate Written informed consent for participation was obtained from all patients.

Consent for publication Written informed consent for publication was obtained from all patients including personal information or images of patients.

Conflict of interest None of the authors have a relevant conflict of interest.

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