

Magnetic Resonance Imaging Evidence of Progression of Subacute Brain Atrophy in Moderate to Severe Traumatic Brain Injury

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ABSTRACT. Ng K, Mikulis DJ, Glazer J, Kabani N, Till C, Greenberg G, Thompson A, Lazinski D, Agid R, Colella B, Green RE. Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2): S35-44.

Objective: To demonstrate subacute progression of brain atrophy (from 4.5–29mo postinjury) in moderate to severe traumatic brain injury (TBI) using structural magnetic resonance imaging (MRI).

Design: Within-subjects, repeated-measures design.

Setting: Inpatient neurorehabilitation program and teaching hospital (MRI department).

Participants: Adults (N=14) with moderate to severe TBI.

Interventions: Not applicable.

Main Outcome Measures: Neuroradiologist readings and volumetric measurements (total brain cerebrospinal fluid and hippocampus) at 4.5 months and 2.5 years postinjury.

Results: Ten of 14 patients showed visible atrophy progression. Significant increase in cerebrospinal fluid (CSF) volume ($t_{13} = -4.073$, $P < .001$) and decrease in right and left hippocampal volumes ($t_{13} = 4.221$, $P < .001$ and $t_{13} = 3.078$, $P < .005$, respectively) were observed from 4.5 months to 2.5 years. Compared with published normative data, patients with TBI showed significantly more pathologic percent annual volume change for the hippocampi ($t_{26} = -3.864$, $P < .001$, right; and $t_{26} = -2.737$, $P < .01$, left), and a trend for CSF ($t_{26} = 1.655$, $P = .059$).

Conclusions: This study provides strong MRI evidence for subacute progression of atrophy, as distinct from early, acute neurologic changes observed.

Key Words: Atrophy; Brain injuries; Magnetic resonance imaging; Follow-up studies; Rehabilitation.

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MODERATE TO SEVERE TBI has an incidence of approximately 200 per 100,000 in developed countries worldwide.¹ Because its prevalence is particularly high in

young adults,¹ TBI can cause decades of disability with associated emotional and financial hardships.² Disability is caused in large part by the cognitive consequences of TBI,³ which are the result of both focal and diffuse injury to the brain,^{4,5} often in combination.⁶ Neuroimaging studies of subacute patients show a range of sequelae that includes generalized atrophy, cortical atrophy, hippocampal atrophy, white matter degeneration, and ventricular dilatation.⁷⁻¹⁶

The natural history of cognitive and functional recovery has been widely studied.¹⁷⁻²⁵ Cognitive recovery is characterized by a period of rapid recovery in the first months postinjury, followed by a plateau in recovery by 6 to 18 months after injury.²⁶⁻³¹ After this period, it is assumed that patients maintain this level of recovery. There have been far fewer studies in TBI of neuroradiologic change over time. Here, research to date suggests that relative to cognitive plateau, the stabilization of neuroimaging findings occurs much earlier, after the acute effects of injury (eg, contusion, hematoma, and edema) have resolved.^{32,33}

There is suggestion in the literature, however, that some subsequent deterioration on cognitive and neuroradiologic indices may occur. A small number of studies on long-term cognitive recovery have shown delayed cognitive decline in 15% to 56% of patients in the samples examined,³⁴⁻³⁷ with 1 study³⁷ demonstrating cognitive decline from as early as 5 months postinjury. These findings raise the question whether observed cognitive decline might be underlain by atrophic changes to the brain.

A small number of human studies^{38,39} and animal studies^{40,41} have investigated the possibility of progressive atrophy of the brain. However, to date, a critical question that persists is whether the observation of change over time in past studies represents secondary atrophy, per se, or rather the natural history of the primary insult itself that takes place during the first months postinjury (eg, clearing of traumatized cells, with

List of Abbreviations

CSF	cerebrospinal fluid
FLAIR	fluid attenuated inversion recovery
FOV	field of view
GCS	Glasgow Coma Scale
GRE	gradient-recalled echo
ICC	intraclass correlation coefficient
IQ	intelligence quotient
IR	inversion recovery
MRI	magnetic resonance imaging
PD	proton density
TBI	traumatic brain injury
3D	three-dimensional
TE	echo time
TI	inversion time
TR	repetition time

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Supported by the Canadian Institutes of Health Research and the Physicians' Services Inc (grant nos. MOP-67072, 05-50) and the Toronto Rehabilitation Institute, which receives funding under the Provincial Rehabilitation Research Program from the Ministry of Health and Long-Term Care in Ontario.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

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0003-9993/08/8912S-00342\$34.00/0

doi:10.1016/j.apmr.2008.07.006

microglial proliferation and edema, hyperemia, global swelling, resolution of edema, hyperemia and loss of inflammatory cells, involuting hematoma, encephalomalacia). This question largely remains because of the timing of the initial examination in past studies, performed within the first months^{38,39} or even days of injury,⁴²⁻⁴⁴ precluding differentiation of secondary atrophy from stabilization of the brain; for example, in 1 longitudinal study, the timing of the first assessment ranged from 7 to 430 days postinjury.⁴⁵

In addition, neuroimaging studies speaking to the question of atrophy have employed different acquisition parameters at the initial and follow-up assessments⁴⁴ or have used experimental designs that were partially or fully cross-sectional.^{27,39,45} Consequently, comparisons across time were vulnerable to confounding by measurement or subject variability. Most past studies have also been retrospective, with sample bias as pointed out by the authors, and with time windows of initial and follow-up assessments that were not predetermined, and sometimes overlapping.⁴³⁻⁴⁵

Further research into the question of progression of atrophy is needed to ascertain whether these preliminary indications of secondary atrophy are bona fide or simply represent the natural progression of the initial lesion. Therefore, in order to build on previous research, we performed a prospective, within-subjects study with a predetermined time window after injury for the initial scan (3.5–5.5mo postinjury) and for the follow-up scan (2–3.5y postinjury), without overlap between the initial and follow-up time windows. Identical MRI parameters were employed across the assessments, and critically, the time window for the initial imaging session was selected to be late enough that brain changes caused by the acute injury would have resolved, but early enough to avert overlap with the onset of putative postrecovery atrophy.

We extended previous studies by including a combination of expert visual ratings of MRI with volumetric assessments, employing parameters of the latter that have been used in previous studies examining this question (ie, CSF and hippocampal volume).^{38,45} We compared volumetric change over time in our study to age-stratified and sex-stratified normative data published in the literature.^{10,46}

We hypothesized that there would be evidence of delayed progression of atrophy after the initial period of stabilization in a percentage of patients after TBI, detectable on both visual ratings and volumetric analyses, and that the extent of volumetric change would be greater than that estimated for healthy controls.

METHODS

Participants

The participants in this study were 14 patients recruited from a larger, ongoing prospective study of cognitive and motor recovery from TBI, which included 2 subacute phase structural MRI assessments.

Patients from the larger study were recruited from the Neurorehabilitation Program of the Toronto Rehabilitation Institute, in a large, urban rehabilitation hospital.

The study protocol was approved by the research ethics board at the Toronto Rehabilitation Institute, and the procedures of the study were in accordance with the standards of the research ethics board.

Eligibility for the neurorehabilitation program includes the potential to benefit from rehabilitation, age 16 years or older, willingness to participate in all components of the program, and medical stability. Patients may have minimal to severe physical deficits. Patients from the clinical program were eligible for inclusion in the larger TBI recovery study if they met the following

criteria: (1) acute care diagnosis of TBI, (2) posttraumatic amnesia 1 hour or more and/or GCS of 12 or less either at emergency room or the scene of accident (note that, if blood alcohol level was elevated and suspected to have suppressed GCS score, then the higher GCS score was used as the inclusion criterion), and/or positive acute care computed tomography or MRI findings (based on clinical records), (3) age between 18 and 80 years, (4) able to follow simple commands in English based on speech language pathologist intake assessment, and (5) competency to provide informed consent for the study or availability of legal decision-maker. Participants were excluded on the basis of the following criteria: (1) orthopedic injuries affecting both upper extremities and/or both lower extremities; (2) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer type, Parkinson disease, multiple sclerosis, Huntington disease, systemic lupus erythematosus, or stroke, based on medical records and screening of family members for patients over 60 years regarding any definite or possible prior diagnosis of dementia; (3) history of psychotic disorder; (4) not emerged from post-traumatic amnesia by 6 weeks postinjury, as measured by the Galveston Orientation Amnesia Test⁴⁷; (5) TBI secondary to other brain injury (eg, a fall caused by stroke); and (6) metal implants that preclude MRI.

To be eligible for the current study, participants needed additionally to have completed the 4.5-month neuroimaging assessment, to have reached the long-term follow-up stage, and to have not developed further neurologic complications (eg, subsequent brain injury, hydrocephalus). There were 18 eligible patients. Four of these were lost to follow-up (unable to reach via their supplied contact details), leaving 14 patients available to participate in the follow-up assessment. Thus, the retention rate was 73.7%, which is very high compared with many longitudinal studies of TBI.^{2,34,36}

Table 1 shows the injury and demographic information of each participant in the study. Overall, the group was a typical group of patients with moderate to severe TBI, with a greater proportion of male subjects, average estimated premorbid IQ, and moving vehicle collisions the most common cause of injury, followed by falls.

Inspection of the mean values in table 1 reveals that the 4 patients who did not return for follow-up were slightly higher functioning as a group, although this was driven in large part by a single patient who was a top tier health care professional with 21 years of education. Unpaired, 2-tailed tests showed no significant differences between the 2 groups nor differences approaching significance for age ($t_{17} = -.40$, $P > .10$), premorbid intelligence ($t_{13} = 1.67$, $P > .10$), socioeconomic status⁴⁸ ($t_{17} = .37$, $P > .1$), years of education ($t_{17} = -1.3$, $P > .10$), and GCS score ($t_{15} = -.39$, $P > .10$). There were proportionately more female subjects and motor vehicle collisions in the tested group. However, the low attrition, the absence of significant differences (or trends), and overall similarity between the groups (aside from the 1 patient mentioned) indicates that the study did not suffer from selective attrition and that the sample tested at the 2 time points was a representative sample of Canadian patients referred for inpatient neurorehabilitation in an urban setting.

Imaging Protocol

MRI scans were acquired on a Signa-Echospeed 1.5 Tesla high definition scanner,^a using an 8-channel head coil. Sequences included the following: sagittal T1 (TR/TE=300/13ms), slice thickness equal to 5mm, space 2.5mm, matrix 256 × 128; axial GRE (TR/TE=450/20), flip angle equal to 20°, slice thickness equal to 3mm no gap, matrix 256 × 192; axial FLAIR TR/TE equal to 9000/45ms, TI equal to 2200ms, slice thickness equal to 5mm no gap, matrix 256 × 192; axial fast

Table 1: Demographic and Injury Data of Participants Included in the Study as Well as Those Lost to Follow Up

	Sex	Age	Injury	GCS (lowest)	Estimated PTA (wk)	SES*	Acute LOS	Years of Education	Estimated Premorbid Intelligence
Participants (N=14)									
1	Female	24	MVC (ped)	3	>2	4	24	8	NA
2	Male	58	MVC	13	>0.5	4	33	12	NA
3	Male	41	MVC	13	>0.5	3	35	9	78
4	Female	52	MVC (ped)	13	0.5	3	—	12	113
5	Male	21	MVC	8	3	4	17	9	NA
6	Male	22	Fall	4	2	2	29	9	85
7	Male	42	Fall (bike)	5	1	4	24	17	119
8	Male	20	MVC	5	>1	2	17	13	80
9	Male	32	Fall	13	>1	2	37	16	83
10	Male	42	MVC	3	>3	4	45	11	99
11	Male	19	MVC	—	1.2	4	14	9	103
12	Female	43	MVC	3	NA	—	88	13	108
13	Male	31	MVC	6	4–6	2	53	16	97
14	Female	44	Fall (bike)	6	NA	2	24	16	120
Mean (totals)	(10 Male/4 female)	35.1	(9 MVCs, 4 fall)	7.3		3.08	33.9	12.1	98.6
Lost to follow-up (n=4)									
1	Male	49	Sport fall	13	1	1	38	21	123
2	Male	36	MVC	11	2	4	21	9	81
3	Male	41	MVC	6	1	2	37	15	108
4	Male	20	Fall	3	>1.5	2	49	12	108
Mean (totals)	(4 Male)	36.5	(2 MVCs/2 falls)	8.25	1.33	2.25	36.25	14.25	105

Abbreviations: LOS, length of stay; MVC, motor vehicle collision; NA, not applicable; ped, pedestrian; PTA, posttraumatic amnesia. *SES denotes socioeconomic status, as measured by the Hollingshead⁴⁸ classification: 1 (major business/professional); 2 (medium business/minor professional, technical); 3 (skilled craftsperson, clerical, sales worker); 4 (machine operator, semiskilled worker); 5 (unskilled laborer, menial service worker).

spin-echo PD/T2 TR/TE equal to 5500/30.90ms, slice thickness equal to 3mm no gap, matrix 256 × 192. All aforementioned sequences were obtained with a 22-cm FOV. The high-resolution isotropic T1-weighted, 3D IR prepped radio-frequency spoiled-GRE images (TI/TR/TE=300/12/5, TI, flip angle=20°, slice thickness=1mm no gap, matrix=256 × 256) were acquired in the axial plane using a 25-cm FOV. The entire scanning session lasted approximately 55 minutes.

Design and Procedures

The study was a within-subjects, repeated-measures design. All participants were required to pass a rigorous clinical screening procedure prior to the first MRI assessment. All MRIs were conducted at the same center, a teaching hospital in an urban setting. All equipment and acquisition parameters were identical for the initial and follow-up assessments. One of 2 MRI technologists performed all MRIs. The first assessment was conducted at a mean ± SD of 4.5±0.5 months postinjury. Participants were contacted by telephone to arrange the date of the follow-up scan, which took place at a mean ± SD of 29.3±4.1 months postinjury. The mean time ± SD between scans was 24.8±4.4 months (range, 20.2–34.5mo).

Once all data were collected, the images were analyzed by 2 different methods, as follows, in order to ascertain change over time.

Classification of images based on expert reader ratings. Three experienced staff neuroradiologists reviewed all pairs of imaging studies for each patient. They were informed that all patients had sustained a TBI and that each patient had been scanned at 2 different times after injury. The early and late scans were then randomized to the top and bottom rows of a workstation, with the readers kept blinded to the temporal sequences of the scans and all clinical data.

Readers were asked to use all available sequences including sagittal T1, axial T1 3D IR prepped radio frequency spoiled-GRE, axial PD and T2, axial FLAIR, and axial GRE in order to independently document whether the scans were the same or if 1 scan showed deterioration or improvement, based on the following key criteria: extent of T2 signal abnormalities seen on FLAIR, volume extent of tissue loss, and generalized volume in CSF spaces. Note that the GRE sequence was not used for assessment of progression, but just to direct attention to areas of injury because changes in iron deposition over this time frame were not observed.

For each of the 14 subjects, an ordinal scale was used by the neuroradiologists to rate change between the 2 MRI scans (ie, deterioration, no observable change, improvement). Interrater reliability for the coding of MRI change by each radiologist was assessed by using the ICC. Because there exists no widely accepted method for investigating interrater agreement using ordinal data, it was necessary to choose between methods for determining interrater agreement for continuous data (ie, ICC) and those used for nominal data (ie, Fleiss κ). While it can be argued that our data more closely approximate nominal data, the appropriate kappa statistic for studies with nominal data and more than 2 raters, Fleiss multirater kappa, is known to be influenced by prevalence (ie, the true proportion of cases of various types in a population) and bias (ie, the bias of 1 rater relative to another),⁴⁹ which can lead to the paradox of high agreement but low kappa.⁵⁰ It also assumes that raters are restricted in how they can distribute cases across categories, which is not a typical feature of many agreement studies, including the current study.⁵¹ Furthermore, much controversy surrounds the appropriate use and interpretation of kappa statistics in general.^{50,52} Although ICC is used for continuous

data, it was chosen for the current study because it would provide a conservative estimate of interrater agreement because the main problem that results from treating ordinal data as continuous is that it makes correlations smaller than they should be, so any value obtained would underestimate the actual ICC. ICC was calculated in a 2-way random model based on consistency agreement, in which each MRI is rated by each rater with a confidence interval of 95%.⁵³ Level of clinical significance was defined according to conventional criteria (>.74, excellent; .60–.74, good; .40–.59, fair; <.40, poor).⁵⁴ A random-effects model was used under the assumption that the raters represent a random sample of a larger pool of raters.

Volumetric data analysis. The high-resolution isotropic axial T1 3D IR prepped radio frequency spoiled-GRE images were submitted for volumetric analysis. CSF and hippocampal volumes were obtained for all 14 patients. The MRIs were transferred to an external workstation, with image processing and image data analysis carried out at the Sunnybrook Health Sciences Centre by a technician blinded to the clinical findings. The scans were received in the Digital Imaging and Communications in Medicine file format and were subsequently converted into Medical Imaging Network Common Data form.⁵⁵

A number of image processing steps were performed in order to make the MRI data usable for image analysis. The first step was the intensity nonuniformity correction.⁵⁶ The images were linearly registered (aligned) into stereotaxic coordinates⁵⁷ based on the Talairach atlas.⁵⁸ The linear registration to Talairach coordinates was accomplished through 3D cross-correlation between a given volume and an average brain MRI previously converted into the Talairach coordinate system.⁵⁷ After the registration, the images had the same size and orientation, allowing for direct anatomical comparisons between subjects. A second nonuniformity correction was performed after the registration, which helped to remove any residual nonuniformity artifacts.

Every voxel was then classified into CSF, gray matter, or white matter using an automated tissue classification algorithm.⁵⁹ Subsequently, cortical surface extraction from the tissue-classified images was performed, resulting in a 3D reconstruction of the cortical surface.

Both hippocampi were segmented manually using DISPLAY software.^{60,6} This tool allows for viewing images simultaneously in the sagittal, coronal, and horizontal planes. The details of manual segmentation for each structure have been described by Pruessner et al.⁶¹ The structures were labeled on each slice of an image using coronal, sagittal, and horizontal views, and their individual volumes were calculated automatically in DISPLAY. The same well-trained technician performed the manual segmentation for both the initial and follow-up scans for each patient.

Use of normative data. We compared our CSF volume changes to the normative data from Blatter et al.⁴⁶ that were published for the purpose of a reference standard. (Absolute change across assessments could not be compared because parameters of the acquisition differed across our 2 studies.) The data from Blatter⁴⁶ include mean CSF volumes for male and for female subjects across five 10-year stratifications, from ages 16 to 25, 26 to 35, 36 to 45, 46 to 55, and 56 to 65. Mean education \pm SD of the normative sample was 15.5 ± 2.7 years.

In order to control for differences in the test interval between scans in our study versus the intervals in the study by Blatter,⁴⁶ we computed the annual percent change from the 2 studies. For data from our study, we divided the percent change by the time interval between the 2 scans for each patient. To compute the annual percent increase from the normative data,⁴⁶ we computed a separate value for the sex and age-band stratifications

that matched each patient in our sample. We first calculated a change score taking the mean CSF volume in the age band after the age band of interest and subtracted the mean CSF volume of the age band preceding the age band of interest. We then divided the change score by 20 (because the mean span across these stratifications was 20 years) and then calculated the annual percentage change from this. For example, for a 40-year-old female patient in our sample, the normative data of relevance would be the mean CSF volumes for female patients from 26 to 35, 36 to 45, and 46 to 55 years. We would therefore subtract the mean CSF volume for the 46 to 55 year age-band from the 26 to 35 year age-band, divide by 20, and then calculate the annual percentage change. Note that where the age of a patient within our study fell within the first age-band (such that there were no prior age-band normative data), we calculated the annual percent volume using the first age-band CSF volume and the one after it, and dividing by 10. Where the age of the patient within our study fell within the last age-band, such that there were no subsequent age-band normative data, we computed the annual percent volume using only the last age-band and the one preceding it, and again dividing by 10.

In short, for each patient's annual percent change score, there was an annual percent change score computed from an age-matched and sex-matched normative sample. This allowed us to examine whether the CSF increases observed in patients in the present study were greater than those expected for people of comparable age and sex.

The annual percent change for each hippocampal volume was computed in the same way as above, using the normative data from Bigler et al.¹⁰

Statistical analyses. Based on specific hypotheses, all within-subjects comparisons of CSF and hippocampal volumes from the first to the second assessment were carried out with 1-tailed paired *t* tests. All comparisons of computed annual percent change in our patients versus the computed annual percent change from published normative data were conducted with 1-tailed Student *t* tests without equal variance assumed.

Spearman rank correlations were used to compare expert ratings (progression vs no progression) to the volumetric scores (annual percent change scores). Pearson moment correlations were used to compare the volumetric change scores to one another (ie, CSF to hippocampus; hippocampus right to hippocampus left).

RESULTS

Visible Lesion Changes

The average measure ICC (ie, reliability of all raters averaged together, also known as Cronbach α) was .797, which indicates excellent interrater reliability. For 9 of 14 pairs of scans, all 3 blinded readers showed unanimous agreement (8 progression of atrophy; 1 stable); for 2 of the scans, there was agreement by 2 of the 3 reviewers (progression of atrophy); for 3 scans, there was no agreement. All individual ratings are presented in table 2.

The number of scans for which 2 of 3 raters identified the follow-up MRI as displaying increased progression of lesion was 10 (71.43% of the pairs), with 8 of these receiving unanimous agreement. Two pairs of scans illustrating visible lesion progression are shown in figure 1. There were no instances in which 2 or 3 of the readers selected the early MRI as showing progression of atrophy.

Volumetric Changes

Cerebrospinal fluid volume increase. Table 3 shows that, as expected, there was a mean increase in CSF volume from the

Table 2: Comparison of Expert Rating and Volumetric Analyses on Progression of Atrophy

Subject	Expert Rating				Volumetric Analysis			
	Rater 1	Rater 2	Rater 3	Consensus Rating	CSF Volume Increase Greater Than Normative Increase	Hippocampal Volume Loss Greater Than Normative Loss		
						Right	Left	
1	A	A	A	Atrophy	No	Yes	No	
2	A	A	I	Atrophy	No	No	Yes	
3	A	A	A	Atrophy	Yes	Yes	Yes	
4	A	A	A	Atrophy	Yes	Yes	No	
5	A	I	S	No consensus	Yes	Yes	Yes	
6	A	A	A	Atrophy	Yes	Yes	Yes	
7	A	A	A	Atrophy	Yes	Yes	Yes	
8	I	A	S	No consensus	No	Yes	Yes	
9	A	A	A	Atrophy	No	Yes	Yes	
10	A	A	I	Atrophy	Yes	Yes	Yes	
11	S	A	I	No consensus	Yes	Yes	No	
12	A	A	A	Atrophy	Yes	Yes	Yes	
13	S	S	S	No atrophy	No	No	Yes	
14	A	A	A	Atrophy	Yes	Yes	Yes	

Abbreviations: A, atrophy; I, improvement; S, stable.

first to the second scan. This increase in volume was highly significant ($t_{13} = -4.073, P < .001$). In order to ascertain the clinical significance of this change, and to provide evidence that this change was not attributable to age-related decline over the test-retest period, we compared the magnitude of change to that computed from age-stratified normative data⁴⁶ as described. The mean annual percent increase \pm SD in CSF volume in the present study was $4.25 \pm 4.18\%$ per year compared with only $2.33 \pm 1.15\%$ in the normative sample. This difference approached significance ($t_{26} = 1.655, P = .059$).

Hippocampal volume loss. The data for the hippocampal volumetric analyses are presented in tables 4 (right hippocampus) and 5 (left hippocampus). Table 4 illustrates that, as predicted, the right hippocampus showed an overall loss of volume over the study period that was statistically significant ($t_{13} = 4.221, P < .001$). Table 5 shows that the left hippocampus also showed a significant decrease in volume ($t_{13} = 3.078, P < .005$).

In order to provide evidence that these changes, too, were not attributable to age-related decline over the test-retest period, we compared the hippocampal volume change in our study to normative data.¹⁰ The mean annual percent decrease \pm SD in right hippocampal volume was $-2.30 \pm 2.12\%$, which was markedly larger than the average annual percent change computed from the normative data ($-0.098 \pm 0.20\%$). This difference was highly significant ($t_{26} = -3.86, P < .001$). For the left hippocampus, the mean annual percent volume decrease was $-2.11 \pm 2.67\%$, while the average annual percent decrease computed from the normative data was only $-0.15 \pm 0.11\%$, a difference that was statistically significant ($t_{26} = -2.73, P < .01$).

Comparison of Visual and Volumetric Changes

Table 2 illustrates the results of expert rater and the respective CSF and hippocampal volume changes. There was some concordance between the 2 types of ratings. Seven of the 10 patients rated as showing progression of atrophy by the expert raters also showed CSF volume increase greater than that of healthy controls. For the remaining 2 patients rated as showing atrophy across the study period, there was hippocampal volume loss greater than observed in the normative data in 1 or both hippocampi.

Two of the 4 patients without evidence of atrophy on the visible ratings showed no overall increase in CSF volume greater than that of controls, though 1 did show increased hippocampal volume loss in 1 hippocampus, and the other showed hippocampal volume loss (greater than healthy controls) in both hippocampi.

Using Spearman rank correlations, there were no significant correlations between the expert ratings (atrophy vs no evidence of atrophy) and annual percent change for the CSF or hippocampal volumes; effect sizes were small and nonsignificant ($r = .04, P > .1, CSF; r = .28, P > .1, right hippocampus; r = .24, P > .1, left hippocampus$). Correlations among volumetric measures were stronger. Pearson correlations between annual CSF volume change and hippocampal volume change (individually) were very small and not significant, but Pearson correlation between the annual hippocampal volume change for the left and right hippocampus was statistically significant ($r = 0.61, P < .05$).

DISCUSSION

The natural history in patients with TBI after the initial period of rapid recovery is not completely understood. Most patients appear to remain at this new, recovered baseline level of cognition, with many showing further improvement; however, there are scattered reports of delayed cognitive decline.³⁴⁻³⁷

We prospectively compared imaging performed at 4.5 months postinjury with follow-up imaging at 2.5 years postinjury. We found strong evidence of secondary progression of encephalomalacia that was visible to expert neuroradiologist readers. For 8 of 14 patients, there was unanimous agreement for progression of atrophy. For 2 further patients, there was majority (2 of 3) agreement of atrophy. For the remaining 4 patients, there was consensus of stability for 1 patient, and a lack of consensus for the other 3. Thus, a substantial proportion of our sample demonstrated visible progression of lesions during this subacute period. The volumetric analyses were globally consistent with these findings in that significant atrophy was observed. There was significant CSF volume increase over the same period. The annual CSF volume increase in our

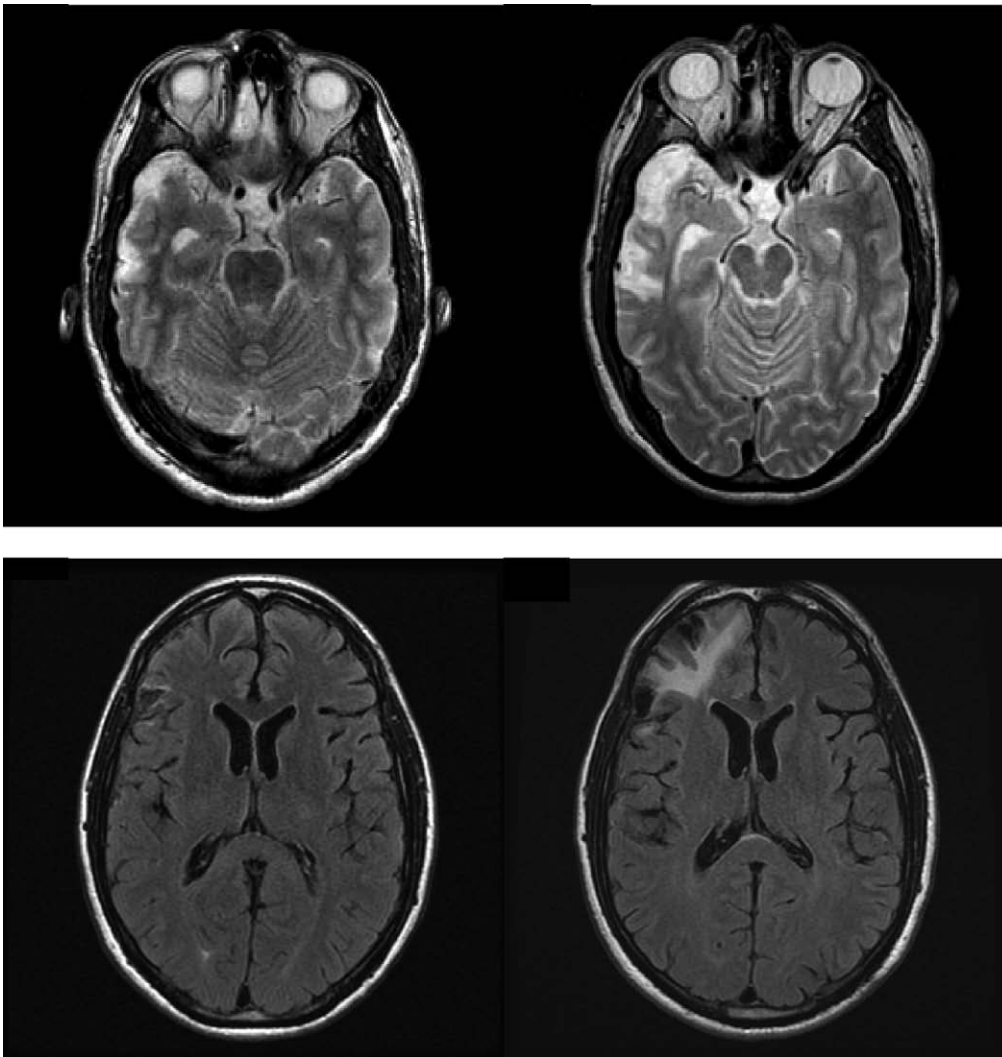


Fig 1. Example of lesion progression from 4.5 months postinjury (left) to 2.5 years postinjury (right) in 2 different patients. Top, T2 axial images demonstrate significant progression of localized atrophy of the right temporal pole extending posteriorly to the mid right temporal lobe that lies superior to the petrous temporal bone. There is also localized dilatation of the right temporal horn. Bottom, FLAIR axial images demonstrate marked progression of localized atrophy in the right frontal lobe with associated adjacent gliosis, where there were only subtle changes on the initial MRI.

patients was nearly double that estimated for healthy controls.⁴⁶ Hippocampal shrinkage showed the same pattern relative to control data,¹⁰ and even more dramatically.

However, it was of interest to note that the 2 patients with the highest increase in total CSF volume (23.95% and 20.43%) did not show visible progression of atrophy based on the expert rater observations. Moreover, several patients with overt progression of lesions on consensus agreement demonstrated no greater CSF increase than that of controls. Finally, there were no significant correlations between expert ratings and volumetric findings. These disparities in the findings offer several possible explanations.

The most probable explanation for disparity between CSF volume and visible lesion progression is that visible lesion volume changes may contribute only minimally to overall CSF volume changes. CSF volume increases reflect global atrophy of the brain, which may be associated with global loss of healthy neurons (or loss of dendritic arborization) resulting from gradual loss of functional connectivity caused by brain injury-related disuse (ie, negative neuroplasticity)⁶² or by delayed apoptosis (see further discussion of this topic below) which has been observed in animal models of brain injury.^{40,63}

Another explanation is that the expert raters may not have been able to see changes detected by the computerized volu-

metric measurements. For example, it is not easy to see hippocampal change with the naked eye, especially in the axial plane (high-resolution coronal images—not employed in the current study—are needed to detect changes in hippocampal volume visible to naked eye), unless exceedingly obvious. Furthermore, the relationship between gliosis and local atrophy may not be as strong as expected in all cases. This underscores the clinical importance of volumetric analysis of scans.

Still another possible explanation concerns a limitation of the study. The normative data from outside of our study, show wide individual differences in CSF volumes, and were derived from cross-sectional samples. The age stratifications were across decades. To compute annual change in volumes, we treated annual change as a linear increment; however, the relationship between age and CSF increase is nonlinear. Taken together, it is possible that the normative data employed may not have provided a valid comparator for our sample. Future research employing longitudinal, control data from within the same study at the same time intervals would provide a better reference for change.

Compatibility with previous studies. A confounding issue from previous studies was their very early initial scanning within days or weeks of injury in most cases. This precluded definitive differentiation of atrophy caused by the natural his-

Table 3: Change in CSF Volume From Assessment 1 to Assessment 2

Subject no.	CSF Absolute Volumes (mm ³)		CSF Volume Change	CSF % Volume Change	Computed Annual % Change	Normative Annual % Change
	Scan 1	Scan 2	Scan 2-1	Scan 2-1		
1	201,900	207,951	6051	3.00	1.04	1.35
2	223,733	236,918	13,185	5.89	2.42	3.71
3	220,550	241,038	20,488	9.29	3.49	1.17
4	188,913	205,854	16,941	8.97	4.06	1.76
5	217,311	269,364	52,053	23.95	11.96	3.42
6	188,090	215,112	27,022	14.37	7.12	3.42
7	206,627	213,372	6745	3.26	1.69	1.17
8	216,945	222,475	5530	2.55	1.16	3.42
9	226,944	232,539	5595	2.47	1.32	3.28
10	254,047	272,612	18,565	7.31	3.95	1.17
11	164,002	197,505	33,503	20.43	11.58	3.42
12	251,124	290,025	38,901	15.49	9.09	1.04
13	268,176	258,174	-10,002	-3.73	-2.15	3.28
14	226,752	237,316	10,564	4.67	2.76	1.04
Mean ± SD	218,222.4±27,950.61	235,732.50±28,026.87*	17,510.07±16,086.06	8.42±7.68	4.25±4.18	2.33±1.15†

NOTE. Total percent CSF change between scan 1 and scan 2, computed annual percent change, and normative annual percent change are presented.

*Difference between scans 1 and 2 significant at $P<.001$.

†Difference between computed versus estimated normative change approached significance, $.05<P<.10$.

tory of the primary insult itself from true delayed secondary atrophy.⁴²⁻⁴⁴

A small number of studies conducted neuroimaging assessments more than a month postinjury. One study by van der Naalt et al³⁹ reported that atrophy can be observed from early postinjury to the latter part of the first year of injury (6-12mo postinjury). In this case, the initial MRI was performed within 1 to 3 months of the injury, later than in the aforementioned studies, but perhaps again too early to be confident that the initial insult had not yet resolved. Indeed, 1 of their cases was reported as showing a persistent contusion with surrounding edema at the time of the first scan. This provides some evidence that acute lesion effects had not yet resolved in at least

some of the patients in their study. Similarly, Trivedi et al³⁸ showed significant decrease in percent brain volume change (%BVC) in patients with TBI compared with healthy controls. They, too, acknowledged that "... it is possible that the clearing of brain edema over time might be responsible for the substantial %BVC observed in the TBI group ..."^{38,p.770} Their first scan took place at more than 2 months postinjury on average, but some patients were seen as early as 39 days postinjury. MacKenzie et al⁴⁵ examined progression of atrophy on measures of volume of brain parenchyma, total CSF, and percent volume of brain parenchyma (an index of brain volume that incorporates CSF volume) in mild and moderate TBI across the first year of brain injury. In this retrospective study,

Table 4: Volume Change in Right Hippocampus From Assessment 1 to Assessment 2

Subject no.	Hippocampus Absolute Volumes (mm ³)		Absolute Hippocampal Volume Δ	% Hippocampal Volume Δ	Computed Annual % Change	Normative Annual % Change
	Scan 1	Scan 2	Scan 2-1	Scan 2-1		
1	2708	2545	-163	-6.02	-2.09	0.15
2	3467	3470	3	0.086	0.04	-0.24
3	3152	2854	-298	-9.45	-3.55	-0.28
4	3602	3506	-96	-2.67	-1.21	-0.14
5	3607	3458	-149	-4.13	-2.06	0.15
6	2701	2656	-45	-1.67	-0.83	0.15
7	2873	2496	-377	-13.12	-6.78	-0.28
8	3287	3037	-250	-7.6	-3.47	0.15
9	3870	3743	-127	-3.28	-1.76	-0.19
10	3349	3157	-192	-5.73	-3.10	-0.28
11	3439	3421	-18	-.52	-0.30	0.15
12	3711	3337	-374	-10.08	-5.91	-0.28
13	4159	4199	40	0.96	0.56	-0.19
14	2463	2393	-70	-2.84	-1.69	-0.28
Mean ± SD	3313.43±486.63	3162.29±525.77*	-151.14±133.97	-4.72±4.16	-2.30±2.12	-0.098±.20†

NOTE. Total percent change from scan 1 to 2 is presented. Computed annual percent change is provided for each participant as well as estimated annual percent change of age and sex-matched normative sample.

*Difference between scans 1 and 2 significant at $P<.001$.

†Difference between computed versus estimated normative change significant at $P<.001$.

Table 5: Volume Change in Left Hippocampus From Assessment 1 to Assessment 2

Subject no.	Hippocampus Absolute Volumes (mm ³)		Absolute Hippocampal Volume Δ	% Hippocampal Volume Δ	Computed Annual % Change	Normative Annual % Change
	Scan 1	Scan 2	Scan 2-1	Scan 2-1		
1	2298	2486	188	8.18	2.84	-0.08
2	3194	2988	-206	-6.4	-2.65	-0.47
3	3279	3020	-259	-7.90	-2.97	-0.13
4	3729	3791	62	1.66	0.75	-0.25
5	3681	3620	-61	-1.66	-0.83	-0.08
6	3081	3005	-76	-2.47	-1.22	-0.08
7	3130	2806	-324	-10.35	-5.35	-0.13
8	3302	3051	-251	-7.6	-3.46	-0.08
9	3713	3513	-200	-5.39	-2.88	-0.15
10	3295	2976	-319	-9.68	-5.24	-0.13
11	2947	3033	86	2.92	1.65	-0.08
12	3431	3051	-380	-11.08	-6.5	-0.13
13	4119	3952	-167	-4.05	-2.34	-0.15
14	2384	2332	-52	-2.18	-1.29	-0.13
Mean ± SD	3255.93±497.43	3116±459.65*	-139.93±170.12	-4.00±2.65	-2.11±2.67	-0.15±0.11†

NOTE. Total percent change from Scan 1 to 2 is presented. Computed annual percent change is provided for each participant as well as estimated annual percent change of age and sex-matched normative sample.

*Difference between scans 1 and 2 significant at $P < .005$.

†Difference between computed versus estimated normative change significant at $P < .01$.

7 patients were observed longitudinally and compared with 4 controls, who were also assessed at 2 time points. The authors found no change in volume of brain parenchyma or CSF, but did observe change in percent volume of brain parenchyma relative to the controls. However, because the first examination ranged from 7 to 430 days postinjury, again, it is not clear whether the change represents bona fide secondary atrophy or resolution of acute mass effect and swelling associated with edema, hemorrhage, and tissue hyperemia.

In another retrospective study designed to examine brain-behavior relationships in chronic TBI, Blatter et al²⁷ studied 123 patients with TBI and measured the volume of brain and CSF using MRI. Patients were divided into subgroups based on time since injury to the MRI. However, MRI was performed on the basis of clinical indications. Thus, while patients scanned at a later date showed more atrophy compared with patients scanned earlier (as well as compared with healthy controls)⁴⁶ the sample may have been a biased one selected for poor clinical recovery. As well, the comparisons were cross-sectional.

We therefore believe this study provides the most conclusive evidence to date for chronic lesion progression and atrophy in TBI. Our study is also consistent with findings from animal studies, which show preliminary indications of subacute progression of atrophy. Smith et al,⁶³ for example, demonstrated progressive tissue loss with associated ventricular dilatation in rats at multiple intervals up to a year after injury. Dixon et al⁶⁴ showed behavioral deficits that progressed over the course of the first year after injury.

Mechanisms of decline. Some studies have looked at potential mechanisms of this delayed decline, and several possibilities have been proposed. Using the terminal deoxynucleotidyl transferase-mediated biotinylated deoxyuridine triphosphate nick-end labeling histochemical technique, Williams et al⁴¹ demonstrated long-term deoxyribonucleic acid fragmentation within white matter up to 12 months after TBI in humans. Delayed apoptosis appears to occur in rats after TBI^{40,63} and progressive, delayed, and remote damage has been focally observed in the thalamus,^{65,66} presumably because of the apoptotic removal of axonal projections and subsequent deafferentation of remote relay stations.

The presence of delayed inflammation has also been examined. Gentleman et al⁶⁷ reported persisting inflammation associated with the interleukin-1 genotype. Rodriguez-Paez et al⁶⁸ observed persistent edema with an associated inflammatory infiltrate using light and electron microscopy 6 months after TBI in various structures. Active inflammation as long as 1 year after TBI has also been reported.⁶⁹ In addition, abnormal protein accumulation, such as β -amyloid precursor protein, in damaged axons and other neuronal compartments^{66,70,71} has also been implicated.

Understanding the mechanisms underlying this delayed neuroanatomical and cognitive decline is an important area of further research, because potential treatment regimens such as various neuroprotective agents⁷² can be targeted to these areas. For example, mild hypothermia has been shown to target multiple injury cascades after acute brain injury in humans.⁷³ Importantly Bramlett et al⁶⁵ showed that post-TBI hypothermia conveyed significant improvement in lateral ventricular dilation in animal models, indicative of its chronic neuroprotective properties. Schouten et al⁷⁴ have suggested cellular transplantation strategies to promote recovery in animal models.

Study Limitations and Future Directions

There were several limitations of this study. First, sample size was only 14, thus limiting the reliability of the findings, particularly given the demographic and neurologic heterogeneity of the sample. We did not include cognitive or functional findings in the current study. Future research, with larger sample size, should address the clinical implications of progression of atrophy. For example, changes in cognitive and motor assessment findings could be correlated with changes in neuroradiologic findings. Functional outcomes in patients who do and do not demonstrate progression of atrophy could be compared. Single case studies correlating cognitive and/or motor findings to discrete lesion changes would be informative for both clinical and scientific purposes.

CONCLUSIONS

There is compelling visual and volumetric evidence that delayed progressive atrophy occurs in patients with TBI after

the presumed initial period of stabilization and recovery, and long after the direct mechanical effects of the traumatic event have resolved. Our prospective study showed that 85.71% of our cohort of patients showed robust signs of delayed progressive atrophy on MRI after the initial scan at 4.5 months after injury. The extent of decline was more than we anticipated, and much more than is generally accepted.

These findings are in agreement with various other studies that have employed different design parameters with less conclusive findings. The findings are also compatible with the appearance of new symptomatology and the reports of cognitive decline during the same time frame. The exact reasons and nature of this further decline are not yet entirely known, but various theories seem plausible and are potential targets for new treatment regimens.

Acknowledgments: The authors acknowledge the support of Toronto Rehabilitation Institute who receives funding under the Provincial Rehabilitation Research Program from the Ministry of Health and Long-Term Care in Ontario. The views expressed do not necessarily reflect those of the Ministry.

We are grateful to Kadeen Johns, BA, and Areeba Adnan, for their meticulous support in preparation of the manuscript, and Gary Turner, PhD, for his input on the manuscript.

Finally, we gratefully acknowledge Joel Verwegen for his numerous, valuable contributions to the manuscript.

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