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Computer-Assisted Quantitation of Enhancing Lesions in Multiple Sclerosis: Correlation with Clinical Classification

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PURPOSE: To study the utility of a computer-assisted method of quantitating enhancing multiple sclerosis (MS) lesions and to correlate this quantitation with the type and duration of disease. **METHODS:** Forty untreated patients with MS were studied. The patients had been classified clinically as having either relapsing-remitting (n = 27) or chronic-progressive (n = 13) disease. Postcontrast contiguous 3-mm-thick MR images of the brain were obtained for up to 3 years. The computer program selected potential lesion sites automatically on the basis of the theory of "fuzzy connectedness," which was incorporated into 3DVIEWNIX software. True lesions were selected from these previously detected potential lesions by means of yes/no responses to the program query. The number of enhancing lesions and the enhancing lesion volume were subsequently computed. **RESULTS:** The enhancing lesion volume in patients with relapsing-remitting disease was statistically significantly higher than that of patients with chronic-progressive disease. There was a strong positive correlation between the number of enhancing lesions and the enhancing lesion volume. No significant correlation was noted between the change in score on the expanded disability status scale (EDSS) and the change in the number of enhancing lesions, or between the change in EDSS score and the change in enhancing lesion volume. A negative correlation was found between enhancing lesion volume and duration of disease, and between the number of enhancing lesions and duration of disease in the patients who had enhancing lesions. **CONCLUSIONS:** Our data suggest that enhancing lesion volume reflects differences in the classification of clinical MS and in the disease activity over time. Computer-assisted quantitation of enhancing lesion volume is a robust, practical, and objective measure of MS activity.

Index terms: Sclerosis, multiple; Brain, magnetic resonance; Brain, measurements; Computers

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Magnetic resonance (MR) imaging has been established as the imaging method of choice for monitoring multiple sclerosis (MS) lesions (1–4). A pathologic hallmark of an active MS lesion is the presence of perivenous inflammatory changes. Concomitant with some of these changes are transient abnormalities in the blood-brain barrier that are thought to be responsible for contrast enhancement in MR imaging. Contrast-enhanced MR images are more sensitive in showing lesion activity than are images obtained with a long repetition time (TR) (3, 5). Computer-assisted volumetry is needed to develop a method that objectively quantitates enhancement and determines efficacy in clinical therapeutic trials, because manual measurement is time consuming and can produce unacceptably high intraobserver and interobserver variability. In most of the previous studies, investigators have monitored enhancement by manually counting lesions or manually measuring the diameter of enhancing lesions (6–13), although there have been many attempts to measure the volume of MS lesions on T2-weighted MR images (14–21). A few studies

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have investigated enhancing lesion volume (ELV) (22, 23). Smith et al (22) and Frank et al (23) measured ELV by means of a computer software application; however, they did not describe the technique they used in that software. In this study, we used a newly developed computerized method to analyze lesion enhancement in the brain quantitatively and studied the utility of this method for quantitating enhancing MS lesions and for correlating this quantitation with the type and duration of disease.

Materials and Methods

Forty patients, 29 women and 11 men, 20 to 62 years old, with clinically definite MS as defined by Poser criteria (24), were entered into a prospective study. Among these, 28 patients were recruited from the Comprehensive Multiple Sclerosis Center of the Hospital of the University of Pennsylvania and were under the care of a neurologist specializing in MS. These patients were not enrolled in other clinical studies and were receiving only symptomatic treatment, such as antispasticity agents, analgesics, and bowel/bladder management when necessary. None were receiving immunomodulating therapy or chronic steroid therapy. Acute exacerbations were treated with brief courses (<15 days) of corticosteroids. An additional 12 patients with relapsing-remitting disease were recruited from an ongoing randomized double-blind placebo-controlled study of relapsing-remitting MS. Similar to the original 28 patients, these "placebo" patients received no immunomodulating therapy or chronic steroids and were treated for acute exacerbations with brief courses of corticosteroids when considered appropriate by their treating neurologist. The extent of disability was graded according to the Expanded Disability Status Scale (EDSS) (25). The patients had been classified clinically into either relapsing-remitting (n = 27) or chronic-progressive (n = 13) groups as follows: relapsing-remitting patients had at least two relapses over the preceding 2 years, with relapses defined as a new neurologic deficit or exacerbation of a previous deficit occurring in a previously stable patient confirmed by examination and developing over a period of 1 to 5 days and lasting at least 48 hours; chronic-progressive patients had an increase in their EDSS score of at least 1.0 over the preceding year without an acute exacerbation. Clinical examinations were carried out in a nonblinded manner by neurologists who specialize in the care of patients with MS. Written informed consent was obtained from each patient. All MR studies (129 for relapsing-remitting patients, 36 for chronic-progressive patients) were performed with a 1.5-T imager and with a quadrature transmitter/receiver head coil. These patients were imaged immediately after administration of 0.1 mmol/kg gadopentetate dimeglumine with a T1-weighted spin-echo sequence (600/27/1 [repetition time/echo time/excitation]), a 256 × 192 matrix, a 22-cm field of view, and interleaved, contiguous 3-mm-thick sections. In the period of more than 3 years, six patients were scanned once, four patients twice, six patients three times, eight patients four times, four patients five times, seven patients six times, two patients seven times, two patients eight times, and one patient nine times.

All raw image data were transferred from the scanner directly to a Sun Sparc 20 (Sun Microsystems, Mountain View, Calif) workstation (one processor, 256 MB RAM) via the picture archiving and communications system of our department. Our software running on the workstation selected and delineated potential lesion sites automatically using a method based on a new theory of "fuzzy connectedness" (26). The algorithms, described in a separate article (27), were implemented on this workstation with an internal version of a software system called 3DVIEWNIX developed in our department. A neuroradiologist then indicated which were the true lesions among these computer-detected potential lesions by clicking a mouse button (Fig 1). The total ELV and number of enhancing lesions (NEL) from each study were subsequently computed. It took about 5 minutes for the software to select and delineate potential lesion sites in one postcontrast MR examination comprising 48 sections. It took approximately 5 minutes to learn to use the software and approximately 1 minute of operator time per MR examination. The software had been tested by four examiners (seven patients, 336 sections), with 0% intraobserver and interobserver variability (27). The software had also been shown to have 1.3% false-negative volume fraction (27) (that is, the volume of the false-negative lesions as a percentage of the total true lesion volume).

To correlate NEL with ELV, data from the first studies of patients who had at least one enhancing lesion were used and Spearman's test was applied for analysis. To correlate change in EDSS score with change in NEL/ELV, data from the first and second studies of each patient who was scanned more than once were used and Spearman's test was applied. To analyze the change in ELV over the duration of the study, the ELV of the first and the last studies of each patient who was scanned more than once were used and Student's t test was applied. To correlate ELV with duration of disease, the average ELV per patient (ELV of all studies/number of studies for the patient) and average duration of disease among patients who had at least one enhancing lesion were used and Spearman's test was applied. Wilcoxon's rank sum test was used to compare ELV of the relapsing-remitting group with that of the chronic-progressive group and to compare NEL and ELV of the natural history group with those of the placebo group.

Results

Among the 165 studies, 55 (33%) showed at least one enhancing lesion in a total of 22 patients (55%). Eighteen (67%) of the relapsing-remitting patients and four (31%) of the chronic-progressive patients had at least one

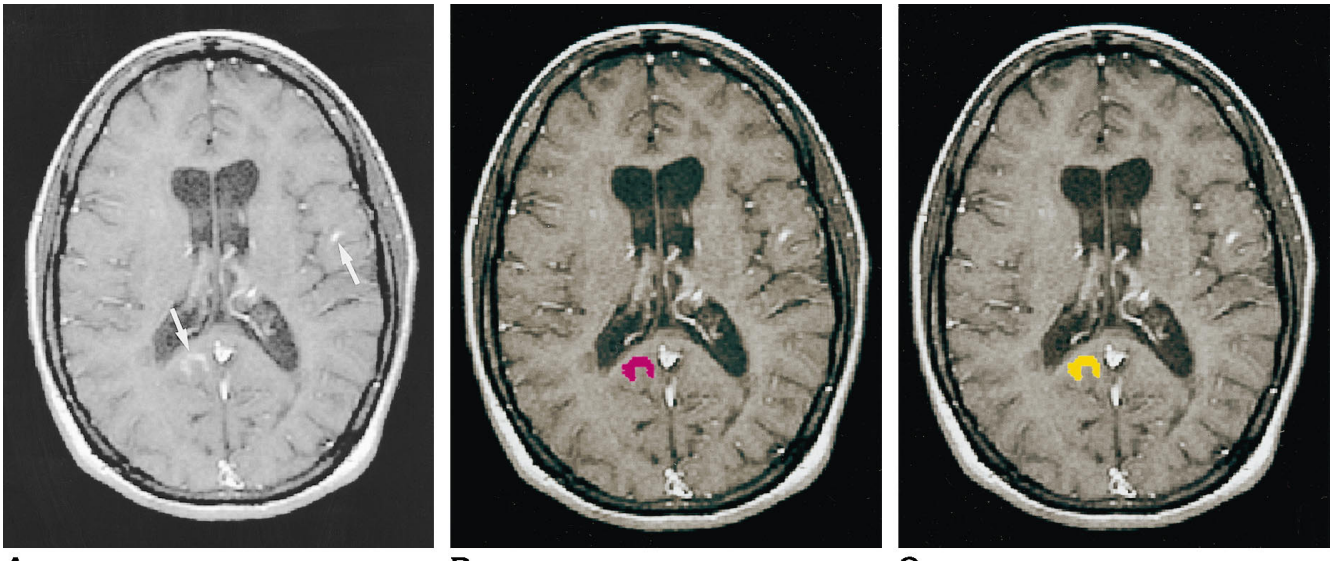

Fig 1. *A*, Contrast-enhanced T1-weighted MR image shows enhancing MS lesions (*arrows*).
B, During the verification step, the software shows potential lesions one by one (in red) to the operator.
C, After a "yes" response from the operator, the software changes the color of the lesion display (to yellow) to confirm acceptance of the potential lesion as a true lesion.

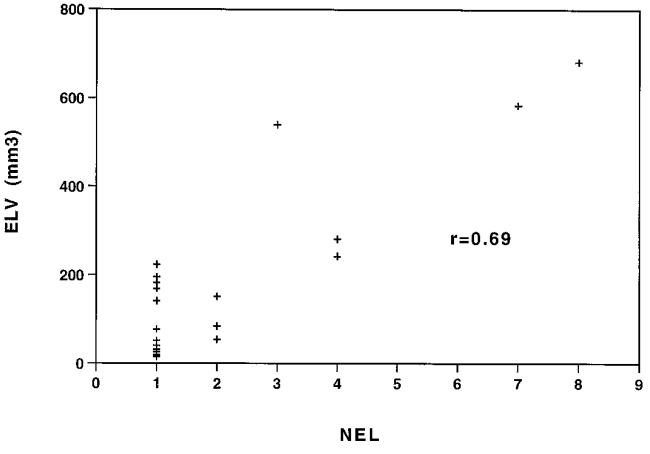

Fig 2. ELV is plotted versus NEL for the first study of each patient who had at least one enhancing lesion. The correlation coefficient is indicated (*r*). A strong positive correlation was noted between the NEL and the total ELV of each study.

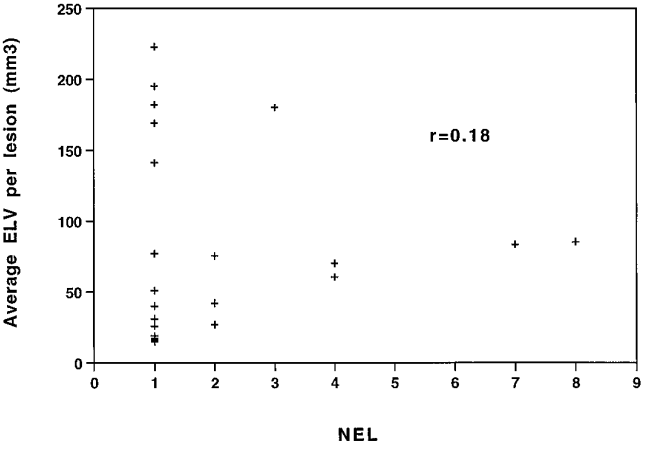

Fig 3. The average ELV per lesion is plotted versus NEL for the first study of each patient who had at least one enhancing lesion. The correlation coefficient is indicated (*r*). No correlation was noted between NEL and average ELV.

enhancing lesion. The average NEL over all studies was 0.92. The average NEL for the relapsing-remitting group was 1.01 (maximum, 15); the average NEL for the chronic-progressive group was 0.36 (maximum, 4). The average ELV over all studies was 62.7 mm^3. The average ELV for the relapsing-remitting group was 74.9 mm^3 (maximum, 1140 mm^3); the average ELV for the chronic-progressive group was 18.9 mm^3 (maximum, 281 mm^3).

We found a strong positive correlation between NEL and ELV ($r = .69$, $P = .0004$) (Fig 2), but no correlation between NEL and average ELV per lesion (ELV/NEL for each study) ($r = .18$, $P = .42$) (Fig 3). No significant correlation was noted between the change in EDSS score and the change in NEL ($r = -.28$, $P = .11$), or between the change in EDSS score and the change in ELV ($r = -.31$, $P = .07$) (Fig 4). A significant negative correlation was found between the average ELV per patient and average duration of disease ($r = -.62$, $P = .002$) (Fig 5) and between the average NEL per patient and average duration of disease ($r = -.44$, $P = .04$) for the patients who had at least one enhancing lesion. No relationship was found between du-

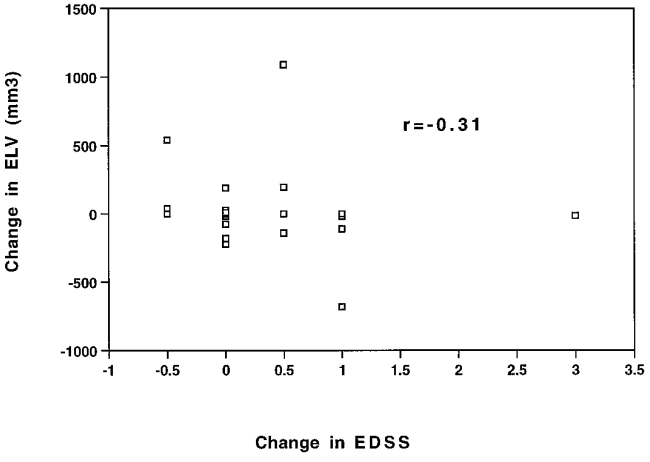

Fig 4. Change in ELV is plotted versus the change in EDSS score (unit changes of 0.5 U) between the first and second studies of each patient. The correlation coefficient is indicated (*r*). No correlation was noted between the change in the EDSS score and the change in ELV.

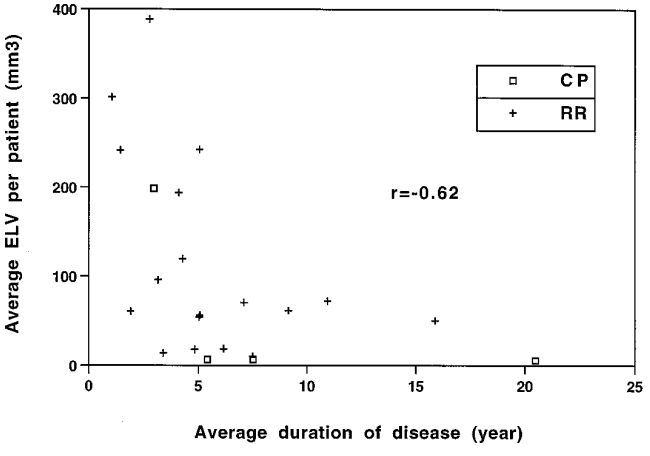

Fig 5. The average ELV is plotted versus average duration of disease in each patient who had at least one enhancing lesion. A statistically significant negative correlation was noted between ELV and duration of disease. The correlation coefficient is indicated (*r*). *CP* indicates patients with chronic-progressive disease; *RR* patients with relapsing-remitting disease.

ration of disease and proportion of patients with enhancing lesions. The ELV for the relapsing-remitting group was statistically significantly larger than that for the chronic-progressive group ($P = .04$). No significant differences were observed in ELV changes over the duration of the study between the two groups ($P = .83$). No significant difference of ELV or NEL was noted between the natural history study group and the placebo group ($P = .47$ and $P = .50$, respectively).

Discussion

MS lesions enhance after injection of contrast media because of a transient abnormality in the blood-brain barrier produced by a perivenous inflammatory process. Histopathologically, active lesions have been correlated with contrast enhancement (3, 28). Clearly, then, as a potential marker for histopathologic changes as well as for possible clinical changes in patients, it is important to quantitate enhancement to know the effect of therapeutic trials on disease activity. In this regard, both NEL and ELV are useful parameters to follow, since independent changes in either NEL or ELV have already been reported (22).

Many investigators have reported the findings in serial enhanced studies of MS (5, 6, 8–13, 22, 23, 29–41). In the two studies that investigated ELV with computer methodology, Smith et al (22) and Frank et al (23) used the computer software program Analyze (5.0.1) to measure ELV; they did not describe what technique they used on that software. Our study is based on the notion that computer algorithms are superior to humans in the delineation of objects and that humans are superior to computer algorithms in most recognition tasks. In our study, the functions of detecting potential lesion sites and determining their extent were fully automated on the basis of the theory of fuzzy connectedness in conjunction with fuzzy topological concepts (26), which enabled the suppression of intraobserver and interobserver variability of lesion delineation. Images are by nature fuzzy. Objects in the images, such as lesions, have two important characteristics: they have a graded constitution (ie, they are not binary) and the elements forming the object hang together in a fuzzy way. Both these characteristics are handled effectively by the fuzzy connectedness method.

In our method, an operator selects true lesions and discards false lesions from the computer-detected lesions. Thus, operator variability comes from the recognition task and not from the process of delineation. All computer-selected false lesion sites in this study were hyperintensities from vessels, fat, choroid plexus, or phase artifacts derived from blood flow, and were clearly differentiated from lesions by an experienced neuroradiologist (27). Our software was tested in seven patients (336 sections) by four examiners, with no intraobserver and interobserver variability (27). We

also used 3-mm-thick images to minimize problems with volume averaging that could have resulted in erroneous conclusions about lesions disappearing, decreasing, or increasing in size (42). More important, erroneous conclusions were minimized by the three-dimensional nature of the method, which detects each 3-D lesion as a 3-D fuzzy connected object, and by the fuzzy nature of delineation. We emphasize that lesion delineation in all 165 studies was determined to be accurate by visual examination by the neuroradiologist who participated in the verification step. We note that establishing the true accuracy of delineation in tasks in which true delineation cannot be established is still an open problem in image processing.

We found a statistically significant strong positive correlation between NEL and ELV (Fig 2), which is consistent with the findings by Smith et al (22), who reported that the ELV fluctuated in parallel with the NEL. There was no correlation between NEL and average ELV per lesion (Fig 3), suggesting that the volume of each lesion is independent of NEL. No correlation was noted between change in EDSS score and change in NEL/ELV (Fig 4), which is in contrast to the reports by Frank et al (23) and Khoury et al (43). This is not surprising, because enhancement per se does not necessarily equate with symptomatic lesions (6, 8), because some lesions may be located in areas in which they cannot cause physical disability, and because spinal cord lesions, which occasionally do cause severe disabilities, were not measured in this study. A negative correlation was found between average disease duration and average ELV/average NEL for each patient who had enhancing lesions, although there was no relationship between duration of disease and proportion of patients with enhancing lesions. This suggests that inflammation becomes less prominent as time goes on. This is also consistent with the notion that some relapsing-remitting diseases progress to chronic-progressive disease (44), which may have implications for therapeutic protocols. Although the relationship between blood-brain barrier disruption (enhancement) and long-term disability has not been established (23), it may be useful to have a long-term follow-up study of patients who have significant ELV in the early stage of their isease to understand the nature and variety of MS.

In our study, the ELV for the relapsing-remitting group was statistically significantly larger than that for the chronic-progressive group, which should be kept in mind in therapeutic protocols.

In conclusion, our data suggest that ELV reflects differences in the clinical MS classification and in the disease activity over time. Computer-assisted ELV quantitation is a robust, practical, and objective measure of activity of MS, which can be used to examine the efficacy of any existing or future therapeutic trials.

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