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MR-Based Brain and Cerebrospinal Fluid Measurement after Traumatic Brain Injury: Correlation with Neuropsychological Outcome

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PURPOSE: To determine the magnitude and time course of changes in the volume of brain and intracranial cerebrospinal fluid (CSF) spaces in patients who have sustained traumatic brain injury and to assess the relationship between these findings and long-term cognitive outcome. METHODS: Axial intermediate and T2-weighted MR images of 123 patients with traumatic brain injury were quantified using a multispectral segmentation algorithm. Measurements were corrected for differences in age, sex, and head size using a previously reported normative database. Brain morphology was compared across groups formed on the basis of chronicity of injury. Cognitive functioning and severity of injury were statistically correlated with brain measurements. RESULTS: Time-dependent expansion of CSF spaces and decreases in brain volume were observed. Increases in ventricular CSF volume, particularly in the temporal horns and third ventricle, preceded subsequent changes in total brain and subarachnoid CSF. High and moderate correlation was observed between volume measures and cognitive outcome and injury severity. Particularly strong was the relation between the volume of the left temporal horn and verbal IQ scores. CONCLUSION: Predictable time-dependent atrophic changes occurring after traumatic brain injury can be quantified using MR volumetric studies. Our results suggest significant contributions by both diffuse and focal mechanisms of injury. In the postacute period (more than 70 days after injury), MR volumetric studies may be predictive of eventual cognitive outcome.

Index terms: Brain, injuries; Brain, measurements; Brain, magnetic resonance


The basic pathology of traumatic brain injury has been described with increasing refinement over four decades (1–8). Based primarily on postmortem material, these studies have provided a detailed understanding of the spectrum of lesions, from focal to diffuse, that occur in the brain after blunt trauma. With the development of computed tomography (CT) and, subsequently, magnetic resonance (MR) imaging, the basic radiologic-pathologic correlates in traumatic brain injury have been reported at a descriptive level (9–16). More recently, methods of MR-based volumetric quantification have been developed (17–19) and successfully applied to the study of a variety of abnormalities of the central nervous system (20–24). Focal and diffuse lesions seen in traumatic brain injury can cause abnormal signal intensity on MR images and may result in atrophic changes. MR-based volumetric studies are ideally suited to the quantitation of these atrophic changes in vivo. To that end, we prospectively studied a cohort of patients with traumatic brain injury, quantifying volumes of brain and intracranial cerebrospinal fluid (CSF) compartments. Individual measurements were corrected for differences related to age and sex as well as for differences in total intracranial volume based on a recently reported normative database (25). A cross-sec-
tional characterization of the time course of these morphologic changes and their relationship to neuropsychological outcome are the focus of this article.

Subjects and Methods

Subjects

One hundred ninety-eight healthy volunteers, including males and females in each decade from 16 to 65 years, constituted the control population of our study. Images of these subjects formed the database for a recently reported MR-based study of the changes in brain and CSF volume that occur with normal aging (25). These volunteers were recruited primarily from hospital and university staff and their friends and family. Exclusion criteria consisted of previous head injury causing loss of consciousness; any disease primarily affecting the nervous system, including dementia or psychiatric illness; and a history of alcohol or drug abuse.

The traumatic brain injury group consisted of 123 patients who met the minimum criteria for brain injury as delineated by Evans (26). Injuries were generally in the moderate to severe range. The mean admission score on the Glasgow Coma Scale (GCS) was 8.07 (standard deviation [SD], 3.75; range, 3 to 15). Of the 123 patients included in the study, 112 were initially admitted to the hospital trauma service. Eleven additional patients were initially treated elsewhere. In 59 patients, MR images were obtained during admission to the intensive care unit or rehabilitation facility on the basis of clinical indications. In addition, all patients admitted to the rehabilitation unit were invited to participate in the study by undergoing MR and neuropsychological testing in follow-up studies 6 to 18 months after injury. Participation was limited, however, on the basis of patients' proximity to the hospital and by their consent and that of their families. Patients who were too severely impaired to undergo neuropsychological testing were excluded. The images and subsequent analyses were performed in compliance with a protocol established by an institutional review board, and all participants gave informed consent.

To understand the time course of changes in the volume of brain and CSF after traumatic brain injury, we divided the patients' studies into five arbitrarily determined subgroups on the basis of the delay from injury to MR examination. Group 1 included all patients imaged 1 to 21 days after injury (mean, 13 days; n = 19); group 2 comprised patients imaged 22 to 70 days after injury (mean, 42 days, n = 22); group 3 was made up of patients imaged 71 to 210 days after injury (mean, 136 days, n = 22); group 4 included patients imaged 211 to 500 days after injury (mean, 310 days, n = 30); and group 5 contained all patients imaged more than 500 days after injury (mean, 1367 days, n = 44). Twenty-one subjects were imaged at two different times and are thus included in more than one group. An additional comparison group was made up of the imaging studies of 129 healthy subjects from the first three decades of the previously described normative database (16 to 45 years) (25).

Imaging

MR images were acquired on a GE Signa scanner at 1.5 T with the use of both 4x and 5x software platforms (General Electric, Milwaukee, Wis). Sagittal T1-weighted (500/11/2 [repetition time/echo time/excitations]) images were acquired and used for location. Axial intermediate and T2-weighted (3000/31.90/1) spin-echo images were then obtained covering the area from the foramen magnum to the convexity of the inner table of the skull. The section thickness was 5 mm with an interspace gap of 1.5 or 2.0 mm. A 22-cm field of view was used with a 256 × 192 acquisition matrix. Imaging parameters included flow compensation, an inferior saturation pulse, and variable bandwidth.

Volumetric Image Analysis

The axial intermediate and T2-weighted spin-echo images were processed using Analyze (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn) (27) running on Sparc 10 work stations (Sun Microsystems, Mountain View, Calif). Because Analyze requires the multispectral segmentation only with eight-bit images, the original 16-bit images were converted by linear interpolation to eight-bit images using the load command. The images were then archived permanently onto an optical disk using a lossless compression algorithm. A multistep volume analysis was then performed using several image processing tools available in Analyze, including multispectral tissue segmentation, interactive image editing, and region-of-interest pixel counting. The multispectral tissue segmentation was performed in a manner similar to that described in a previous report (25). Regions of CSF, white matter, and gray matter were defined by the user and plotted in a two-dimensional feature space in which the pixel signal intensity on the T2-weighted sequence was the value on the x-axis and the pixel intensity on the intermediate-weighted image was the value on the y-axis. A k-nearest neighbor multispectral algorithm (28, 29) was then applied to the pixels of the entire section. Because of inhomogeneity in the sensitivity of the radio frequency coil, the same feature-space map could not be applied successfully to all the images of the study, particularly the more inferior sections, in which the sensitivity of the radio frequency coil was slightly decreased. For these sections, separate feature-space maps were generated.

The classified images were edited using a manual trace tool to remove pixels representing the calvaria and extracranial soft tissues. The inner table of the skull was used as the landmark for separation of intracranial versus extracranial compartments. All the pixels assigned to each segmented category (gray matter, white matter, CSF) were then summed over all of the classified, edited images from foramen magnum to vertex. Subregions of interest that included the lateral ventricles, the temporal horns of
Correction was performed by multiplying each measured volume, nor do they differ between the sexes (25). This correction is necessary as long as all of the desired CSF-containing structure was included along with some surrounding brain parenchyma. The pixels assigned to CSF in these subregions were summed.

The total brain volume was determined by summing the white and gray matter pixels and then multiplying by the voxel dimension. Total ventricular volume was obtained by summing the measurements of the lateral ventricles and the third and fourth ventricles. The subarachnoid CSF volume was obtained by taking the difference between total CSF volume and total ventricular volume. The total intracranial volume was obtained by summing the total brain and total CSF volumes. The ventricle-to-brain ratio was calculated by dividing the total ventricular volume by the total brain volume and multiplying by 100.

Operator processing time for volumetric analysis was about 30 minutes per patient. Intrarater and interrater reliability have been reported previously (25). Reliability for most measures exceeded a correlation of \( r = .90 \), except for the third ventricle, which was \( r = .86 \).

Neuropsychological Tests

Neuropsychological testing was administered via established methods (30). Because of the multitude of potential neuropsychological measures of cognitive outcome and the potential for type I statistical error, we restricted the neuropsychological analysis to a measure of global intellectual function, the Wechsler Adult Intelligence Scale–Revised (31), and a measure of memory function, the Wechsler Memory Scale–Revised (32). These functions are typically affected in traumatic brain injury and scores on these measures can be considered critical global indicators of cognitive outcome (33).

The timing of the neuropsychological testing was dependent on the patient’s functional status. For patients in whom MR studies had been obtained in the early period following injury, the neuropsychological testing was usually delayed until late in the rehabilitation stay. For patients studied in the follow-up period, the neuropsychological testing was nearly always obtained on the day of the MR examination. For patients with neuropsychological data available from both early and late time periods, the later data were considered to reflect cognitive outcome most accurately and were used for correlation with volume measurements. The mean delay from injury to cognitive testing was 470 days (SD, 674 days).

Correction for Head Size

The total intracranial volume was used to correct all the other measures for head size, except the temporal horns, since these do not correlate with age or total intracranial volume, nor do they differ between the sexes (25). This correction was performed by multiplying each measured volume by a ratio of the mean total intracranial volume for the entire normative population divided by the observed total intracranial volume for each subject.

Two further corrections were used. One correction was obtained by dividing the total intracranial volume–corrected measurement by the appropriate age and sex group mean (also total intracranial volume corrected) for that structure. This normalization yields a ratio for which the expected value is 1; that is, the patient value divided by the mean of the appropriate age and sex group in the normative database. The other correction procedure used standard scores (z scores) based on the expected value (mean) of the normative sex and age groups.

Statistical Analysis

Volume measurements for all six groups were subjected to simple one-way analysis of variance (ANOVA). In this comparison, the volume measures of patients with traumatic brain injury and control subjects were corrected for differences in total intracranial volume, but not for possible differences based on sex and age. This way, volume measures could be reported (see Table 1). Further graphical analyses of group means that characterize postinjury atrophic change were also performed, in which each patient’s volume measures were normalized to the expected value for their age and sex.

Volume measures were correlated with neuropsychological measures of outcome. For these correlations, volume measures were first converted to z scores using the appropriate age decade and sex of the normative group. We used this method of normalization because a ratio correction introduces additional variance into the correlation that may make it less interpretable. Further, the covariance with total intracranial volume was partialled out of each correlation.

Results

Demographics

The 123 patients with traumatic brain injury included 83 male and 40 female subjects. The mean age at injury of the entire population was 22 years (SD, 9; range, 16 to 68 years). There were no significant differences in age at injury based on sex or delay to imaging. Similarly, there were no significant differences in the initial GCS score based on sex or delay to imaging. The mean initial GCS score was 8.07 (SD, 3.51; range, 3 to 15).

Volume Changes after Injury

Table 1 provides a comparison of the brain and CSF volumes between healthy subjects and patients with traumatic brain injury. The patients’ studies were divided into five groups on
the basis of time between injury and imaging. As expected, total intracranial volume did not change significantly among groups. However, systematic changes in the brain and ventricular volume measurements were observed in the patients with traumatic brain injury as compared with the control group. By the fifth group, all intracranial structures, with the exception of the fourth ventricle, were significantly different from those of control subjects. Five CSF compartments in group 5 were significantly different from those in group 1, and two CSF compartments (total CSF and subarachnoid CSF) were also significantly different from group 2. In group 4, brain volume was statistically different from that of control subjects and from patients in group 1, and brain volume in group 5 also differed from that in group 2. Measurements of the left temporal horn, the third ventricle, and the lateral ventricle were the first to become significantly different from normal, reaching significance by group 2.

Time Course of Change after Injury

The mean normalized ratios for each group are plotted in Figure 1. Since these are normalized values, the zero time point in Figure 1 represents the mean value from the normative database and is always equal to one. The changes in brain volume are shown in Figure 1A and B. In Figure 1A, the mean brain volume is shown by group. There was a small but nonsignificant increase in brain volume in group 1 compared with control subjects. Since the mean delay in this group was only 13 days, this may represent residual cerebral edema. Beginning with group 2, there was a progressive decrease in total brain volume from normal continuing through group 5 and reaching significance in groups 4 and 5. In Figure 1B, the mean normalized brain volume for each group is plotted with the x-axis representing the postinjury delay in days rather than by group number. It can be seen that after the slight increase observed in group 1, the subsequent decline qualitatively appears to be exponential in nature. Since the traumatic brain injury volumes are normalized for age and sex, any decline in the traumatic brain injury population curve due to aging should have been eliminated. The rate of change in brain volume associated with normal aging is shown for comparison. In previous work, we observed that in a healthy male population, an early linear decline in total brain volume occurred during the four decades from 16 to 55 years at the rate of approximately 0.265% per year (25). The decline for a similar healthy female population was 0.223% per year.

Significant enlargement in the subarachnoid CSF volume was observed that almost exactly mirrored the changes in total brain volume (Fig 1A) where significant differences were observed in groups 4 and 5. Changes in the ventricular system are shown in Figure 1C. Enlargement of the ventricles, particularly the temporal horns, occurred earlier and were relatively much larger than changes in the total brain volume. The

<table>
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<th>TABLE 1: Quantitative volume measures: comparison of control subjects and patients with traumatic brain injury</th>
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<td>Control Group</td>
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<td>(n = 129)</td>
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<td>Mean</td>
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<td>Total intracranial volume</td>
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<td>Ventricle-to-brain ratio</td>
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Note.—All measures excluding temporal horns are corrected for total intracranial volume.
* Significantly different from control group ($P < .05$), using Tukey’s Studentized range statistic.
† Significantly different from injury group 1 ($P < .05$), using Tukey’s Studentized range statistic.
§ Significantly different from injury group 2 ($P < .05$), using Tukey’s Studentized range statistic.
mean temporal horn volume showed a 2.3-fold increase in group 1 patients, progressing to a 3.7-fold increase in group 3 patients. In group 4, the temporal horn volume returned somewhat to normal, yet remained significantly enlarged. The volume of both the lateral and third ventricles showed a relatively smaller but progressive increase among the first three groups. Subsequent to group 3, the third ventricle remained relatively constant. The volume of the lateral ventricle and temporal horn increased again in the last group.

Correlation with Neuropsychological Outcome

Table 2 gives data for cognitive performance after injury. Consistent with previous reports, we observed significant reductions in the scores on verbal, performance, and full-scale IQ tests as compared with normative standardized test scores. Verbal and general memory indexes were also significantly reduced, whereas visual memory was not significantly below normal for this sample of patients.

In Table 3, the volume standard scores were correlated with selected neuropsychological tests where covariance with total intracranial volume was removed from the correlation. In order to minimize type I statistical error, and because the volume measurements were undergoing significant change during the first weeks after injury, correlations are shown only for group 3 (70 to 210 days after injury). A highly significant correlation was observed between verbal IQ score and left horn volume ($r = -.74$, $P = .0001$). Total brain volume also correlated with verbal IQ score ($r = .57$, $P = .007$). Significant correlations were observed between performance IQ score and volume measures that reflect global atrophy, including brain volume and total CSF, lateral ventricle, and third ventricle volumes. Only one of these global volume measures, brain volume, correlated with verbal IQ score. Third ventricle and brain volumes
were the only measures that related significantly to verbal memory. Visual memory was not correlated with any volume measurement. The admission GCS score was significantly related to several volume measurements. In particular, high correlations were observed between GCS score and third ventricle volume \((r = .52, P = .003)\) and between GCS score and lateral ventricle volume \((r = .55, P = .001)\).

To show how the relationship between cognitive outcome and MR volumetric studies changed with time, Figure 2 plots the correlations between left temporal horn volume and verbal IQ score and between lateral ventricle volume and performance IQ score as a function of time (delay group). Figure 2A shows the relationship between the left temporal horn volume and verbal IQ score. In group 1, a significant positive correlation was found \((r = .67, P = .015)\). No significant correlation was observed in group 2. In group 3, the correlation became negative and highly significant \((r = -.74, P = .0001)\). This relationship remained significant in subsequent groups, although the strength of the correlation diminished slightly.

In Figure 2B, the relationship between performance IQ score and lateral ventricle volume is shown as a function of time since injury. In the
first two groups, no significant correlation was observed. In group 3, the correlation became negative and significant \((r = -0.55, P = .01)\). In groups 4 and 5, the correlation remained negative but was statistically significant only for group 5.

**Discussion**

Numerous studies derived from autopsy material have provided an understanding of the basic pathology of lesions that result from non-penetrating traumatic brain injury \((1-6, 8)\). These studies describe evidence of both focal and diffuse brain injury in the neuropathology of patients with acute traumatic brain injury. Focal injury is thought to occur when the brain impacts against the rigid inner table of the skull with resulting areas of direct cortical contusion. Although any region of the brain surface can be involved, these focal, cortical injuries most commonly involve the anterior and inferior frontal and temporal lobes and the occipital lobes.

Although the importance of diffuse injury has been recently reemphasized by several authors \((5-8)\), the mechanisms and neuropathology of diffuse brain injury were described several decades ago \((1-4)\). Complex decelerations, particularly rotational, can result in shearing forces at interfaces of regions of the brain with differing structural integrity, such as at gray–white matter boundaries. Neuronal axons that cross multiple brain regions are particularly vulnerable to injury. Recently, several authors have increasingly ascribed the cognitive and functional impairment that follows traumatic brain injury to this mechanism of diffuse axonal injury \((5-8)\). The imaging correlates of diffuse axonal injury have been extensively described \((9-16)\).

Neuropsychological performance following traumatic brain injury has been shown to correlate with CT-based measurements of ventricular enlargement \((34)\). However, artifacts on CT scans make quantitation difficult in important regions of the brain, and volumetric assessment of the subarachnoid space is impossible because of the partial volume effect of adjacent bone. Thus, CT-based measurements have been limited to planimetric quantification of a restricted number of sections through the lateral ventricles.

Several studies have correlated MR findings with measures of cognitive outcome \((35-37)\). For example, Levin et al \((38)\) studied a sample of 20 patients with moderate traumatic brain injury, comparing MR and CT findings in the first few days after injury and correlating both with neuropsychological test results obtained during hospitalization. A limited number of follow-up examinations at 1 and 3 months after injury were obtained. MR imaging produced higher estimates of lesion volume than did CT. No changes in the appearance of the CSF spaces were mentioned. The estimated lesion volume in the frontal and temporal lobes correlated with diminished performance on tasks assessing frontal and temporal lobe functioning.

Wilson et al \((39)\) reported a remarkably
strong correlation between the degree of cognitive impairment and a four-level classification of injury severity based on the depth of the abnormalities detected on MR images. Ventricular enlargement, subjectively defined as either present or absent, was the hallmark of the most severe category. While late MR imaging (5 to 15 months after injury) correlated strongly with a diminished performance IQ score, early MR imaging correlated weakly with only a single subtest.

In the present study, we quantified the brain and CSF compartment volumes using previously reported normative data to eliminate the variability resulting from sex and age differences (25). In a cross-sectional grouping of patients, the time course of changes that occur after traumatic brain injury were studied. The relationship between volumetric studies and measures of cognitive outcome was investigated. The observations we report are consistent with both focal and diffuse mechanisms of injury. Further, they support the hypothesis that both mechanisms contribute significantly to the cognitive impairment seen after traumatic brain injury.

The gross neuropathologic hallmark of diffuse axonal injury is global atrophy. The significant decrease in total brain volume and increase in lateral ventricle volume reported here are direct in vivo measures of global atrophy. For total brain volume, a biphasic time dependence was observed. Very early after injury, a transient increase in brain volume was observed, consistent with the cerebral edema of acute injury. A subsequent decrease in brain volume continues at a rate greater than that seen with normal aging for up to 3 years after injury. The concomitant expansion in subarachnoid CSF volume mirrored, almost exactly, the reduction in brain volume. This period of ongoing volume loss after injury may be longer than that seen with normal aging for up to 3 years after injury. The correlation between left temporal horn and verbal IQ score persisted throughout the entire postacute period studied (groups 3 through 5). In contrast, the correlation between performance IQ score and lateral ventricle volume did not remain significant in group 4. A possible explanation of these contrasting observations lies in the differing distribution of areas of the cerebrum that are central to the performance of the tasks in these two neuropsychological tests. Performance IQ tests emphasize widely distributed cortical functions that are particularly dependent on the interaction between cortical regions and interhemispheric integration (30). As a result, we would
not expect performance IQ scores to be highly correlated with injury to a localized area of the brain. In contrast, the tasks associated with verbal IQ emphasize the processing and retention of verbal information, functions that tend to be lateralized to the left hemisphere, particularly the temporal lobe. The left temporal horn may be a useful indicator of the integrity of the temporal lobe. Compared with the functions measured in performance IQ tests, verbal processing and retrieval are more sensitive to the effects of focal damage and less likely to be assumed by other, uninjured areas of the brain.

The cause of temporal horn enlargement in patients who have sustained traumatic brain injury remains to be elucidated. In the early period after injury, transient hydrocephalus may contribute. In the postacute period, temporal horn enlargement may result primarily from hippocampal atrophy or, conversely, from global temporal lobe cortical and white matter atrophy. Further detailed studies of temporal lobe anatomy after traumatic brain injury will be useful in elucidating the relative role of the hippocampus and cortical areas in relation to postinjury verbal IQ scores.

These results question the value of early MR volumetric studies in predicting the outcome of traumatic brain injury. Of the structures whose volume we measured, only a diminished left temporal horn bore a significant early correlation with cognitive outcome, and this measure was significant only for the first group, imaged within 21 days after injury. Only after 70 days (group 3) did the relationship between MR estimates of volume and eventual cognitive outcome become significant. Because of the limitations of this cross-sectional study, it is premature to conclude that MR volumetric studies can reliably predict cognitive outcome. Replication of these results in a truly longitudinal study are needed.

References