ORIGINAL ARTICLE

Use of Diffusion-Tensor Imaging in Traumatic Spinal Cord Injury to Identify Concomitant Traumatic Brain Injury

Corie W. Wei, MD, Januthy Tharmakulasingam, BSc, Adrian Crawley, PhD, David M. Kideckel, MSc, David J. Mikulis, MD, Cheryl L. Bradbury, PsyD, CPsych, Robin E. Green, PhD, CPsych

ABSTRACT. Wei CW, Tharmakulasingam J, Crawley A, Kideckel DM, Mikulis DJ, Bradbury C, Green RE. Use of diffusion tensor imaging in traumatic spinal cord injury to identify concomitant traumatic brain injury. Arch Phys Med Rehabil 2008;89(12 Suppl 2):S85-91.

Objective: To characterize and differentiate cerebral white matter (WM) changes related selectively to traumatic brain injury (TBI) or spinal cord injury (SCI) in patients with SCIs in order to improve diagnostic accuracy of TBI in people with SCI.

Design: Diffusion-tensor imaging (DTI)–derived fractional anisotropy (FA) data in WM tracts were compared between a healthy control and 2 patient groups. Between-subject comparisons of FA were performed using region of interest (ROI) analysis and tract-based spatial statistics.

Setting: A large, urban inpatient SCI program.

Participants: Three groups: SCI and concomitant TBI (SCI with TBI, n=7); SCI without TBI (SCI only, n=15); and healthy control subjects (n=12).

Interventions: Not applicable.

Main Outcome Measure: FA was used as a measure of cerebral WM integrity.

Results: ROI analyses showed reduced FA in the genu and splenium of the corpus callosum and forceps minor in patients with SCI with TBI compared with both healthy controls and patients with SCI only. ROI analyses did not show evidence of FA differences in patients with SCI only compared with controls. Tract-based spatial statistics did not demonstrate between-group differences in FA.

Conclusions: DTI is a sensitive tool to detect TBI-related WM damage in patients with SCI who have suffered concomitant TBI. No WM abnormalities on DTI could be attributed to SCI alone, although this finding should be further explored in future studies. Therefore, DTI may be a valuable tool to identify TBI in the SCI population. Further research to produce normative FA values is needed to allow identification of TBI in individual patients with SCI.

From Departments of Medical Imaging (Wei) and Cell and Systems Biology (Tharmakulasingam), University of Toronto; Institute of Medical Science, University of Toronto, University Health Network (Kideckel); Department of Medical Imaging, Toronto Western Hospital, University of Toronto (Crawley, Mikulis); Toronto Rehabilitation Institute (Bradbury, Green); Graduate Department of Rehabilitation Sciences, University of Toronto (Bradbury, Green), Toronto, ON, Canada.

Supported by the Canadian Institutes of Health Research, the Physicians' Services Incorporated, and the Ontario Mental Health Foundation (grant nos. MOP-67072, 05-50, 2005-ABI-392).

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.

Reprint requests to Robin E. Green, PhD, CPsych, Toronto Rehabilitation Institute, The University Centre, 550 University Ave, Toronto, ON, M5G 2A2, Canada, e-mail: *green.robin@torontorehab.on.ca.*

0003-9993/08/8912S-00442$34.00/0
doi:10.1016/j.apmr.2008.07.005

Key Words: Brain injuries; Diffusion magnetic resonance imaging; Rehabilitation; Spinal cord injuries.

THE PRESENCE OF TRAUMATIC brain injury in patients with SCI is a well documented phenomenon. This association is not surprising, given the striking similarities between the TBI and SCI populations in demographic profile as well as in injury circumstances.[1] The incidence of both TBI and SCI is higher in male subjects, with over 50% of the affected population being between the ages of 15 and 30 years.[2,3] In addition, both types of injuries typically result from high-velocity impact such as motor vehicle collisions (50% in both cases), falls (21% in both cases), and sporting accidents.[2] However, the precise frequency of comorbidity of TBI with SCI has not been clearly established. In most studies using 1 or 2 indicators of neurotrauma to diagnose TBI (eg, loss of consciousness, PTA, and/or neuropsychological deficits), the prevalence of TBI in traumatic SCI was estimated to be 40% to 60%.[4-11] However, when structural MRI was combined with neuropsychological testing to evaluate the presence of neurotrauma, 74% of patients of SCI were found to have concomitant brain injury in 1 study.[12] Given the high frequency of the comorbidity, the ability to diagnose or rule out concomitant TBI is a major issue in the treatment and rehabilitation of patients with SCI.

A major goal of neuroradiologic investigations in brain trauma is to identify the presence of DAI, a key mechanism of neural damage after TBI.[13] DAI results from unequal rotational or acceleration/deceleration forces that cause multifocal lesions in WM because of a shear-strain deformation.[14-16] DAI sites of predilection include subcortical WM, corpus callosum, fornix,

List of Abbreviations

ALIC	anterior limb of the internal capsule
ANOVA	analysis of variance
DAI	diffuse axonal injury
DTI	diffusion-tensor imaging
FA	fractional anisotropy
FMRIB	functional magnetic resonance imaging of the brain
gCC	genu of the corpus callosum
GCS	Glasgow Coma Scale
MRI	magnetic resonance imaging
PLIC	posterior limb of the internal capsule
PTA	posttraumatic amnesia
ROI	region of interest
sCC	splenium of the corpus callosum
SCI	spinal cord injury
TBI	traumatic brain injury
TBSS	tract-based spatial statistics
WM	white matter

internal capsule, and infratentorial WM.[17-20] Although conventional MRI techniques can readily visualize posttraumatic focal structural lesions, they are unable to detect microscopic WM damage in DAI. Consequently, the diagnosis of TBI is missed in some patients, particularly those with milder brain injuries.[21]

Recently, DTI has proven fruitful in detecting the loss of axonal organization in TBI.[22-25] DTI is a novel MRI technique that can provide information about the microscopic tissue architecture. The diffusion tensor represents a model of water diffusion in biologic tissues[26] and describes the magnitude, direction, and orientation of the diffusion distribution. FA is an index used to characterize the local coherence of fibers[27] and is one of the most widely used metrics in diffusion anisotropy.[28] FA is a convenient measure because it is scaled from 0 (complete isotropic diffusion) to 1 (complete anisotropic diffusion). In WM, water diffusion is less restricted in the direction parallel to the fiber orientation, whereas it is highly restricted in the direction perpendicular to the fibers.[26] FA is highest in major WM tracts (maximum possible value, 1) while it approaches 0 in cerebrospinal fluid. For example, normative WM tracts with coherently oriented fibers typically exhibit higher FA values, whereas reduced FA usually occurs in WM disease states (although this is not always the case). Reduced FA values have been identified in DAI sites[20,22,23,25,29-37] and are more sensitive than conventional MRI to axonal injury in a mouse model of TBI.[38] Early detection of DAI using diffusion-weighted MRI can not only direct acute neurologic intervention[39] and long-term rehabilitation but also improve outcome prediction in adult TBI.[40]

Before DTI can be reliably used to assess for TBI in patients with SCI, however, several questions need to be addressed. First, does SCI without any comorbidity cause alterations in the human brain? If so, is this injury distinguishable from that caused by TBI? SCI-related brain injury must be documented so the effects of SCI alone are not confounded with the effects of brain injury. A false diagnosis of TBI could have serious clinical, ethical, and financial consequences. If injury caused by SCI can be identified and factored out when using DTI to diagnose TBI, we can greatly improve the diagnostic specificity and reduce the likelihood of a false-positive diagnosis of TBI in patients with SCI. Second, even if SCI does cause alterations to the brain, are there areas of the brain that show reduced FA secondary to TBI, but are nonetheless unaffected by the effects of traumatic SCI?

In this study, we attempted to localize WM alterations in the brain caused by traumatic SCI alone using DTI-derived FA values as a marker of axonal integrity. We also attempted to identify those regions of the brain that would reliably discriminate patients with traumatic SCI plus TBI from patients with traumatic SCI only. We therefore included 3 study groups: (1) patients with SCI and no evidence of TBI (SCI only) based on structural 3 Tesla MRI and collateral neurologic findings, (2) patients with SCI and definitive structural MRI evidence of TBI (SCI with TBI), and (3) healthy controls. We examined the data with 2 approaches. We first investigated between-group FA differences in a priori ROIs, including the ALIC and PLIC, forceps minor, and gCC and sCC. These regions were selected because previous studies have shown that DTI abnormalities in the corpus callosum and forceps are particularly sensitive markers for TBI.[29,33] Moreover, WM tracts in the internal capsule, which conduct sensory afferents, may be a region most sensitive to traumatic SCI. In addition, we explored a novel group analysis technique, TBSS, which allows whole-brain, voxel-wise FA comparisons between groups.[41-44] To date, the application of TBSS has not been used to study TBI or SCI.

We conducted 3 between-group analyses of FA: SCI only versus controls, SCI with TBI versus controls, and SCI only versus SCI with TBI. We hypothesized that (1) compared with both patients with SCI only and normal controls, the SCI with TBI group would show multiple areas of FA reductions in predilection sites of DAI; and (2) in WM fiber tracts containing afferent pathways, both SCI only and SCI with TBI would have reduced FA compared with controls because of loss of afferent projections.

METHODS

Subjects

The study protocol was approved by the research ethics board at the local institution at which the study was conducted, and the procedures of the study were in accordance with the standards of the research ethics board.

Twenty-two patients (15 men, 7 women; mean age, 34.3y; range, 19-53y) with traumatic SCI were recruited from a large urban SCI program within a rehabilitation hospital, to which they were referred for subacute rehabilitation between 2006 and 2008. The demographic and clinical information of the participants in this study is summarized in table 1. All patients underwent an MRI scan of the brain in the subacute period after their traumatic SCI. Each patient was assigned to 1 of 2 groups, SCI with TBI or SCI only, based on MRI findings and collateral information examinations (ie, GCS, PTA, loss of consciousness, neuropsychological assessment). For the SCI-only group, all patients had negative MRIs of the brain. Fifteen patients were assigned to the SCI-only group (13 men, 2 women; mean age, 35.7y; range, 20-54y). All collateral information available at the time of writing is included in table 1, with the exception of invalid information, which was excluded. This included 2 GCS scores, invalid because of alcohol at the time of assessment, and 1 PTA score, invalid because of medications during the period of PTA. Seven patients were assigned to the SCI plus TBI group (5 men, 2 women; mean age, 31.6y; range, 20-50y). All 7 patients had positive MRI findings consistent with previous brain trauma. For this group, only collateral information with positive findings is reported in table 1 (eg, depressed GCS, presence of PTA).

The healthy control group included 12 healthy volunteers (7 men, 5 women; mean age, 34.6y; range, 21-51y) who had had no known history or MRI evidence of central nervous system disease.

Exclusion criteria for all participants included any history of TBI and any history of neurologic or psychotic illness, and prior structural abnormality of the brain. All participants were proficient in English.

The patient groups were well matched on the key parameters. There were no significant differences or differences approaching significance between the 2 patient groups on age, years, or number of days between injury and MRI. There were no differences between either of the patient groups and the healthy control group on age. However, both patient groups differed significantly from the control group on years of education: the SCI-only group differed from controls at the $P<.000$ level of significance; the SCI with TBI group differed at the $P<.001$ level of significance.

Magnetic Resonance Imaging Data Acquisition

All patients and controls were scanned using a GE 3 Tesla MRI scanner[a] equipped with an 8-channel head-coil (MRI devices). Subjects underwent the routine MRI protocol (including T_1-weighted spin-echo, T_2-weighted spin-echo, T_2*-weighted