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AJNR Am J Neuroradiol 1999, 20 (10) 1951-1955
http://www.ajnr.org/content/20/10/1951

AJNR Am J Neuroradiol 20:1951–1955, November/December 1999

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BACKGROUND AND PURPOSE: **Multiple sclerosis (MS) is a demyelinating disease most often associated with progressive physical impairment; however, its effects are noted to extend beyond physical disability. Our purpose was to determine the relationship between T2 lesion volume and neurocognitive and physical disability in relapsing-remitting multiple sclerosis.**

METHODS: **We studied a cohort of 19 patients with relapsing-remitting MS. Of this group, there were 15 women and four men from varying socioeconomic backgrounds. This volunteer sample was selected from a larger group of 53 patients with MS in our longitudinal MS study because they had been untreated with any beta-interferon medications, had been followed for at least 12 months, and had a clinical status of relapsing-remitting MS.**

RESULTS: **Of 12 neurocognitive parameters tested, two correlated significantly with lesion loads. The correlation of the Symbol-Digit Modalities test, which analyzes information-processing speed, was significant ($P = .0204$). The correlation of the fifth trial of the Rey Auditory Verbal Learning test, which tests verbal long-term memory, was also significant ($P = .0348$). None of the other 10 neurocognitive examinations, however, showed a significant correlation with total lesion volume (Paced Auditory Serial Addition test-1.6, $P = .7381$; Paced Auditory Serial Addition test-2.0, $P = .4180$; Controlled Oral Word Association test, $P = .8906$; Category Fluency test, $P = .4423$; Bells test, $P = .9097$; Rey Auditory Verbal Learning test-delay, $P = .9843$, Rey Auditory Verbal Learning test-recognition, $P = .7467$; Word Span test, $P = .4939$; Road Map test, $P = 0.4939$). The lesion load also did not correlate with the physical disability scales as rated according to the Expanded Disability Status Scale ($P = .68$) or Ambulation Index ($P = .95$).**

CONCLUSION: **Our results indicate that T2 lesion volume does not seem to be a robust surrogate marker of neuropsychological impairment in patients with MS. We think that global measurements of parameters that are more specific to the disease process may offer more precise correlation with cognitive dysfunction and other disability parameters.**

Multiple Sclerosis (MS) is a demyelinating disease most often associated with progressive physical impairment; however, its effects are noted to extend beyond measures of physical disability. As early as 1877, it was recognized by Charcot that cognitive deterioration often accompanied MS. Cognitive impairment occurs in 40% to 70% of patients with MS (1−4). The estimate of the prevalence of cognitive dysfunction is diverse because of the widely varied populations studied and the differing methods of evaluation used. Disabilities in cognition usually take the form of difficulties with executive function, which includes working memory, problem solving, initiation and inhibition of responses, conceptual ability, strategic planning, and attention deficits. Long- and short-term memory and visuospatial perception are also often affected. Previously thought to be only a feature of advanced disease, cognitive dysfunction may actually begin during the early stages of disease and in the absence of physical disability (5). Recent studies indicate that cognitive impairment is not correlated with age, the level of physical disability, disease duration, disease type, or performance on standardized brief mental status examinations (6, 7). Instead, cognitive dysfunction seems to occur on a patient-specific basis.

Received May 26, 1998; accepted after revision, March 10, 1999.

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This work was supported in part by National Institutes of Health Grants NS29029, 5M01-RR00040, and 1R01-CA56071.

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Previous studies have attempted to show a correlation between MR imaging and the physical manifestations of MS as evaluated through the Kurtzke Expanded Disability Status Scale (EDSS) or the Ambulation Index (AI) (8). Nevertheless, there seems to be little or no correlation between the physical disabilities and lesion burden as reported by MR imaging (9−12). It has been suggested by Comi et al (4) that clinical status may be better correlated with spinal cord damage than with demyelinating plaques in the brain. Lesions in the brain may instead prove to correlate with neurocognitive dysfunction. Investigators have found a strong connection between the total surface area of MS plaques on MR images and cognitive abilities (13, 14). Other associations have been found between corpus callosum atrophy and ventricular dilation and cognitive dysfunction (15, 16). Nonetheless, little is known about the relationship between total lesion volume, as measured on proton density– and T2-weighted images, and neurocognitive ability. Assessing lesion burden in this manner may provide an important correlation with global disability.

This study examined the relationship between total lesion volume, measured by a highly reproducible validated semiautomated computerized technique, and neurocognitive and physical disability in a group of patients with untreated clinically definite relapsing-remitting MS. The neuropsychological tests conducted as part of this evaluation include batteries of tasks that involve working memory, attention, and information-processing speed. These tests are particularly sensitive to cognitive impairment and for predicting subsequent decline in MS. We also administered measures of visual and verbal anterograde memory and a small number of additional measures that have been found to be impaired in limited numbers of patients with MS, such as language and visuoperceptual functioning. As part of our analysis, we examined the lesion volume for each patient in our cohort and their EDSS and AI scores. We also evaluated the neurocognitive tests over time. This included repeat measurements of these tests. It must be noted that because there was no statistical correlation of these tests, no Bonferonni correction was indicated.

Methods

Participants

A cohort of 19 patients (15 women and four men) who were participating in a longitudinal study on the natural history of MS were included in this investigation. The study was approved by our institutional review board, and written informed consent was obtained for all participants. Each patient was diagnosed with clinically definite relapsing-remitting MS as defined by Poser et al (17) and had been followed up for at least 12 months; some had been followed up for up to 64 months. Patients who had been treated with beta-interferon medications were excluded from this study. The participants ranged in age from 26 to 53 years; the mean age was 36 years, with an SD of 7.59. At the time of enrollment in the study, patients underwent a complete neurologic workup, the full battery of neurocognitive examinations, and a comprehensive protocol of MR imaging. The patients underwent follow-up neurologic examination and MR imaging every 6 months after their initial visits. The data used in this study were limited to those obtained from visits during which the patients underwent all three examinations (MR imaging, neurologic examinations, and neurocognitive tests). All tests were completed within 4 weeks of each other.

Spearman correlations were calculated for each patient for each neurocognitive test and volume. The single-sample Wilcoxon test was used to determine whether the median correlation was significantly different from 0. The correlation between volume and time from the first visit was analyzed in this same manner.

Neurocognitive Evaluation

Cognitive functions of the participants were evaluated using a battery of standardized neuropsychological examinations. All testing was conducted by three technicians, trained and supervised by a neuropsychologist (M.G.). The testing was conducted in a quiet room with minimal visual or audible distractions. Periods of rest were provided during testing to minimize the effect of fatigue. The battery of tests can be subdivided into four categories (18). Category 1 includes executive functions and information-processing speed, category 2 consists of verbal long-term memory, category 3 encompasses verbal short-term memory, and category 4 evaluates visuospatial ability.

Category 1 (Executive Function and Information-Processing Speed).—The Paced Auditory Serial Addition test uses the serial addition of pairs of consecutive numbers presented continuously by audio tape at a set speed (19). The patient was asked to perform this serial addition at two speeds, a 1.6- and a 2.0-second interval. The number of consecutive correct additions was used as a score.

The spontaneous production of words beginning with a given letter (eg, ''F,'' ''A,'' and ''S,'') for 1 minute each (20) was tested using the Controlled Oral Word Association test. The number of correct target words that the patient produced on average in 1 minute was counted.

For the Category Fluency test, the spontaneous production of words in the ''animal'' class for 1 minute (21) was required. The number of correct target words that the patient produced in 1 minute was counted.

The Bells test involves the cancellation of target icons that are randomly distributed across a page intermixed with visually similar icons (22). The patient was asked to cancel the target icons, and the number of correctly identified icons was counted.

The oral version of the Symbol-Digit Modalities test requires the decoding of a series of visual symbols according to a template of paired numbers (23). The patient was asked to name the numbers corresponding to the symbol during a 90-second interval.

Category 2 (Verbal Long-term Memory).—The Rey Auditory Verbal Learning test, including delayed recall, consists of learning a list of 15 words that are orally presented. This test includes measures of learning over five learning trials, retrieval of the target list after presenting a distracter list and after a 30-minute delay, and recognition of the target words from among distracter words such as semantic and phonemic foils (24). The number of words correctly recalled by the participant on the fifth learning trial, after a 30-minute delay, and the number of target hits from the recognition list were all used in this analysis.

Category 3 (Verbal Short-term Memory).—The Word Span test is the sequential recall of increasingly longer lists of one-syllable words presented at a 1-second interstimulus rate. Stimuli are from three sets: imageable nouns from the same superordinate category, semantically unrelated imageable nouns, and semantically unrelated verbs. Forward and reverse measures were used for analysis.

Category 4 (Visuospatial-Perceptual Processing).—Road Map test was used to test the perception of extrapersonal spa-

TABLE 1: Individual Patient Profiles. Statistical analysis used the single-sample Wilcoxon test in order to determine positive correlations

ID/ Gender	Age at Entry	Months in Study	EDSS/AI Entry	EDSS/AI Exit	Number Neurocognitive Exams	Lesion Burden mm^3 Entry	Lesion Burden mm^3 Exit
1/female	39	43	2.5/1	7.5/7	7	17359	14285
2/male	42	60	2.5/0	2.5/1	9	395	146
3/female	47	51	2.5/1	2.5/1	9	4103	5851
4/female	21	12	1.5/0	2.5/1	3	7007	10492
5/female	38	31	2.5/1	6.0/4	3	11266	16911
6/female	40	14	3.0/2	3.0/2	3	4391	2848
7/female	45	30	4.0/3	3.5/2	5	884	1765
8/female	37	50	1.0/1	2.5/0	9	8547	11778
9/female	47	21	1.5/1	2.5/1	4	10592	10209
10/female	35	24	2.5/2	3.0/2	5	5144	4878
11/female	39	35	2.0/1	3.5/0	3	19277	9682
12/male	28	43	2.5/2	3.5/2	7	11122	11957
13/female	27	18	2.5/2	2.5/2	4	6462	13291
14/female	45	53	4.5/4	6.5/6	11	16607	13590
15/male	26	40	3.0/2	5.5/3	7	10417	14983
16/male	34	60	3.5/3	3.5/2	11	14239	10681
17/female	28	25	2.0/2	2.0/1	5	20884	34964
18/female	33	64	2.0/1	2.5/1	8	4185	2904
19/female	33	25	2.5/1	1.5/0	5	13129	12776

TABLE 2: Summary of clinical test results. Values represent correlations and significance between clinical performance versus T2 lesion volume

T2 Lesion Volume Versus:	*P* Value
EDSS	0.68
AI	0.95
Disease Duration	0.40
PASAT 1.6	0.74
PASAT 2.0	0.42
Controlled Oral Word Association Test	0.89
Category Fluency Test	0.44
Bells	0.91
*Symbol-Digit Modalities	0.02
*RAVALT-5	0.03
RAVALT-delay	0.98
RAVALT-recognition	0.75
Word Span	0.49
Road Map	0.49

* Indicates statistical significance.

tial relations. The patient was asked to describe the turns necessary to follow a route on a topographic map (25). The number of correct responses was used for analysis.

Imaging and Volume Estimation

MR studies were obtained approximately every 6 months using a Signa 1.5-T unit with a standard General Electric quadrature head coil. The imaging protocol consisted of 3-mm interleaved contiguous sections, covering the entire brain, with fast spin-echo sequences (16,60/2500 [first-echo TE, second-echo TE/TR]) with an echo train length of 8.

Using the theory of fuzzy connectedness (26–28), an internal version of the 3DVIEWNIX software system was used to detect, delineate, and quantitate lesions on the T2-/proton density–weighted images. The system selected potential lesion sites automatically. A qualified user then identified authentic lesions by responding yes to a yes/no software query regarding whether the selected region was in fact a lesion. The software program then calculated lesion volumes, taking into account all selected lesions. The inter- and intraobserver variability of this method has been shown to be low, with a 0.9% coefficient of variation for total lesion volume and a high sensitivity with a false-negative volume fraction of 1.3% (29). A single observer obtained all of the measurements.

Physical Evaluation

The extent of physical disability was determined by grading patients according to their EDSS and AI scores (8). These examinations were performed in a nonblinded manner by a single neurologist who specializes in the treatment of patients with MS (D.K.). For the EDSS evaluation, functional systems scores are given (range, score of 0–6) for each of eight areas of neurologic function: pyramidal, cerebellar, brain stem, mental, sensory, bowel and bladder, visual, and other. The EDSS is then determined from the functional systems scores, in conjunction with assessment of ability to walk, with a range from 0 to 10 (0 = completely normal, 10 = death as a result of MS). AI scores are evaluated based solely on the patient's ability to walk and reliance on an aid, such as from unilateral or bilateral support or wheelchair. The scores for this test range from 0 to 9.

Results

Table 1 shows the relevant patient parameters included in this study. For each patient, we list the EDSS and AI scores at entry and exit from the study along with total T2 lesion volume of the entire brain at both points. The total T2 lesion volume was compared with the neurocognitive test results and clinical test results for each patient over the duration (Table 2). Of 12 neurocognitive parameters tested, two correlated significantly with T2 lesion volume. The Symbol-Digit Modalities test, which analyzes information-processing speed, was significant, with a *P* value of .0204. The correlation of the fifth trial of the Rey Auditory Verbal Learning test, which tests verbal long-term memory, was also significant, with a *P* val-

ue of .0348. None of the other 10 neurocognitive examinations, however, which cover other tests of executive function, information-processing speed, and verbal short-term memory, showed a significant correlation with total lesion volume.

Furthermore, the T2 lesion volume also did not correlate with EDSS ($P = .68$) or with AI ($P = .95$). Table 2 summarizes the correlations between the lesion load measurements and the neurocognitive as well as physical tests.

Discussion

Although it has been reported that secondary progressive MS causes more frequent and severe cognitive deficits than relapsing-remitting MS, patients with relapsing-remitting MS have also reported a decline in cognitive function (30, 31). It is interesting to note that our group found no significant change in neurocognitive examination data over the duration of the study. Additionally, our results reveal a significant correlation between clinically definite relapsing-remitting MS and performance on only two of 12 standardized neuropsychological tests. The tests reflect performance of executive function and learning. There may be several possible explanations for this result. The neuropsychological testing may be relatively insensitive, T2 lesion volume is nonspecific with a spectrum of pathologic abnormalities appearing similar (high signal on T2-weighted images), and lesion location, which we did not assess, may be important. Some or all of these variables may act together to influence cognitive disability.

MS lesions are heterogeneous histopathologically, consisting of areas with gliosis, demyelination, remyelination, edema, and neuronal loss. The relationship between high-intensity abnormalities on MR images and the pathologic substrate is not fully understood. Several recent publications, however, have suggested that T2-weighted images are not adequately sensitive to predict the pathologic basis of hyperintense lesions (32–34). More sensitive imaging techniques, including MR spectroscopy, magnetization transfer, and T1-weighted hypointensity measurements may produce more robust correlations with neurocognitive data and other disability measurements (35, 36).

The ultimate effect of white matter disease on the neuron is still in question. Using MR spectroscopy, it is possible to observe a decrease in the ratio of *N*-acetylaspartate to creatine with severe acute or chronic demyelination. In their 1994 study, Arnold et al (33) found statistically significant changes in *N*-acetylaspartate:creatine ratios without statistically significant changes in total MR imaging lesion volume. This indicates that MR spectroscopy may be a more sensitive index of disease progression and may yield more significant correlations than does MR imaging. Furthermore, normal-appearing white matter on T2-weighted images may contain microscopic changes that are significant in terms of brain function. Narayanan et al (34) compared average metabolite levels and T2-weighted images, noting that diffuse axonal volume loss or dysfunction extends beyond areas of inflammation and could be caused by microscopic disease or wallerian degeneration. T1 and T2 relaxation times in normal-appearing white matter were reported to be significantly abnormal in patients with MS compared with those normal participants (37–39). Other studies using magnetization-transfer imaging have also revealed abnormalities in normal-appearing white matter (40, 41).

Lesions that appear similar on T2-weighted images may have profoundly different effects on neuronal function and neurologic performance. Comi et al (11) believe that cognitive dysfunction seems to be determined by the disruption of neuronal connections in the cortical associative areas and those areas between the cortical and subcortical structures. This interference seems to be induced by demyelination and axonal degeneration. Thus, lesions that are similarly hyperintense on T2-weighted images can have variable histopathologic substrates and potentially very different effects on cognitive performance.

Our studies indicate that T2 lesion volume in cases of MS is correlated to several specific markers of cognitive function (Symbol-Digit Modalities test and Rey Auditory Verbal Learning test), but the T2 lesion volume is not predictive of global cognitive dysfunction. In addition, we did not find a relationship between lesion load and disability as measured by EDSS or AI. This also may reflect the lack of histologic specificity of T2 lesions, the insensitivity of the EDSS system to subtle changes in neurologic function, and the reliance on intracranial lesion measurements exclusive of the spinal cord, which has a predominant role in motor disability (a significant portion of EDSS or AI) in cases of MS. The lack of better correlations may also be due in part to the relatively small number of patients examined in this particular study or to the fact that our participants were limited to patients with relapsing-remitting MS. In their 1989 article, Rao et al (13) suggested that a critical threshold of lesion load must be surpassed for cognitive dysfunction to be detected. In our series of patients, it may be that those who had lower lesion loads were experiencing some cognitive dysfunction that was missed by our test battery. It has also been suggested that lesion load may be less important than lesion location when determining cognitive disability (38). A small lesion in a critical area could do more damage than a large lesion in a less eloquent area of the brain. Because we did not segregate lesions in terms of location, our results do not reflect this possibly important differentiation.

We recognize that clinical function in patients with MS is highly variable. Therefore, as has been suggested by Beatty et al (31), correlating a unified neuropsychological profile to T2 lesion volume in patients with MS may be as difficult as correlating other clinical parameters, such as EDSS and AI

(31). We think that more specific global measurements of disease may offer more precise correlation with cognitive dysfunction and other disability parameters.

Conclusion

Our results indicate that T2 lesion volume does not seem to be a robust surrogate marker of neuropsychological impairment in patients with MS. We think that global measurements of parameters that are more specific to the disease process may offer more precise correlation with cognitive dysfunction and other disability parameters.

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