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AJNR Am J Neuroradiol 1998, 19 (2) 235-238

<http://www.ajnr.org/content/19/2/235>

Increased Spatial Resolution Using a Three-dimensional T1-Weighted Gradient-Echo MR Sequence Results in Greater Hypointense Lesion Volumes in Multiple Sclerosis

Massimo Filippi, Mara A. Rocca, Mark A. Horsfield, Marco Rovaris, C. Pereira, Tarek A. Yousry, B. Colombo, and Giancarlo Comi

PURPOSE: Our goal was to evaluate whether improved spatial resolution of MR images results in the detection of higher volumes of hypointense lesions in patients with multiple sclerosis (MS).

METHODS: A magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence with subsequent reconstruction of axial sections with 5-, 3-, and 1-mm thickness and a dual-echo sequence were obtained in 16 patients with relapsing-remitting or secondary-progressive MS. The volumes of MR imaging abnormalities present on each of these studies were measured using a semiautomated segmentation technique based on local thresholding. The hypointense lesion volumes seen on the three reconstructed MP-RAGE sets of images were compared using the Friedman test and correlated with the hyperintense lesion volume on proton density-weighted images and with scores on the Expanded Disability Status Scale using Spearman's rank correlation coefficient.

RESULTS: The median volume of hypointense lesions increased from 1.2 mL (range, 0 to 14.9 mL) on the 5-mm-thick MP-RAGE images to 1.7 mL (range, 0 to 15.8 mL) on the 3-mm-thick images, and to 1.9 mL (range, 0 to 16.2 mL) on the 1-mm-thick images. The hypointense lesion volumes measured on the three MP-RAGE images correlated significantly with the degree of disability, whereas this correlation was not significant with the T2-weighted lesion load.

CONCLUSION: Our findings indicate that a significant increase in the volume of potentially disabling MS lesions is observed when obtaining MR images with thin sections.

The change in lesion load on yearly conventional T2-weighted magnetic resonance (MR) images of the brain is used as a secondary end point to monitor the effect of treatment in phase-III clinical trials in patients with multiple sclerosis (MS) (1). However, the correlation between changes in disability and T2-weighted lesion load is modest (2). More recently, measures obtained from several other MR tech-

niques, including MR spectroscopy (3, 4), magnetization-transfer imaging (5, 6), analysis of magnetization decay curves (7), hypointense lesion load on T1-weighted images (8, 9), and measurements of cervical cord cross-sectional areas (10, 11) have been found to correlate better with clinical disability. In particular, the percentage of change in the area of hypointense lesions on T1-weighted images correlates strongly with changes in disability in patients with secondary-progressive MS who have been followed up for about 4 years (8, 9).

Recently, it has been shown that the total lesion volume detected on unenhanced T2-weighted images of the brain using a section thickness of 3 mm is on average about 9% higher than that detected with conventional 5-mm-thick sections (12). Similar results have also been found for contrast-enhancing lesions using a magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence (13). This is a three-dimensional MR sequence that produces T1-weighted images with thin sections (14–16). The mag-

Received May 22, 1997; accepted after revision August 4.

Presented at the fifth meeting of the International Society for Magnetic Resonance in Medicine, Vancouver, British Columbia, Canada, April 1997.

From the Department of Neurology, MS Biosignal Analysis Center, Scientific Institute Ospedale San Raffaele, University of Milan (Italy) (M.F., M.A.R., M.R., C.P., B.C., G.C.); the Division of Medical Physics, University of Leicester (United Kingdom) (M.A.H.); and the Department of Neuroradiology, Klinikum Grosshadern, University of Munich (Germany) (T.A.Y.).

Address reprint requests to Massimo Filippi, MD, MS Biosignal Analysis Center, Department of Neurology, Scientific Institute Ospedale San Raffaele, Via Olgettina, 60, 20132 Milan, Italy.

netization is prepared using a 180° inversion pulse to give T1 contrast before two-dimensional phase encoding in a gradient-recalled echo sequence with low flip angle read-out pulses, producing a 3-D image volume. The 3-D image can be reconstructed in any plane and with different section thicknesses.

After imaging with the MP-RAGE sequence, we reconstructed axial sections of the brain in MS patients down to a 1-mm thickness in order to determine whether high-resolution MR imaging allowed detection of greater volumes of hypointense lesions than seen with conventional imaging.

Methods

Patients

Patients with either relapsing-remitting or secondary-progressive MS (17) were recruited from our MS population. To be included, patients must not have taken immunosuppressive or immunomodulating medications (including steroids) for at least 6 months prior to the study. In addition, the last relapse must have subsided at least 3 months before the study. At the time MR imaging was performed, each patient was examined neurologically, and disability was assessed by a single observer using the Expanded Disability Status Scale (EDSS) (18). Ten sex- and age-matched healthy volunteers were also imaged. Written informed consent was obtained from all subjects before inclusion in the study.

Sixteen patients (10 women and six men; 11 with relapsing-remitting MS and five with secondary-progressive MS) entered the study. The mean age (SD) was 32 (8.7) years, the mean duration (SD) of the disease was 5.8 (2.0) years, and the median EDSS score was 2.0 with a range of 1.0 to 5.5. For the 10 healthy volunteers (six women and four men), the mean age (SD) was 31 (4.5) years.

MR Imaging

Brain MR images were obtained using a system operating at 1.5 T. First, dual-echo spin-echo images were obtained with parameters of 2400/25–90/1 (repetition time/echo time/excitations), 5-mm contiguous axial sections, a matrix of 256×256 , and a field of view of 230 mm. Then, after intravenous administration of a standard dose (0.1 mmol/kg) of gadopentetate dimeglumine, the MP-RAGE sequence was used to acquire images with a sagittal acquisition slab. For the MP-RAGE sequence, the parameters were 10/4/1, an inversion time (TI) of 700, a relaxation time (TD) of 960, a flip angle of 10° , a matrix size of $256 \times 192 \times 160$, a field of view of 250 mm, a section thickness of 160 mm, and an acquisition time of 9 minutes 34 seconds. The effective TI (the time to the midline of k-space) was 1660 (Fig 1). This sequence was judged to result in good suppression of cerebrospinal fluid, very little gray/white matter contrast, and a hypointense lesion distribution similar in appearance to that of a conventional spin-echo sequence with short repetition and echo times (8, 9). The very short echo time minimized susceptibility-induced artifacts, even at the base of the skull. Reformatting of the original data was performed for the whole brain, and three sets of axial images, parallel to the line connecting the inferoposterior to the inferoanterior border of the corpus callosum (19), with section thicknesses of 5, 3, and 1 mm, were reconstructed for each patient. Reformatting was performed using the standard vendor-supplied multiplanar reformatting software available on the operator's console of the MR system.

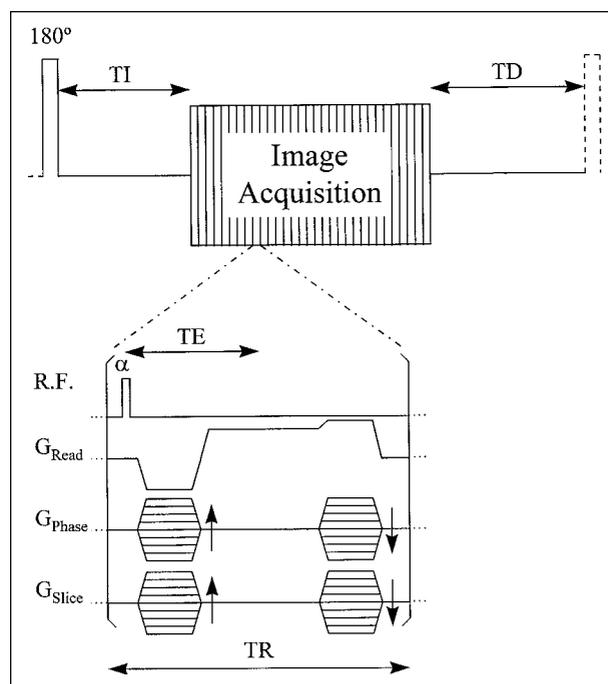


FIG 1. Schematic representation of the MP-RAGE pulse sequence. Magnetization is prepared with an inversion pulse and allowed to recover during the TI period, giving T1 contrast. The longitudinal magnetization is then sampled during the image acquisition phase. The image is formed by multiple, rapid repetitions of the pulse sequence, which is shown expanded. This is a gradient-echo sequence with a low flip angle of the read-out (α) pulses and phase encoding in two dimensions. The TD delay allows magnetization to return toward equilibrium before the next inversion pulse. The whole sequence is repeated (for our images, 160 times) with a different phase-encoding gradient amplitude in the section direction for each repetition. Thus, a 3-D T1-weighted data set was acquired in less than 10 minutes. The image contrast is determined largely by the time between the inversion pulse and the center of the image acquisition block; for our sequence, this was 1660 milliseconds.

Quantification of MR Imaging Abnormalities

Two observers evaluated the three sets of MP-RAGE sequences, each with different section thicknesses, and judgments were reached by consensus. Another independent observer, unaware of the aims of the present study, evaluated whether any abnormality was present on the images obtained in the control subjects. Hypointense lesions, judged as areas within the brain white matter with a signal intensity lower than that of the surrounding tissue, were marked on the hard copies for each of the MP-RAGE image data sets. Only hypointense areas that were considered lesions by both raters with high confidence were recorded as lesions (when possible, dual-echo images were used to increase the confidence for equivocal lesions). The same observers also marked the lesions present on the proton density-weighted images.

The volumes of hyperintense lesions on proton density-weighted images and of hypointense lesions on the three MP-RAGE sequences were measured by a single observer using the marked hard copies as a reference using a semiautomated segmentation technique based on local thresholding and characterized by high intraobserver and interobserver reproducibility (20, 21). With this method, the observer points the computer's mouse-controlled cursor near the edge of a lesion. The computer then searches an area around this point for the maximum local intensity gradient, which it considers to be the border of the lesion. It then follows a contour of isointensity so that the lesion is defined as an area of either hypoin-

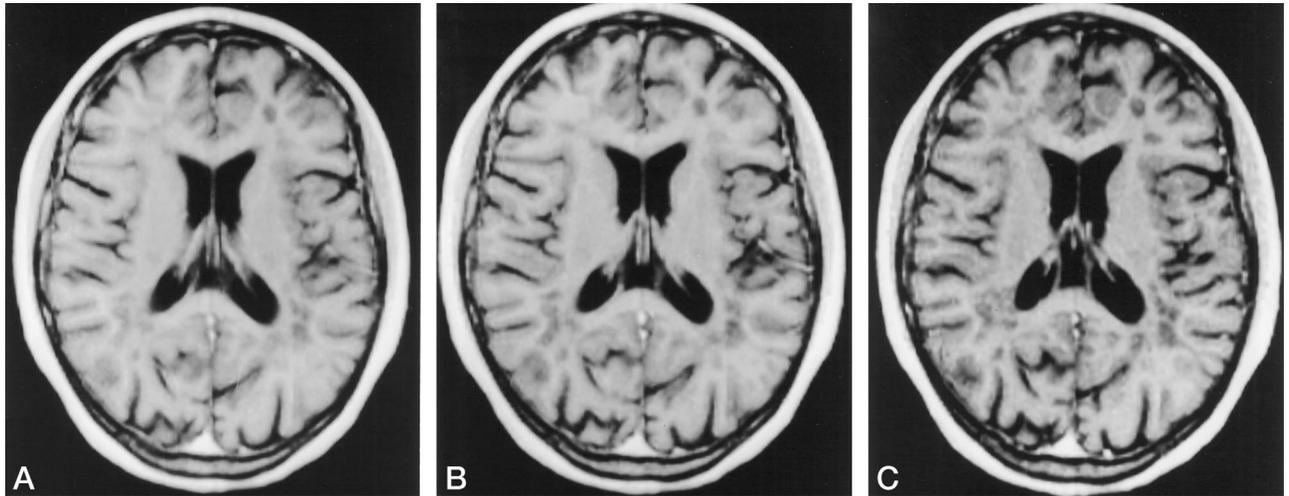


FIG 2. Axial MP-RAGE images of a patient with relapsing-remitting MS reconstructed at section thicknesses of 5 mm (A), 3 mm (B), and 1 mm (C). Some small hypointense lesions that are hardly visible in A are apparent in the deep white matter of the left hemisphere in B and with even greater clarity in C.

tensity (for lesions on the MP-RAGE images) or hyperintensity (for lesions on the proton density-weighted images) within the contour line.

Statistical Analysis

For each patient, the differences between hypointense lesion volumes seen on the three reconstructed MP-RAGE sets of images with different section thicknesses were calculated by using the Friedman test. Post-hoc analysis was performed using Wilcoxon's signed rank test. Correlating the volumes of the hypointense lesions on the three MP-RAGE sequences and the volumes of the hyperintense lesions on the proton density-weighted images with the EDSS scores was done by using Spearman's rank correlation coefficient (SRCC).

Results

No abnormalities were seen on any of the three MP-RAGE sequences in the healthy volunteers. The median volume of hypointense lesions increased from 1.2 mL (range, 0 to 14.9 mL) on the 5-mm MP-RAGE sequences to 1.7 mL (range, 0 to 15.8 mL) on the 3-mm MP-RAGE sequences (average increase, 22%) and to 1.9 mL (range, 0 to 16.2 mL) on the 1-mm MP-RAGE sequences (average increase versus 5-mm MP-RAGE, 33%; average increase versus 3-mm MP-RAGE, 14%) ($P = .0001$) (Fig 2). At post-hoc analysis, all the comparisons resulted in statistically significant differences (5-mm MP-RAGE versus 3-mm MP-RAGE, $P = .001$; 3-mm MP-RAGE versus 1-mm MP-RAGE, $P = .002$; 5-mm MP-RAGE versus 1-mm MP-RAGE, $P = .001$).

The hypointense lesion volumes measured on the three MP-RAGE sequences correlated significantly with the degree of disability (SRCC = 0.58, $P = .02$). The strength of the correlation was not different for the three MP-RAGE sequences, as the increased spatial resolution yielded a higher hypointense lesion load in all the patients studied, thus not changing the ranks of the correlation. The median lesion load on

the proton density-weighted images was 13.2 mL (range, 2.6 to 79.2 mL). The median ratio of MP-RAGE to proton density-weighted lesion load was 0.10 (range, 0 to 0.41). The lesion volume on proton density-weighted images was strongly correlated with the hypointense lesion volume on 5-mm MP-RAGE images (SRCC = 0.85; $P = .0001$), but not significantly correlated with the degree of disability (SRCC = 0.37).

Discussion

As previously demonstrated for lesion volumes on unenhanced T2-weighted images (12) and for the number of enhancing lesions on postcontrast MP-RAGE images (13), we found that the volumes of hypointense lesions also increase with improving MR spatial resolution.

Hypointense lesions on T1-weighted spin-echo images are considered evidence of a destructive pathologic process (8, 9, 22–24) and of a failure of remission (9), and changes in their area over time correlate well with changes in disability associated with MS (8, 9). The ability to monitor the evolution of such lesions over time is, therefore, of importance when planning phase-III clinical trials. This is reinforced by the fact that conventional T1-weighted spin-echo sequences are easier to obtain and to standardize than are other MR techniques. MP-RAGE sequences also yield T1-weighted images (14–16), which can be reconstructed in any plane and with different section thicknesses, thus allowing for a more complete evaluation of the hypointense lesion load present in patients with MS.

We found good correlation between hypointense MP-RAGE lesion load and disability, similar to that found previously using conventional T1-weighted spin-echo images (8, 9). When evaluating hypointense lesion volumes on T1-weighted images, it was previously speculated that using MP-RAGE sequences would increase the T1 contrast, making a broader

range of lesions hypointense, and resulting in a loss of specificity (9). However, the image parameters for the MP-RAGE sequence used in our study resulted in image contrast similar to that seen on a conventional short-repetition-time spin-echo image. This was evidenced by the fact that the hypointense lesion volume was still only 10% of the hyperintense lesion load on the T2-weighted images. In addition, the strength of the correlation between disability and hypointense lesion load using MP-RAGE was similar to that reported in two other studies (8, 9), and much higher than that found for the T2 lesion load, both in the present study and in previous investigations (2).

We obtained the MP-RAGE images after injection of contrast agent, as did van Walderveen et al (8) and Truyen et al (9). Thus, it is possible that some hypointense areas may have been missed because they enhanced and became isointense or hyperintense with respect to white matter. However, since contrast enhancement is thought to occur in lesions in which there are active pathologic processes, it may be that the removal of these lesions from an assessment of hypointense lesion burden increases the specificity when using this quantity as a marker for established disability.

Conclusion

We believe that the use of MP-RAGE sequences in MS is promising. This sequence can be performed in a reasonable amount of time, it is not difficult to standardize, and it enables the spatial resolution of MR imaging to be improved dramatically, thus allowing a more complete evaluation of the true burden of MS.

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