# Might Misdiagnosis of Multiple Sclerosis Compromise Outcomes of Clinical Trials?

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## Introduction

Multiple sclerosis (MS) is a neurological disorder characterized by inflammatory demyelination and abnormal neurological function. The histopathologic hallmarks of MS are plaques of demyelination restricted to the central nervous system (CNS). Magnetic resonance imaging (MRI) is the diagnostic technique of choice, and provides an essential component of modern diagnosis of MS based on the McDonald criteria. These guidelines have been periodically revised. The most current criteria state that a patient must present with signs or symptoms "of an acute inflammatory demyelinating event in the CNS … with duration of at least 24 hours, in absence of fever or infection," coupled with standardized MRI findings, which include evidence of dissemination of lesions in space (DIS) and time (DIT).[1] While these criteria work well for most patients, some patients present with atypical MRI lesions. MS can be a difficult disease to recognize and diagnose, due to the variety of patient presentations encountered by physicians. This, when coupled with MRI findings that can be misleading, can be a challenge for even experienced neurologists. Patients who present with atypical MRI findings, yet may be diagnosed with MS might skew MS clinical trial results. This study was designed to categorize and quantify lesion patterns in patients enrolled into a phase III clinical drug trial for MS. We suspected that patients with atypical lesion patterns upon entry into the trial might have different on-study outcomes than those with more typical MRI findings.

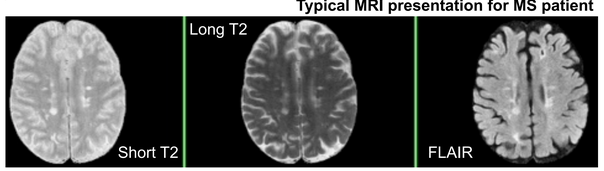
## Materials

This project utilized the resources of the University of Texas MRI Analysis Center (UT MRI-AC), MRI databases from a phase III MS clinical trial (CombiRx) that spanned 7 years of preplanned follow-up,[2] locally developed MRI analysis software, and the statistical program JMP 10.

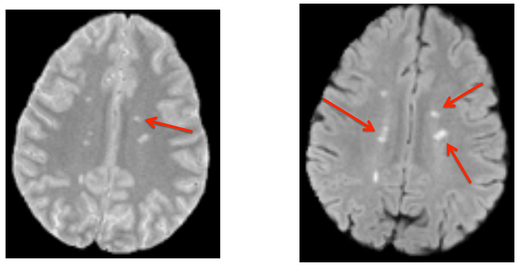
## Methods

MRI scans from 1008 randomized and 98 non-randomized patients were reviewed. The scans were processed in the UT MRI-AC. They consisted of a dual echo T2-weighted, FLAIR, and pre and post gadolinium (Gd)-enhanced T1-weighted image series for each patient. Scans were reviewed, lesions categorized and counted, and any "special features" were noted. Lesions were grouped into categories as prescribed by the McDonald criteria and calculations were made to determine whether a particular patient met the 2005 and or 2010 McDonald criteria. Scans were also categorized as either "typical" or "atypical" lesion patterns on MRI. "Atypical" lesion presentation included patients who presented with any of the following primary special features: leukodystrophy-like, NMO-like, normal brain, small vessel disease, and tumefactive lesions. On-study MRI and clinical behavior were evaluated and comparisons were made between McDonald criteria groups, and typical and atypical patient groups. Randomized patient scans were evaluated for: presence of Gd enhancement, total lesion volume (BOD), combined unique lesion activity (CUA), protocol-defined exacerbations (PDEs), clinical progression (PROG), disease activity-free status (DAFS) and clinical activity-free status (CAFS).[2] For the 98 scans from patients who were not randomized, CAFS, CUA, DAFS, PDEs and PROG data were not obtained, and could not be evaluated. Statistical analyses were performed among subgroups. The p-values reported are calculated from the Pearson chi-square test and t-test. The cutoff for significance used in this study was p<0.01.

**Typical MRI presentation for MS patient**



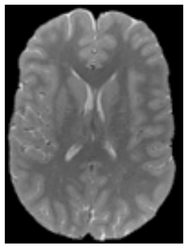

### Typical MRI presentation for MS patient



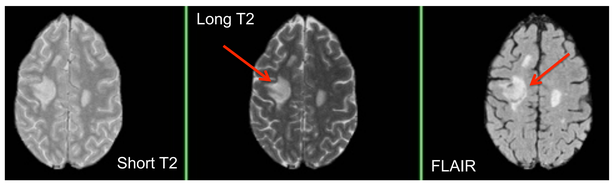
Short T2 FLAIR

These findings are very consistent among MS patients. Many lesions are periventricular and oblong ("Dawson Fingers"), and others reach out into the subcortical white matter.

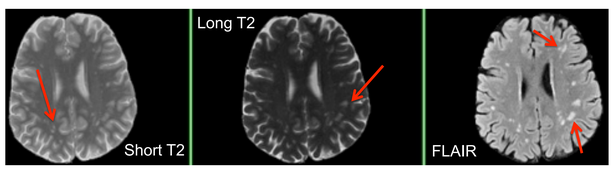
### Atypical MRI presentation for MS patient



This short echo T2-weighted scan is a normal-appearing brain without evidence of inflammation or T2 hyperintense lesions of the type seen in MS.




An example of a patient with a "tumefactive" type lesion in the right posterior frontal lobe.




Example of a patient with possible small vessel disease, i.e. hypertension. The lesions do not surround the ventricles and do not touch the cortical "U-fibers".

## Results

### Randomized Patients

**2005 McDonald Criteria**

| Subgroup | Value | Subgroup | Value | Significance |
|---|---|---|---|---|
| Met criteria | 83.43% | Failed criteria | 16.57% | - |
| With Gd+ Lesions | 45.78% | With Gd+ Lesions | 8.38% | p<0.0001 |
| Mean BOD (95% CI) | 14.01 (13.15;14.86) | Mean BOD (95% CI) | 2.99 (1.08;4.91) | p<0.0001 |
| New CUA on Study | 64.92% | New CUA on Study | 35.39% | p<0.0001 |
| DAFS on Study | 23.07% | DAFS on Study | 38.32% | p<0.0001 |

Results comparing CAFS, PDEs and PROG on study did not differ significantly.

**2010 McDonald Criteria**

| Subgroup | Value | Subgroup | Value | Significance |
|---|---|---|---|---|
| Met criteria | 90.18% | Failed criteria | 9.82% | - |
| With Gd+ Lesions | 42.79% | With Gd+ Lesions | 10.10% | p<0.0001 |
| Mean BOD (95% CI) | 13.145 (12.3;13.99) | Mean BOD (95% CI) | 3.33 (0.79;5.88) | p<0.0001 |
| New CUA on Study | 62.38% | New CUA on Study | 39.39% | p<0.0001 |
| DAFS on Study | 24.97% | DAFS on Study | 31.31% | p=0.1698 |

Results comparing CAFS, PDEs and PROG on study did not differ significantly.

**Typical vs. Atypical**

| Subgroup | Value | Subgroup | Value | Significance |
|---|---|---|---|---|
| Typical | 95.34% | Atypical | 4.66% | - |
| Met 2005 criteria | 85.54% | Met 2005 criteria | 40.43% | p<0.0001 |
| Met 2010 criteria | 91.99% | Met 2010 criteria | 53.19% | p<0.0001 |
| With Gd+ Lesions | 41.21% | With Gd+ Lesions | 6.38% | p<0.0001 |
| Mean BOD (95% CI) | 12.46 (11.62;13.29) | Mean BOD (95% CI) | 6.54 (2.77;10.32) | p=0.0027 |
| New CUA on Study | 62.54% | New CUA on Study | 10.64% | p<0.0001 |
| DAFS on Study | 24.77% | DAFS on Study | 42.55% | P=0.0064 |

Results comparing CAFS, PDEs and PROG on study did not differ significantly.

### Non-Randomized Patients

**2005 McDonald Criteria**

| Subgroup | Value | Subgroup | Value | Significance |
|---|---|---|---|---|
| Met criteria | 71.43% | Failed criteria | 16.57% | - |
| With Gd+ Lesions | 47.14% | With Gd+ Lesions | 7.14% | p=0.0002 |
| Mean BOD (95% CI) | 18.14 (14.13;22.15) | Mean BOD (95% CI) | 2.17 (-4.17;8.51) | p<0.0001 |

**2010 McDonald Criteria**

| Subgroup | Value | Subgroup | Value | Significance |
|---|---|---|---|---|
| Met criteria | 82.65% | Failed criteria | 17.35% | - |
| With Gd+ Lesions | 41.98% | With Gd+ Lesions | 5.88% | p=0.0047 |
| Mean BOD (95% CI) | 15.97 (12.08;19.85) | Mean BOD (95% CI) | 2.20 (-6.28;10.69) | p=0.0043 |

**Typical vs. Atypical**

| Subgroup | Value | Subgroup | Value | Significance |
|---|---|---|---|---|
| Typical | 87.76% | Atypical | 12.24% | - |
| Met 2005 criteria | 77.91% | Met 2005 criteria | 25.00% | p<0.0001 |
| Met 2010 criteria | 87.21% | Met 2010 criteria | 50.00% | p=0.0014 |

Comparisons of Gd enhancement status and BOD at screening did not differ significantly.

## Conclusions

In the 1008 patients who were randomized, having Gd enhancements and a higher BOD at baseline corresponded with meeting both 2005 and 2010 McDonald criteria more often. Thus, more stringent entry criteria may assure more on-study events, a finding consistent with analysis of an earlier independent trial.[3] This was also evident when evaluating comparisons between the 2005 and 2010 McDonald criteria. The MRI component of the 2010 criteria is less stringent, enabling subjects with less MRI-defined disease, earlier in their clinical disease course to enter trials and as a consequence may lower their proportionate contribution to on-study events. However, having more MRI features at study entry did not correspond with differences in on-study clinical events (as evidenced by the pure clinical measures of CAFS, PDEs, and PROG). In addition, having more MRI features considered as typical of MS at study entry corresponded with more on-study activity in the face of partially effective treatments. This held true for MRI-based on-study activity (CUA) and a combination of MRI and clinical-based activity (DAFS). It did not correspond with differences in on-study purely clinically defined events (CAFS, PDEs, and PROG). Furthermore, the presence of typical MRI lesion patterns met both 2005 and 2010 McDonald criteria more often, had Gd enhancements, and a higher BOD at baseline. These results suggest that although patients with atypical lesion patterns sometimes showed baseline or on-study MRI activity, they did not show any difference in clinical disease progression.

Of the 98 patients who were not randomized, those with more features at screening (including Gd enhancements and higher BOD) and typical cerebral MRI lesion patterns more often met both the 2005 and 2010 McDonald criteria. As these patients did not enter the study no on-study data was gathered.

## Acknowledgements

This project was funded through a grant from the Foundation of the Consortium of Multiple Sclerosis Centers' MS Workforce of the Future program. The CombiRx study was funded by the NINDS (UO1NS045719, R21NS41986) with study agents kindly provided by Biogen Idec and Teva Pharmaceutical. CFM thanks Dr. Wolinsky for this opportunity and continued support and mentorship, and the entire UT MRI Analysis Center team for their help and support.

## References

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3. Barkhof F, et al. (2003) Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta-1a. *Ann Neurol* 53:718.