Published in final edited form as:

J Neuroimaging. 2017 September ; 27(5): 447–452. doi:10.1111/jon.12465.

7T MRI Visualization of Cortical Lesions in Adolescents and Young Adults with Pediatric-Onset Multiple Sclerosis

Ritobrato Datta, PhD^{1,2}, Varun Sethi, PhD³, Sophia Ly⁴, Amy T. Waldman, MD^{1,2}, Sona Narula, MD^{1,2}, Blake E. Dewey, NMD³, Pascal Sati, PhD³, Daniel Reich, MD, PhD³, and Brenda Banwell, MD^{1,2}

¹Division of Neurology, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania

²Department of Neurology, University of Pennsylvania, Philadelphia, PA

³Translational Neurology Section, Division of Neuroimmunology and Neurovirology, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

⁴Department of Biology, University of Pennsylvania, Philadelphia, PA

Abstract

Background—Cortical pathology in multiple sclerosis (MS) has been associated with prolonged and progressive disease. 7T MRI provides enhanced visualization of cortical lesions (CLs). Hence we conducted a pilot study to explore whether CLs occur early in MS, as evidenced by pediatric-onset patients.

Methods—8 pediatric-onset MS patients were imaged using 7T MRI. CLs were annotated on T1-weighted MPRAGE images as leukocortical, intracortical or subpial. Total CLs, age at onset, age at scan, disease duration, total relapses and Expanded Disability Status Scale (EDSS) score were recorded.

Results—A median of 120 (range: 48-144) CLs were identified in 8 MS patients (3 female, all with relapsing remitting MS, mean age at scan 21yrs $\pm$ 3.5SD, mean age of disease onset 15yrs $\pm$ 2.3SD, mean disease duration 5.3yrs $\pm$ 3.4SD, median EDSS 2.0). Nearly all the lesions identified were leukocortical.

Conclusions—Many CLs are detectable using 7T MRI in patients with pediatric-onset MS despite relatively brief disease duration, absence of progressive disease, and very limited physical disability- supporting early cortical involvement in MS.

Keywords

MS; pediatric; 7T; cortical lesions

Corresponding Author: Brenda Banwell, MD, FRCPC, FAAN, 3401 Civic Center Blvd, Philadelphia PA 19104, banwellb@email.chop.edu, Phone: 215-590-1710.

Disclosure: Dr. Banwell receives financial remuneration for work as a central MRI reviewer for Novartis. Drs. Datta, Sethi, Waldman, Narula, Sati and Reich have nothing relevant to disclose. Ms. Ly and Mr. Dewey have nothing to disclose.

Background

MS during childhood and adolescence manifests with a relapsing-remitting course at onset, with secondary disease progression typically noted only after more than 20 years.¹ If cortical involvement in MS occurs only in later, progressive phases of the disease, then CLs should be rare in pediatric-onset patients studied early in their disease course.

Absinta et al., using a 3T MRI double inversion recovery (DIR) sequence in 24 children with MS, found CLs in only 2 patients, as well as a lower number and volume of CLs in these patients relative to the 15 adults with MS that were also studied.² A subsequent study by the same group, using the same 3T MRI DIR sequence detected CLs in 5 of 41 pediatric MS patients³. In a study using 1.5T MRI DIR sequences in 35 pediatric- and 57 adult-onset MS patients demonstrated that only 12 (34%) pediatric patients had at least one CL detected, which differed significantly from the 35 (61%) of adult-onset patients (all participants imaged within one year of first attack).⁴ However, accrual of new CLs (mean 1.5, SD 1.3) and change in gray matter fraction (reduction of 0.5% per year) over the 3-year study period was similar in pediatric- and adult-onset MS patients.

Pathology studies in adults with MS have emphasized a far greater extent of cortical disease than is appreciated by conventional 1.5 and 3T imaging.^{5;6} Postmortem analyses, however, are largely restricted to older adults with longstanding, and typically progressive, MS. Appreciation of cortical involvement in younger MS patients requires lesion detection by MRI. As most CLs are small, the signal-to-noise ratio and image resolution of 1.5T, and even 3T MRI, have rendered such images largely insensitive to cortical pathology.⁷ Several factors, such as low levels of inflammatory cell infiltration,⁸ partial volume effects resulting from the close proximity of CLs to the CSF, the absence of substantial blood-brain barrier damage in acute CLs,⁹ and low cortical myelin density, work to decrease the contrast of lesions on T2-weighted MRI sequences and make the identification of CLs by conventional MRI difficult. Specialized sequences, such as phase sensitive inversion recovery (PSIR),¹⁰ double inversion recovery (DIR),¹¹ and magnetization transfer ratio imaging (MTR)¹² performed using 3T MRI, have proven more sensitive than conventional approaches and have documented CLs in adults with MS. Recently published consensus guidelines for MS CL scoring at 3T recommended using DIR as the gold standard,¹³ though other studies have demonstrated that PSIR has better sensitivity to detect CLs.¹⁰

Ultra-high-field 7T MRI provides greater signal-to-noise ratio and increased spatial resolution compared to magnets with lower field strengths.¹⁴ In adult MS studies, various pulse sequences at 7T, including magnetization-prepared rapid acquisition of gradient echoes (MPRAGE) and fast low-angle shot (FLASH) T2* allow enhanced detection of CLs.^{15;16}

In this pilot 7T MRI study, we evaluate the frequency of CLs in adolescent and young adult pediatric-onset MS patients.

Methods

Participants

Pediatric-onset MS patients (onset $\leq$ 18 years) were enrolled from the MS clinic at the Children's Hospital of Philadelphia. Patients were required to be more than 3 months from a recent relapse and more than 30 days from corticosteroid exposure. Age at first attack, age at imaging, disease duration, total number of relapses, medication exposures, and Expanded Disability Status Scale (EDSS)¹⁷ score were recorded. Informed consent was obtained from all participants. The study was approved by the Institutional Review Boards (IRB) at The Children's Hospital of Philadelphia and the University of Pennsylvania.

Image acquisition

All participants were scanned on a single 7T Siemens Magnetom MRI scanner at the University of Pennsylvania, using a 32-channel phased-array head coil. Pulse sequences included: (i) 3D T1-MPRAGE: slices = 256, resolution = 0.7 mm isotropic; (ii) 3D T2-FLAIR: slices = 176, resolution = 0.8 isotropic on 3 patients and T2-TSE images (same parameters) on the other 5 patients; and (iii) T2*-weighted GRE: slices = 25, resolution = $0.2 \times 0.2 \times 1.0$ mm, two acquisition slabs covering the vertex to the rostral midbrain.

Image Preprocessing

Images were preprocessed using ANTS.¹⁸ Pre-processing of the images included spatial inhomogeneity correction,¹⁹ skull-stripping,²⁰ and rigid coregistration of the T1-MPRAGE and T2/FLAIR images.

Cortical Lesion Identification Protocol

Published recommendations for CL detection at 3T served as the primary guiding principle.¹³ Criteria for CL identification at 7T were further refined by in-person consensus of three experienced raters. A training set of images obtained from adult MS patients imaged at 7T refined the criteria. Prior to scoring the pediatric-patient scans, all scans were windowed in MIPAV (<http://mipav.cit.nih.gov>) by adjusting the brightness and contrast levels, and the level of windowing was consistently maintained. MPRAGE and T2* sequences were utilized to mark the lesions. CLs were scored on the using the following guidelines:

- **Cortical Lesion Intensity** – CLs should appear clearly hypointense to the surrounding normal-appearing GM on MPRAGE. Within the boundaries of a given lesion, voxels should appear isointense and consistently hypointense to surrounding non-lesional GM. Focal areas of cortical hypointensity were considered to be Virchow-Robin spaces if they had an internal mesh-like appearance.
- **Cortical Lesion Size** – A CL should comprise a minimum of 4 voxels in-plane (based on 0.7×0.7 mm² in-plane resolution) and should be present in at least 2 consecutive slices in the inferior-superior direction.

- Cortical Lesion Type – CLs were subgrouped based on their appearance on MPRAGE images as leukocortical (LC - that include both cortical GM and subjacent WM), intracortical (IC, lesions entirely within the cortex, with lesion borders that do not touch either the pial or gray-white border), and subpial (lesions abutting the pial surface and extending into the cortex). Although FLAIR sequences are used to verify CL detection at 3T,¹³ on 7T images the FLAIR images did not improve CL detection and were not used for this purpose. Furthermore, MPRAGE sequences did not identify subpial lesions, and thus the T2* images were used for this purpose, as per published studies in adult MS cohorts.^{21;22}

Each of the three raters then applied the scoring guidelines to images from four patients, scoring and annotating lesions on each scan three times, in random order, while remaining unaware of patients' clinical features. A second in-person meeting was held, during which the lesion maps for each of the four patients were reviewed, all annotated lesions adjudicated by consensus, and a final CL count for each patient derived. The lead rater then independently scored the remaining four patients' scans using the principles and experience garnered during the consensus scoring sessions. A total CL count for all 8 patients was then established. Relationships between CL count, age at MS onset, age at scan, disease duration, and EDSS were evaluated using Spearman's rank correlation coefficients.

WM lesions: As part of our new 7T MRI sequence optimization, we obtained either FLAIR or T2 acquisitions, and thus did not have consistent T2-weighted sequences for all 8 subjects. WM lesions were segmented manually on either FLAIR images or T2 images using ITK SNAP (<http://www.itksnap.org>). WM lesion volume was computed using FSL²³. Correlations between CL counts and WM volume was performed using Spearman rank correlation.

Results

Eight pediatric-onset MS patients were included and the demographic and clinical features of these patients are delineated in Table 1.

CLs were demonstrated in all eight patients. Table 1 provides the total CL counts (847 CLs; median 120, range 48-144). During the consensus scoring, 36 putative lesions detected on scans from the MS patients were rejected. Almost all lesions identified were classified as LC, and only one of the three raters identified a few purely IC lesions (Figures 1 and 2). Hence, the subclassification of lesions into LC and IC is not reported. Only 3 subpial lesions could be identified on the T2*-weighted images (Figure 3).

There was no significant relationship between lesion count and subject age at scanning, age at onset, or disease duration. All patients were receiving disease modifying therapies for MS. WM lesion volume (mean 17.8; SD 13.5; median 15.6, range 5 – 42.5 mL) did not correlate with CL count (magnitude of correlation =0.58, p-value 0.15).

Discussion

In this pilot study, we demonstrate that CLs can be detected using ultrahigh field MRI in pediatric-onset MS patients, and that despite their youth and relatively brief disease duration, pediatric-onset MS patients have substantial detectable cortical pathology. We were able to document CLs in all 8 of our patients, contrasting with the much lower published CL detection rate in pediatric MS cohorts studied using lower field strength MRI. None of our participants showed signs of secondary progressive MS, and all were within 10 years of their first attack.

Although MS is largely described as an inflammatory disease of central nervous system WM, the involvement of gray matter (GM) is also well-recognized. In 1962, Brownell and Hughes studied 22 MS brains and described that 26% of the MS lesions affected GM and 77% of the CLs involved the subcortical WM.²⁴ Lumsden et al., found that out of 60 MS cases studied, 93% had cortical involvement, with some patients having few CLs and others having as many as 465 'gyral plaques.'²⁵ Recent neuropathological studies have consistently identified subpial, IC, and LC lesions in adults with MS studied at autopsy.^{6;26-33}

We detected LC and IC lesions in all eight of our pediatric-onset MS patients. However, we were able to identify only three clear subpial lesions (Figure 3). In a study of 16 adult-onset MS patients evaluated using 7T MRI, a total of 100 subpial lesions were identified.³⁴ These lesions were best identified using T2* sequences, and appear either as small focal lesions or as band-like areas of hyperintensity that involved the outer cortical laminae and extend over an entire gyrus or multiple gyri. Despite using a comparable T2* sequences, we did not detect large numbers of subpial lesions. Whether subpial lesions would be demonstrated following further sequence optimization, or whether subpial lesions – unlike LC lesions – are indeed rare in pediatric-onset MS, remains to be determined.

We did not detect relationships between CL counts and clinical features, or CL counts and WM lesion volumes, potentially due to our small sample size.

All patients were receiving MS related medications, which conceptually may have influenced the number of CLs. Treatment effect on the accrual of white matter lesions has served as key secondary outcomes in pivotal clinical trials, but the ability of treatment to mitigate cortical pathology in MS has not been a major component of such trials.

Detection of CLs is influenced by the MR sequence and MR scanner strength. Our MPRAGE sequence was optimized to match the protocol proposed by Harrison et al, given that this group were able to detect cortical lesions in 97% of 36 adult MS patients imaged at 7T.¹⁵ These authors pre-selected MPRAGE over DIR based on earlier publications comparing the relative cortical lesion detection rate of these two sequences at 3T³⁵. We did obtain FLAIR sequences, however, 7T provided poor contrast on these sequences, which has been the experience of other investigators.³⁶ We found gradient-echo T2* images to be helpful in evaluating subpial lesions, but found that the long acquisition time of this sequence led to motion artifact which proved sub-optimal for overall CL detection.

In a study of 18 adult MS patients, 7T magnetization transfer (MT) imaging detected more IC lesions (mean 20 lesions per patient) compared to T2* images (mean 13 lesions), 7T MPRAGE images (mean 16 lesions), and 3T 3D DIR (mean 17 lesions).³⁷ We did not obtain MT images, as Siemens does not offer this sequence at 7T.

Automated lesion detection methods are not yet available for CL detection on 7T, and given the relatively limited experience with 7T MRI in MS, we employed an experiential learning curve approach to define our CL detection method. As we anticipated, manual identification of CLs is time-consuming, CLs are subtle, and consensus adjudication was essential to ensure confidence in CL identification. As such, the methods employed in this pilot work are not immediately translatable to inexperienced raters, but will inform our future optimization methods.

This study represents a pilot analysis of a small cohort of pediatric-onset patients, and our findings clearly await replication in a larger sample. We deliberately focused on adolescents and young adults, as these participants were able to tolerate scanning without sedation. We did not have IRB approval to scan healthy age-matched volunteers, but now that we have been able to demonstrate that 7T MRI was well tolerated, we will perform 7T MRI studies in both in MS patients and in age-matched controls in order to more precisely determine whether CLs are present in the youngest MS patients and to ensure that areas of cortical hypointensity are not 7T MRI features in normal youth.

Finally, given that 30-50% of pediatric MS patients have cognitive, but not physical disability³⁹, future studies will evaluate whether cortical pathology correlates with early cognitive impairment.

Acknowledgments

This study was supported by Institutional funds provided by The Children's Hospital of Philadelphia, and by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke.

Reference List

1. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med*. 2007; 356:2603–13. [PubMed: 17582070]
2. Absinta M, Rocca MA, Moiola L, et al. Cortical lesions in children with multiple sclerosis. *Neurology*. 2011; 76:910–3. [PubMed: 21383327]
3. Rocca MA, De ME, Amato MP, et al. Cognitive impairment in paediatric multiple sclerosis patients is not related to cortical lesions. *Mult Scler*. 2014; 21:956–9. [PubMed: 25392332]
4. Calabrese M, Seppi D, Romualdi C, et al. Gray matter pathology in MS: a 3-year longitudinal study in a pediatric population. *AJNR Am J Neuroradiol*. 2012; 33:1507–11. [PubMed: 22422186]
5. Geurts JJ, Bo L, Pouwels PJ, Castelijns JA, Polman CH, Barkhof F. Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology. *AJNR Am J Neuroradiol*. 2005; 26:572–7. [PubMed: 15760868]
6. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain*. 2005; 128:2705–12. [PubMed: 16230320]
7. Seewann A, Kooi EJ, Roosendaal SD, et al. Postmortem verification of MS cortical lesion detection with 3D DIR. *Neurology*. 2012; 78:302–8. [PubMed: 22218278]
8. Kidd D, Barkhof F, McConnell R, Algra PR, Allen IV, Revesz T. Cortical lesions in multiple sclerosis. *Brain*. 1999; 122:17–26. [PubMed: 10050891]

9. van HJ, Brink BP, de Vries HE, van d V, Bo L. The blood-brain barrier in cortical multiple sclerosis lesions. *J Neuropathol Exp Neurol*. 2007; 66:321–8. [PubMed: 17413323]
10. Sethi V, Yousry TA, Muhler N, et al. Improved detection of cortical MS lesions with phase-sensitive inversion recovery MRI. *J Neurol Neurosurg Psychiatry*. 2012; 83:877–82. [PubMed: 22807559]
11. Calabrese M, De SN, Atzori M, et al. Detection of cortical inflammatory lesions by double inversion recovery magnetic resonance imaging in patients with multiple sclerosis. *Arch Neurol*. 2007; 64:1416–22. [PubMed: 17923625]
12. Chen JT, Easley K, Schneider C, et al. Clinically feasible MTR is sensitive to cortical demyelination in MS. *Neurology*. 2013; 80:246–52. [PubMed: 23269598]
13. Geurts JJ, Roosendaal SD, Calabrese M, et al. Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI. *Neurology*. 2011; 76:418–24. [PubMed: 21209373]
14. de Graaf WL, Kilsdonk ID, Lopez-Soriano A, et al. Clinical application of multi-contrast 7-T MR imaging in multiple sclerosis: increased lesion detection compared to 3 T confined to grey matter. *Eur Radiol*. 2013; 23:528–40. [PubMed: 22898935]
15. Harrison DM, Roy S, Oh J, et al. Association of Cortical Lesion Burden on 7-T Magnetic Resonance Imaging With Cognition and Disability in Multiple Sclerosis. *JAMA Neurol*. 2015; 72:1004–12. [PubMed: 26192316]
16. Nielsen AS, Kinkel RP, Tinelli E, Benner T, Cohen-Adad J, Mainero C. Focal cortical lesion detection in multiple sclerosis: 3 Tesla DIR versus 7 Tesla FLASH-T2. *J Magn Reson Imaging*. 2012; 35:537–42. [PubMed: 22045554]
17. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983; 33:1444–52. [PubMed: 6685237]
18. Avants BB, Tustison NJ, Stauffer M, Song G, Wu B, Gee JC. The Insight ToolKit image registration framework. *Front Neuroinform*. 2014; 8:44. [PubMed: 24817849]
19. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging*. 2010; 29:1310–20. [PubMed: 20378467]
20. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008; 12:26–41. [PubMed: 17659998]
21. Mainero C, Louapre C, Govindarajan ST, et al. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging. *Brain*. 2015; 138:932–45. [PubMed: 25681411]
22. Cohen-Adad J, Benner T, Greve D, et al. In vivo evidence of disseminated subpial T2* signal changes in multiple sclerosis at 7 T: a surface-based analysis. *Neuroimage*. 2011; 57:55–62. [PubMed: 21511042]
23. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. *NeuroImage*. 2012; 62:782–90. [PubMed: 21979382]
24. Brownell B, Hughes JT. The distribution of plaques in the cerebrum in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1962; 25:315–20. [PubMed: 14016083]
25. Lumsden C. The neuropathology of multiple sclerosis. *Handb Clin Neurol*. 1970; 9:217–309.
26. Peterson JW, Bo L, Mork S, Chang A, Trapp BD. Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Ann Neurol*. 2001; 50:389–400. [PubMed: 11558796]
27. Bo L, Vedeler CA, Nyland HI, Trapp BD, Mork SJ. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J Neuropathol Exp Neurol*. 2003; 62:723–32. [PubMed: 12901699]
28. Vercellino M, Plano F, Votta B, Mutani R, Giordana MT, Cavalla P. Grey matter pathology in multiple sclerosis. *J Neuropathol Exp Neurol*. 2005; 64:1101–7. [PubMed: 16319720]
29. Kutzelnigg A, Faber-Rod JC, Bauer J, et al. Widespread demyelination in the cerebellar cortex in multiple sclerosis. *Brain Pathol*. 2007; 17:38–44. [PubMed: 17493036]
30. Albert M, Antel J, Bruck W, Stadelmann C. Extensive cortical remyelination in patients with chronic multiple sclerosis. *Brain Pathol*. 2007; 17:129–38. [PubMed: 17388943]
31. Geurts JJ, Bo L, Roosendaal SD, et al. Extensive hippocampal demyelination in multiple sclerosis. *J Neuropathol Exp Neurol*. 2007; 66:819–27. [PubMed: 17805012]

32. Papadopoulos D, Dukes S, Patel R, Nicholas R, Vora A, Reynolds R. Substantial archaeocortical atrophy and neuronal loss in multiple sclerosis. *Brain Pathol.* 2009; 19:238–53. [PubMed: 18492094]
33. Gilmore CP, Donaldson I, Bo L, Owens T, Lowe J, Evangelou N. Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. *J Neurol Neurosurg Psychiatry.* 2009; 80:182–7. [PubMed: 18829630]
34. Mainiero C, Benner T, Radding A, et al. In vivo imaging of cortical pathology in multiple sclerosis using ultra-high field MRI. *Neurology.* 2009; 73:941–8. [PubMed: 19641168]
35. Nelson F, Poonawalla A, Hou P, Wolinsky JS, Narayana PA. 3D MPRAGE improves classification of cortical lesions in multiple sclerosis. *Mult Scler.* 2008; 14:1214–1219. [PubMed: 18952832]
36. Zwanenburg JJ, Hendrikse J, Visser F, Takahara T, Luijten PR. Fluid attenuated inversion recovery (FLAIR) MRI at 7.0 Tesla: comparison with 1.5 and 3.0 Tesla. *Eur Radiol.* 2010; 20:915–922. [PubMed: 19802613]
37. Abdel-Fahim R, Mistry N, Mouglin O, et al. Improved detection of focal cortical lesions using 7T magnetisation transfer imaging in patients with multiple sclerosis. *Mult Scler Relat Disord.* 2014; 3:258–65. [PubMed: 25878014]
38. Akbar N, Banwell B, Sled JG, Binns MA, Doesburg SM, Rypma B, Lysenko M, Till C. Brain activation patterns and cognitive processing speed in patients with pediatric-onset multiple sclerosis. *J Clin Exp Neuropsychol.* 2016; 38:393–403. [PubMed: 26695705]

Figure 1. Cortical lesions visualized on 7T MRI

Figure 1 illustrates the appearance of cortical lesions (yellow and cyan arrows) in a 16 year old male patient diagnosed with MS six months prior to imaging. Yellow arrows point to leukocortical lesions (spanning the gray/white junction), cyan arrows to intracortical lesions (fully contained within the cortex). 1A shows the lesions identified in axial plane with inset magnified to demonstrate the cortical lesions in detail. 1B and 1C shows cortical lesions in sagittal and coronal planes, respectively.

Figure 2. Cortical lesions visualized on 7T MRI

Figure 2 shows leukocortical lesions in an 18 year old male MS patient, diagnosed with MS six years ago. a .

Figure 3. Subpial Lesions

Across the 8 MS patients studied, only 3 subpial lesions were identified on the T2* images. The T2* images had two echoes (echo 1 – brighter image, echo 2 – darker image). The subpial lesions identified were viewed simultaneously on the magnitude images for both echoes. In 3A, the arrows point to a representative subpial lesion that engulfs the whole sulcal/gyral crown on a T2* magnitude image (echo 2), while in 3B, the arrows point to a different subpial lesion that engulfs the whole sulcal/gyral crown on a T2* magnitude image (echo 1).

Table 1
Subject demographics, clinical information and cortical lesion counts

Subject	Age	Sex	Age at first attack (yrs)	Disease duration (yrs)	Annualized relapse rate	EDSS	Current disease modifying therapy	Total number of CLs	WM lesion volume (ml ³)
1	20	F	12	8	0.9	1.5	Natalizumab	60	7.1
2	18	M	12	6	0.3	1	Interferon beta-1a	144	8.8
3	20	M	17	3	1.2	0	Interferon beta-1a	117	26.5
4	25	M	17	8	0.4	3.5	Dimethyl fumarate	128	24.5
5	16	F	14	1.5	2	2	Interferon beta-1a	60	5.2
6	24	M	15	10	0.4	1	Natalizumab	124	42.5
7	16	M	16	0.5	0.3	3.5	Rituximab	166	22.5
8	22	F	18	3.9	0.8	2	Glatiramer acetate	48	5.0

Legend Table 1: cortical lesions (CL); Expanded Disability Status Scale (EDSS); female (F); male (M); white matter (WM); years (yrs)