Differentiating Cirrhosis from Healthy Controls using T1 Signal Intensity Rather than Normalized Signal Intensity Ratio

Abstract:

Background: T1 shortening on brain MRI is a marker of Manganese deposition among those with liver failure and portal hypertension. This study evaluates a fully automated approach to identify increased T1 signal intensity in the brain using FreeSurfer.

Method: 3T brain MRI and single -voxel proton MRS on 26 participants with cirrhosis secondary to non-alcoholic steatohepatitis (NASH), 7 with hepatic encephalopathy (HE) and 19 without, and 30 healthy age matched controls. Cerebral cortex, white matter, putamen, globus pallidus and brainstem are the five relevant regions of interest selected. Concentration of Ins, T1 signal intensity of these five regions, and orthotic normalized signal ratio of basal ganglia region over non basal ganglia are obtained.

Results:

Conclusion:

Increased T1 signal intensity was noted in all brain regions studied in those with cirrhosis, with or without HE, compared to controls (p<<0.001). A decrease in T1 signal was noted in all brain regions in NASH+HE compared to NASH only, which may indicate presence of brain edema.

Introduction:

Since the original finding by Inoue *et al* in 1991, it has been well documented that patients with cirrhosis have an increased ratio of T1 signal intensity of the basal ganglia compared to frontal cortex on magnetic resonance imaging (MRI)1. The current literatures suggest that portal hypertension leads to manganese deposition that preferentially occurs at the basal ganglia compared to the rest of the brain2,3. While hyperintensity of basal ganglia is well represented, diffuse deposition in the brain has not been previously observed. However, autopsies of multiple etiologies of cirrhosis with portal hypertension suggest that deposition is not limited to basal ganglia4. These findings disrupt the long-standing notion that manganese deposition is limited to the basal ganglia, and the accuracy of using frontal cortex as a point of comparison for unaffected tissue.

In normal clinical practice, MR images are calibrated by native software on the scanner into interpretable radiographs prior to clinician review [REF]. Calibration is guided by enhancing images to detect ratio of differences of abnormal hyperintensity or hypo-intensity compared to areas of normal intensity [REF]. The neurological manifestation of portal hypertension previously noted exemplifies one type of ratio that may be used for calibrating images. However, as a side effect, MRI intensities may be artificially reduced or even erased in lieu of enhancing images for comparison purposes. While manual re-calibration may be performed to recalibrated radiographic to incorporate excluded differences, this is time and resource intensive.

Therefore, there is considerable interest in development of automated tools to assist with disease screening and diagnostics, particularly in resource limited situations5,6. Improvements in computational power and machine learning to assist with radiographic evaluation of disease, including in chest, brain and liver6-9. Several automated approaches already exist; however, they are primarily used for research with potential for clinical translation.

In this study, we re-visit the paradigm of manganese deposition in the brain which is one of the complications of portal hypertension in advanced liver disease. Herein, we sought to characterize manganese deposition through the brain by automatically quantifying T1-shortening on T1-weighted images with image analysis software in a population of Nonalcoholic steatohepatitis (NASH) patients compared to controls and to NASH with hepatic encephalopathy (NASH+HE).

Method:

In this IRB-approved study with written consent, 26 NASH (7 HE, 19 Non-HE) patients and 30 age-matched controls were examined on a General Electric (GE) 3 Tesla scanner, demographics are shown in Table 1. Standard 3D T1 FSPGR (TE:2.41ms; TR:6.75ms; TI:600ms; slice thickness=1.2mm; matrix 256 x 256; flip angle: 8) and single voxel, short echo time point-resolved spectroscopy (PRESS) in the posterior gray matter (PGM) and parietal white matter (PWM) were obtained. Hepatic encephalopathy is brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.

Averaged T1 intensity values of the left and right side of cerebral cortex (CC), cerebral white matter (CWM), globus pallidus (GP), putamen and brainstem were obtained from automated Freesurfer image analysis suite 6.010. The image used to obtain SI come from the brain extracted image (brain.mgz) using the segmentation labels (aparg+aseg.mgz). Average intensity ratios of GP and putamen with respect to CC, CWM, and brainstem were also calculated. Spectroscopy data was analyzed using Linear Combination Model (LC Model) to quantify brain metabolites, including myo-inositol (Ins).

ANOVA was applied to analyze SI ratio of GP and putamen with respect to CC, CWM, and brainstem and SI of CC, CWM, GP, putamen and brainstem regions between controls and NASH, and NASH+HE. ANOVA p-values were adjusted for false discovery rate and level of significance was set at p<.05. There was no additional independent effect related to sex, and it was not included in the models. Where ANOVA was significant, between-group differences were assessed using tukey’s honest significant difference test. Two-tailed tests with multiple comparison correction using the Benjamin-Hochberg False Discovery Rate (FDR)11, where p-values presented are already FDR corrected. General linear regression is used to evaluate T1 SI of these 5 regions and Ins concentration with class difference adjusted. All statistical analysis was performed with JMP Pro version13 (SAS, Cary NC).

Results:

Patients with advanced liver disease have signal shortening at the globus pallidus shown in T1 sequence12,13. Figure 1 shows unadjusted window or level of a sample brain axial views, control on the lest and a cirrhotic participant on the right. Table 2 reported both the normalized T1 SI ration and the T1 SI of all five region under the ANOVA test showed between group differences among control, NASH and NASH+HE. Figure 2 reports normalized T1 SI ratios for between group difference among controls, NASH and NASH+HE. Although the SI ratio of putamen over CC (Figure 2A) or GP over CC (Figure 2D) did not show a significant in between group difference for the control versus NASH and that of putamen over CWM (Figure 2E) only showed a trend, SI ratio indicates significant difference among controls, NASH and NASH+HE (Figure 2B, 2C and 2F). Further, the SI ratio increase from NASH to NASH+HE among the cirrhosis patients and some actually reached between group differences, such as that of GP with respect to CC (Figure 2A), GP with CWM (Figure 2B), and putamen with CWM (Figure 2E).

Figure 3 looked at the SI of putamen (Figure 3A), GP (Figure 3B), CC (Figure 3C), CWM (Figure 3D), and brainstem (Figure 3E) independently. It shows the consistent result of significant SI abnormality between control and cirrhosis. However, it presented two additional information. One, there is significant SI difference between NASH and NASH+HE in the CC (Figure 3D) and CWM (Figure 3E) regions. And there is a trend between group difference between NASH and NASH+HE in putamen (Figure 3A) brainstem area. On the side, although the difference is not significant, the GP area show a observable SI decrease from NASH to NASH+HE (Figure 3B).

SI increase on FSPGRE 3D sequence seems to increase with Ins concentration as measured by MRS (Table 3). This table also present that SI of CC CWM, putamen, GP and brainstem is significantly correlated with Ins concentration. Further, after adjusting the influence of Ins on SI, the SI difference between NASH and NASH+HE diminished. Ever more noticeable is the F-distribution of putamen, CC, and brainstem is nearly 1 (Table 3).

**Discussion**:

T1 SI shortening in the basal ganglia region is an established MR marker for patients with liver failure1,14. In this study, we evaluated the brain MR T1 image SI change associated with hepatic cirrhosis. The intension is to quantify the effect of cirrhosis in the brain in a radiographic perspective rather than using it as a screening tool for liver failure. The results of the ANOVA test shown in Table 1 confirms that these results are in agreement with both MRI and autoptic findings for patients with liver failure 2,13,15. If looking into the comparison of each pair such as control vs NASH, control vs NASH+HE and NASH vs NASH+HE, Figure 2 show that normalized SI ratio increases in GP and putamen with respect to regions outside of basal ganglia, such as the CC, CWM, or brainstem. However, only the SI ratio of GP (Figure 1B) and putamen (Figure 1E) over CWM showed significant between group difference for all 3 pairs of tests.

It is true that manganese concentrations are highest in the basal ganglia and T1 shortening is most apparent in this location as shown in Figure 1, likely explaining why imaging studies have focused on this region alone as a marker of cirrhosis. But the inconsistent patterns seen in Figure 2 raise several important questions in studying brain alternations in people with liver cirrhosis. First, is using the normalized T1 SI value an truthful prestation of manganese deposition in the brain? If high concentration of manganese accumulating in the basal ganglia to cause conspicuous T1-shortneing in MR images, then it is not unreasonable to argue that it does not affect other parts of the brain. T1 SI alone of putamen, CP, CC, CWM, and brainstem all showed that the F-distribution <0.0001 among control, NASH and NASH+HE (Table 1). We did not expect to identify significant differences in T1 SI in all brain regions. Yet, SI increase in CC, CWM and brainstem regions (Figure 3) indicates widespread manganese deposition beyond areas, putamen and GP, typically associated with cirrhosis in imaging studies. Changes in signal in all brain regions represents a problem with using ratios between these brain regions as a method to account for technical differences in signal intensity. This finding is concordant with multiple radiological-pathological correlation studies which noted higher manganese deposition throughout the brain in cirrhosis or significant portal hypertension compared to controls4,13,16,17.

Because of the eye-catching brain alteration on T1 sequence among patients with cirrhosis, there is limited studies conducted looking areas other than basal ganglia. This finding is in agreement with a 1996 AJNR study quantified T1 using multiple acquisitions with varying repetition time and showed T1 shortening in the cortex and white matter as well as the basal ganglia of patients with chronic liver disease13. In addition, *Iwasa et al*. performed a study in 1998 evaluating magnetization transfer contrast of different brain regions between control and cirrhotic patients and found abnormal magnetization transfer ratio in otherwise normal appearing cerebral regions 18. Thus, the orthotic method that most clinical studies use, obtaining images on different scanners and make direct comparison of intensity values, is unreliable.

Another phenomenon we observe from this study is the decreased SI intensity of NASH to NASH+HE in all five brain regions (Figure 3). Surprised by this observation, we hypothesized that seldom SI decrease in T1 might be influenced by edema in NAHS+HE. In proton magnetic resonance spectroscopy, Ins is an abundant neuro-biomarker that has previously been associated with brain edema in patients with HE, such as that of astrocyte swelling as a by-product of hyper-ammonic states 14. Therefore, we selected Ins as proxy to track brain swelling in a continuous fashion proportional to severity of HE. After adjusting for Ins concentration on T1 SI for both NASH and NASH+HE, there were almost no differences in manganese concentration between NASH vs. NASH+HE (Table 3). Rather, we found that Ins concentration appears to increase proportionally during acute hepatic encephalopathy, which may represent astrocyte swelling. This radiographic association suggests that cerebral edema provides a second hit for clinically significant hepatic encephalopathy that has not been previously reported.

Since all areas exhibited some degree of T1 signal intensity change as shown in Figure 3, only areas with even more exaggerated differences can therefore be identified. Unfortunately, even for the basal ganglia, this still results in a decrease in statistical power as the normalization factor is also impacted by the disease process being studied. The imaging software, FreeSurfer, provides some degree of standardization by performing automatic correction and standardization of image intensity values [REF]; analyzing signal intensities across scanners will likely require more standardization such as with the use of phantoms and may still require scanner specific reference ranges. New imaging sequences such as synthetic MRI19 which provide T1 and T2 quantification may excel at identifying manganese related T1 shortening.

Although previous studies have reported that neither conventional MRI imaging presented edema in patients with HE 20,21 nor GP T1 hyperintensity correlated with clinical HE 22,23, we propose distinct effects are occurring related to T1 shortening due to manganese deposition in chronic liver disease and T1 prolongation with superimposed brain edema that occurs with HE. In NASH+HE patients, T1 intensity was lower than NASH patients without HE which is consistent with development of subclinical brain edema among those with hepatic encephalopathy2. Variable impact of edema versus manganese in different brain regions may account for differences in some prior studies evaluating correlations between T1 signal and HE [REF]. Automatic identification of T1 SI increase allows for a simple, yet rapid diagnosis and characterization of manganese deposition in advanced liver disease and other pathologies using a relatively ubiquitous imaging modality. Several issues will need to be addressed for widespread clinical adoption. The automated approach used in this study to identify T1 shortening will also reflect gadolinium deposition that may occur after MRI scans with contrast 24. The participants in this study were followed clinically with ultrasound and CT and had not received gadolinium. Current American Association for the Study of Liver Diseases guidelines favor ultrasound rather than gadolinium-contrast for surveillance for hepatocellular carcinoma in patients with cirrhosis25. Confounding due to effects of gadolinium may be less of an issue in the future as linear contrast agents implicated in tissue deposition 26 are replaced with macrocyclic agents.

Hepatic encephalopathy is a complex disease with contributions from multiple pathophysiologic processes27. Magnesium deposition in the brain may promote neurocognitive abnormalities among people with portal hypertension regardless of its relationship to hepatic encephalopathy. The neurocognitive effects of manganese toxicity are not confined to motor functions typically associated with the basal ganglia, and may also contribute to cognitive and psychiatric impairments28. Manganese toxicity disrupts glutamine/glutamate-γ-aminobutyric acid (GABA) cycling between astrocytes and neurons. Glutamine and glutamate are critical neurotransmitters in the brain29. In this study, we are able to assess T1 intensity for individual regions as we used the same scanner and the same sequence. FSPGR technique provides high-resolution images needed for automatic segmentation. This sequence has different signal characteristics compared to standard spin echo sequences typically obtained in the clinic and may be more sensitive to the effects of T1 shortening related to manganese, similar to what has been reported for detection of gadolinium30. Additionally, we used T1 signal intensity values generated as part of the Freesurfer image analysis pipeline, which normalizes images intensity to further minimize remaining technical differences and corrects for fluctuations in signal intensity that may interfere with intensity-based segmentation31.

Further work is needed, however, to determine the sensitivity of different T1 weighted sequences in identifying manganese. A more rigorous approach which would also facilitate clinical use across different scanners may involve standardizing T1 values using a phantom scanned at each site. Alternatively, newer synthetic MRI sequences calculate T1 and T2 relaxation which are objective properties that should not vary between scanners given appropriate quality controls.

Conclusion:

Manganese deposition has been documented to potentiate disruption multiple pathways including ammonia processing through glutamate cycle processing that leads to acute osmotic changes. It is likely manganese deposition provides a backdrop for well documented neurotoxicity that lowers threshold for acute encephalopathic events. By comparison radiographs of patients with and without hepatic encephalopathy, we demonstrate that there is clinically significant increase in T1 shortening that precedes acute encephalopathy. Herein, with automatic process, we provide radiographic evidence of the multi-hit process that leads to hepatic encephalopathic events.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Control | NASH | NASH+HE | *ANOVA Prob > F* |
| (N=30) | (N=19) | (N=7) |
| Age | 62.8±2.4 | 63.1±5.1 | 62.4±5.1 |  |
| Female: Male | 15:15 | 16:3 | 4:3 |  |
|  |  |  |  |  |
| Diabetes Mellitus Type II | 0 | 17 | 6 |  |
|  |  |  |  |  |
| Laboratory and clinical parameters |  |  |  |  |
| Albumin | N/A | 3.98±0.1 | 3.31±0.18 | 0.004 |
| INRa | N/A | 1.09±0.03 | 1.267±0.04 | 0.001 |
| Alanine transaminase (ALT) | N/A | 34.5±3.6 | 29.6±6.2 | 0.5 |
| Aspartate transaminase (AST) | N/A | 40.8±4.7 | 39.4±7.9 | 0.9 |
| Creatinine | N/A | 0.74±0.08 | 1.24±0.13 | 0.002 |
| Sodium | N/A | 140.2±0.7 | 137.5±1.3 | 0.08 |
| a INR: international normalized ratio | | | | |

Table 1: Study population demographics, clinical laboratory parameters.

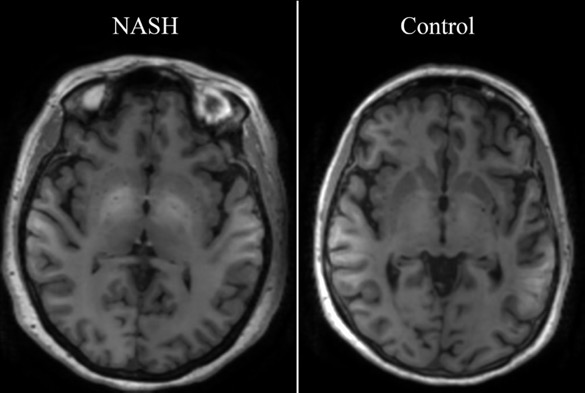


Figure1: Sample 3D T1 FSGPR axial view of Control and a NASH subjects without adjusting image signal intensity.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Control | NASH | NASH+HE | ANOVA | Control vs  NASH | Control vs  NASH+HE | NASH vs  NASH+HE |
|  | n=30 | n=19 | n=7 | prob > F | p-value | p-value | p-value |
| Normalized T1-Singal Ratio |  |  |  |  |  |  |  |
| Globus Pallidus / Cerebral Cortex | 0.96±0.0086 | 1.04±0.011 | 1.11±0.018 | <0.0001 | 0.29 | <0.0001 | <0.0001 |
| Globus Pallidus / Cerebral WM | 1.36±0.023 | 1.42±0.029 | 1.66±0.048 | <0.0001 | <0.001 | <0.0001 | 0.0073 |
| Globus Pallidus / Brainstem | 1.10±0.016 | 1.17±0.020 | 1.21±0.033 | <0.001 | 0.027 | 0.006 | 0.41 |
| Putamen / Cerebral Cortex | 0.84±0.0067 | 0.86±0.0085 | 0.90±0.014 | <0.001 | 0.101 | <0.001 | 0.1 |
| Putamen / Cerebral WM | 1.15±0.020 | 1.17±0.026 | 1.35±0.042 | <0.001 | 0.053 | <0.001 | 0.002 |
| Putamen / Brainstem | 0.93±0.0086 | 0.97±0.011 | 0.98±0.018 | <0.001 | 0.069 | 0.039 | 0.82 |
|  |  |  |  |  |  |  |  |
| Non-normalized T1-Signal Intensity |  |  |  |  |  |  |  |
| Putamen | 72.98±2.92 | 121.35±3.67 | 106.45±6.05 | <0.0001 | <0.0001 | <0.0001 | 0.098 |
| Globus Pallidus | 86.19±3.78 | 146.10±4.75 | 132.83±7.83 | <0.0001 | <0.0001 | <0.0001 | 0.32 |
| Cerebral Cortex | 63.35±2.54 | 103.45±3.19 | 81.22±5.26 | <0.0001 | <0.0001 | 0.0019 | 0.0095 |
| Cerebral WM | 87.25±3.35 | 140.71±4.22 | 119.68±6.95 | <0.0001 | <0.0001 | 0.0003 | 0.033 |
| Brainstem | 78.92±3.23 | 126.08±4.06 | 108.95±6.69 | <0.0001 | <0.0001 | 0.0005 | 0.082 |

Table 1: Normalized T1 SI ratio of globus pallidus and putamen over the cerebral cortex, cerebral white matter, and brain stem and non-normalized T1 SI values of those brain regions (putamen, globus pallidus, cerebral cortex, cerebral WM, and brainstem) show differences among control, NASH and NASH+HE.

A close up of a map

Description automatically generated

Figure 2: Normalized T1 SI of globus pallidus and putamen with respect to cerebral cortex, cerebral white matter and brainstem after adjusted for false discover rate.



Figure 3: Signal intensity without normalization from five regions of interest: putamen (A), globus pallidus (B), cerebral cortex (C), cerebral white matter (D), and brainstem (E) after adjusted for false discover rate.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | [Ins]a | | | NASH vs NASH+HEb |
|  | r2 | pe±se | p-value | ANOVA |
| Non-normalized T1 SI |  |  |  |  |
| Putamen | 0.4 | 51.6±12.7 | 0.0005 | 0.99 |
| Globus Pallidus | 0.4 | 61.8±16 | 0.001 | 0.50 |
| Cerebral Cortex | 0.6 | 48.7±10.1 | <0.0001 | 0.99 |
| Cerebral WM | 0.5 | 44.3±12.3 | 0.002 | 0.07 |
| Brainstem | 0.3 | 35.3±11.8 | 0.005 | 0.99 |

a: p-value adjusted for between group difference

b: ANOVA between NASH and NASH+HE after

pe: parameter estimate

se: standard error

Table 3: General linear regression of myo-inositol (Ins) concentration as dependent variable and non-normalized T1 SI as independent variable. ANOVA analysis of NASH and NASH+HE between group difference are shown in the last column adjusted for Ins concentration.

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