WITHDRAWN: Utility of MRI with QSM in Motor Neuron Disease

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Utility of MRI with QSM in Motor Neuron Disease

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Abstract

Introduction: Currently, we use brain MRI quantitative susceptibility mapping analysis (QSM) to examine susceptibility in the motor cortex, correlating with iron deposition, which is typically increased in motor neuron disease. Familial ALS is most commonly due to the C9ORF72 and SOD1 genes. Pathology studies have demonstrated more protein aggregates in the cerebellum and temporal lobes in C9ORF72 ALS, and more protein aggregates in the frontal and temporal lobes in SOD1 ALS. Other means of looking for protein are not established. We designed a study to retrospectively assess the MRI/QSM correlation with motor neuron disease severity, as measured by MRC, FVC, El Escorial criteria and ALSFRS-R. We also looked for regional changes in genetic ALS patients.

Methods: We retrospectively reviewed the charts of all motor neuron disease patients seen in Neurology at Hospital for Special Surgery from 2013 through 2018 who had MRI with QSM. One neuroradiologist examined the scans and quantified relative susceptibility. We collected values for ALSFRS-R, FVC, El Escorial diagnosis, and sum of MRC, where documented.

Results: Although there is a significant difference between patients with Definite ALS by El Escorial criteria (43.8 ppb) and 'normal,' QSM failed to correlate with ALSFRS-R, FVC, or sum of MRC. Further, we found no distinguishing abnormalities in the brain MRIs of the genetic ALS patients reviewed. QSM of the motor cortices and corticospinal tracts showed qualitative increase in susceptibility, which is not unique to type of ALS.

Discussion: MRI/QSM may not be useful in distinguishing ALS patients by severity or mutation. It may be useful to distinguish ALS from mimic syndromes. This could be because the amount of protein aggregation may not be directly related to axonal loss, or that it affects certain neurons/ tracts more than others.

Introduction

Brain MRI quantitative susceptibility mapping analysis (QSM) identifies degenerating neurons in the motor cortex because of abnormal iron deposition.[3] Currently, we use this technique to examine susceptibility in the motor cortex, which is typically increased in motor neuron disease, correlating with the clinical syndrome and becomes more prominent as the burden of disease increases.[3] Figure 1 shows an example of what this MRI abnormality looks like. The most common form of familial ALS is due to the C9ORF72 gene.[1] Patients with this kind of familial ALS tend to develop more protein aggregates in the cerebellum and temporal lobes on pathology.[1-3] The second most common form of familial ALS is due to the SOD1 gene.[1] Patients with this kind of genetic ALS tend to develop more protein aggregates in the frontal and temporal lobes, in addition to the anterior horns of the spinal cord on pathology.[4-7] Other means of looking for these signs are not established.

We designed a study to retrospectively assess the MRI/QSM in patients with suspected motor neuron disease to determine if level of QSM hyperintensity correlates with disease severity, as determined by several metrics (MRC scores, El Escorial criteria, ALSFRS-R and FVC). We also looked at MRI/QSM in familial ALS patients with C9ORF72 and SOD1 genetic mutations to determine whether there are changes in the cerebellum and temporal lobes (C9ORF72) or frontal, temporal and occipital lobes (SOD1). Our goal was to use MRI/QSM to distinguish ALS patients with the C9ORF72 or SOD1 mutations from other kinds of genetic or sporadic ALS patients.

Methods

All patients with suspected motor neuron disease seen in Neurology at Hospital For Special Surgery from 2013 through 2018 were reviewed retrospectively. The study was approved by the HSS ethics committee and conducted according to the principles of the Declaration of Helsinki. All patients gave written informed consent. Patients were stratified into three groups by level of QSM hyperintensity: normal, mild and moderate/severe and compared with average MRC scores, El Escorial diagnosis and, where available, ALSFRS-R and FVC. Patients were also stratified by mutation for analysis of whether the mutations affect the QSM result:

C9ORF72, SOD1. In the C9ORF72 group, we identified 16 patients, 7 of which had an MRI with QSM. In the SOD1 group, we identified 8 patients, 3 of which had an MRI with QSM. Aside from the initial neuroradiology read, a single neuroradiologist additionally examined the scans of each patient with special attention to the cerebella and temporal lobes in the C9ORF72 group and the frontal and temporal lobes in the SOD1 group, based on typical patterns of iron accumulation on pathology. On chart review, ALSFRS and FVC were not documented for all patients, but were noted in the result chart summary if they were. One patient had SWI (susceptibility weighted imaging), since they were imaged before the institution used QSM.

Data was analyzed to decipher whether there is a correlation between relative susceptibility in ppb of iron and any of the following: El Escorial diagnosis, ALS gene, ALSFRS-R or FVC. This resulted in analysis of the following four groups: Positive C9ORF72 gene mutation (n=6), Definite ALS by El Escorial criteria (n=7), PLS (n=3), and 'normal' (n=7). Some patients in the 'normal group' were ultimately diagnosed with ALS mimic syndromes, such as benign fasciculation-cramp syndrome.

Results

Results are summarized in Tables 1 and 2. We found no abnormalities in the cerebella or temporal lobes of any of the patients with C9ORF72 familial ALS who had MRI/QSM done. Likewise, we found no abnormalities in the frontal or temporal lobes of patients with SOD1 ALS who had MRI/QSM done. None of the C9ORF72 positive patients met El Escorial criteria for Definite ALS, so those two groups had no overlap.

Average relative susceptibility (ppb of iron) in the C9ORF72 group was 39, in the Definite ALS group was 47.9, in the PLS group was 48.9, and 'normal' group was 35.3. There was no correlation between relative susceptibility (ppb of iron) and disease severity at the time of MRI, as measured by MRC, FVC and ALSFRS-R scores. Any perceived difference in susceptibility were qualitative and not reproducible when quantified.

In the normal QSM group (n=2), the patients had no ALS by El Escorial criteria. Sum of MRC scores were 200 (full strength). Relative susceptibility in these patients calculated by quantitative susceptibility mapping was 28.8 ppb of iron deposited. ALSFRS-R was 48 (no impairment) and FVC was 100% of predicted (best of 3 trials).

In the mild QSM group (n=4), all had possible ALS by El Escorial criteria. The average sum of MRC scores was 76.5. Relative susceptibility in these patients calculated by quantitative susceptibility mapping was, on average, 54.45 ppb of iron deposited. ALSFRS-R was averaged at 54, and FVC was only documented on one patient and was 61% of predicted.

In the moderate/severe QSM group (n=3), all patients had definite ALS by El Escorial criteria. The average sum of MRC scores was 5. Relative susceptibility in these patients calculated by quantitative susceptibility mapping was, on average, 27.2 ppb of iron deposited, however one patient was missing the measurement data and the other was measured early in disease course, when the patient's MRC was still 187. When those are excluded, the remaining patient (n=1) had a relative susceptibility value of 37.3, ALSFRS-R was 15 and MRC was 2. FVC was averaged at 67% (n=2, as one patient was missing this data). The finding of increased susceptibility in the motor cortex is not unique to any specific type of ALS. Only minimally increased susceptibility on QSM was seen in the patients with A4V subtype, as expected.

Discussion

The lack of distinguishing imaging findings to reflect pathological findings could mean that the amount of iron deposition may not be directly related to protein aggregation or axonal loss, or that certain neurons or tracts are more affected than others. Susceptibility on QSM seen in patients with A4V subtype has been established to be less than in other types of ALS and our results support this.[8] Since we found no distinguishing imaging features in the MRIs of patients with genetic ALS, we believe that MRI/QSM may not be useful in identifying whether C9ORF72 or SOD1 mutations are the cause of a patient's ALS and genetic analysis will still be needed for this.

Quantitative stratification of QSM did not correlate with ALSFRS-R, FVC or sum of MRC at the time of the MRI. However, there was a significant difference between normal (35.3 ppb) and definite ALS by El Escorial criteria (43.8 ppb), so there may be some diagnostic utility of QSM in ALS. Qualitative evaluation of SWI could probably serve the same purpose and is more cost effective and more widely available.

This study was limited by sample size, given the rarity of the disease and further rarity of its genetic subtypes. Future research to confirm the pathological differences between brain regions and to clarify the role of iron deposition in motor neuron disease would be helpful.

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Table 1: Summary of Results

Subject #	Mutation	Sum of MRC, FVC	Relative Motor Cortex susceptibility (ppb), Qualitative description	Increased T2 Signal in Corticospinal Tract	White matter changes	Atrophy	El Escorial diagnosis	ALSFRS-R
1	C9ORF72	200, 100	Relative Motor Cortex susceptibility (ppb), Qualitative description	None	None	None	No ALS, gene only	48
2	C9ORF72	2, 80	Relative Motor Cortex susceptibility (ppb), Qualitative description	Bilateral	Minimal	None	Definite ALS	15
3	C9ORF72	126, 61	Relative Motor Cortex susceptibility (ppb), Qualitative description	None	Minimal	Mild	Possible ALS	34
4	C9ORF72	Unknown	Relative Motor Cortex susceptibility (ppb), Qualitative description	Bilateral	None	None	Possible ALS	Unknown
5	C9ORF72	6, unknown	Relative Motor Cortex susceptibility (ppb), Qualitative description	Subtle, bilateral	Moderate	Moderate	Definite ALS	Unknown

6	C9ORF72	7, 54	Relative Motor Cortex susceptibility (ppb), Qualitative description	None	Moderate	Moderate	Definite ALS	45 (when sum of MRC was 187)
7	C9ORF72	167, unknown	Relative Motor Cortex susceptibility (ppb), Qualitative description	Bilateral	None	Global	Definite ALS	38
8	C9ORF72	157	Relative Motor Cortex susceptibility (ppb), Qualitative description	None	Moderate	Mild	Definite ALS	30
9	SOD1 A4V	200, 100	Relative Motor Cortex susceptibility (ppb), Qualitative description	None	None	None	No ALS, gene only	48
10	SOD1 A4V	119	Relative Motor Cortex susceptibility (ppb), Qualitative description	None	None	None	Possible ALS	33
11	SOD1 D90	178	Relative Motor Cortex susceptibility (ppb), Qualitative description	Bilateral	Severe	None	Possible ALS	40

Table 2:

Group (C9ORF72, Definite ALS by El Escorial criteria, PLS (primary lateral sclerosis), Not ALS	**Relative motor cortex susceptibility (ppb)**	**ALS-FRS-R at time of MRI**	**Sum of MRC Upper and Lower Extremity Strength Scores at time of MRI**
C9orf72	45.7	38	180
C9orf72	17.1	47	187
C9orf72	28.8		200
C9orf72	37.3	39	134
C9orf72	68.1	34	139
Definite	81.7	30	157
Definite	39.1	38	189
Definite	41.2	38	167
Definite	47.8	33	191
Definite	45.8	37	185
Definite	39.0	40	184
Definite	40.8		174
PLS	51.7	41	190
PLS	45.9	33	160
PLS	49.1	45	200
Not ALS	41.3		200
Not ALS	35.2		199
Not ALS	40.2	36	188
Not ALS	32.3		165
Not ALS	27.6		195
Not ALS	40.1		200

Not ALS	30.3	47	190

Figure 1: MRI with QSM