JOURNAL OF NEUROTRAUMA
Volume 12, Number 4, 1995
Mary Ann Liebert, Inc.

New Magnetic Resonance Imaging Techniques for the Evaluation of Traumatic Brain Injury

DOUGLAS H. SMITH,[1] DAVID F. MEANEY,[2] ROBERT E. LENKINSKI,[3] DAVID C. ALSOP,[3] ROBERT GROSSMAN,[3] HIROHIKO KIMURA,[3] TRACY K. McINTOSH,[1] and THOMAS A. GENNARELLI[4]

ABSTRACT

Although current computerized tomography (CT) and magnetic resonance imaging (MRI) techniques have shown great utility in diagnosing various aspects traumatic brain injury, damage resulting from mild diffuse brain injury often goes undetected with these procedures. Newly developed MRI techniques, including magnetization transfer imaging (MTI) and diffusion-weighted imaging (DWI), have been proposed to have enhanced sensitivities for identifying damage induced by both diffuse and focal brain injury. Results from recent initial studies with experimental models of brain injury suggest that MTI may be useful for evaluating diffuse white matter damage, while DWI may demonstrate regions of focal contusion more acutely and with greater accuracy than conventional MRI procedures.

Key words: diffusion-weighted imaging; magnetization transfer imaging; traumatic brain injury

INTRODUCTION

VARIOUS IMAGING TECHNIQUES, including X-ray computerized tomography (CT) and magnetic resonance imaging (MRI), have been used with great success for diagnosing anatomic and physiologic changes following traumatic brain injury (Levin et al., 1988, 1990; Levi et al., 1990; Zimmerman et al., 1978; Teasdale et al., 1984). These conventional CT and MRI procedures are typically used to identify hemorrhage and edema following brain trauma. CT is thought to be advantageous for the identification of localized accumulation of blood and differentiating hemorrhage from edema, while MRI offers higher resolution imaging and may more accurately detect multiple lesions. However, damage to the skull is much more easily discerned with CT. Despite the sensitivity of these techniques, it has often been observed that CT and MRI evaluation fail to detect abnormalities following brain injury which are commensurate with the extent of presenting or enduring symptoms (Levi et al., 1990). This shortcoming is thought to be due to the limited ability of these techniques to identify minute lesions not associated with hemorrhage or edema. In patients suffering from diffuse brain damage that may not be associated with vascular disruption, utilization of conventional CT and MRI techniques may lead to an underestimation of the severity of injury. Recently, new MRI techniques have been developed that may have enhanced capacities to distinguish and differentiate between various pathologic aspects or categories of brain injury.

[1]Division of Neurosurgery, [2]Department of Bioengineering, and [3]Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania.

[4]Department of Neurosurgery, Hahnemann University, Philadelphia, Pennsylvania.

CLASSIFICATION OF TRAUMATIC BRAIN INJURY AND CURRENT DIAGNOSIS

Although brain injuries vary widely in their etiology and pathophysiology, two main categories of traumatic nonpenetrating brain injury in humans have been established: focal and diffuse brain injury (Graham et al., 1988; Gennarelli, 1993).

Focal Brain Injury

Contact loading, resulting from direct impact to the head, may cause focal brain injuries, which include cerebral contusions and hematomas (Gennarelli, 1993). This focal injury may lead to local mass effects, including brain shifts, herniation, and brain stem compression, which ultimately may lead to coma. Diagnosis of focal injury using conventional CT and MRI (i.e., T2-weighted images) techniques has met with great success due to their sensitivity in demonstrating overt localized pathology or anatomic repositioning related to mass effects following injury (Levin et al., 1988; Teasdale et al., 1984). Focal brain contusions have also been shown to induce cerebral edema formation, which may also be observed with CT and MRI.

Diffuse Brain Injury

Diffuse brain injuries, also commonly referred to as shearing brain injuries, are associated with cerebral concussion and prolonged traumatic coma resulting from diffuse axonal injury (DAI). Diffuse brain injuries are thought to result from inertial loading of the brain producing diffuse shearing and tensile strains of brain tissue (Gennarelli et al., 1982). This injury is almost exclusively observed following motor vehicular accidents, resulting from a sudden change in motion of a person's head during the crash. DAI is commonly diagnosed following head trauma in patients demonstrating prolonged unconsciousness, unaccompanied by an intracranial mass lesion (Graham et al., 1988) and verified histopathologically as diffuse macroscopic and/or microscopic axonal damage in the white matter. Altered neurotransmission due to damage to axonal membranes following diffuse injury has been suggested to produce primary coma, in contrast to secondary coma resulting from compressive lesions. DAI is thought to be present in over half of all severely head-injured patients and in more than 85% of the severe head injuries resulting from vehicular accidents (Graham et al., 1993). In DAI at the highest severity (Grade 3), the microscopic and macroscopic lesions extend more centrally and become visible on conventional CT and MRI examinations, demonstrating hemorrhagic lesions of the basal ganglia and dorsal lateral midbrain as well as tearing of the corpus callosum (Levin et al., 1990; Levi et al., 1990; Teasdale et al., 1984). However, following mild to moderate diffuse brain injury, DAI of Grades 1 and 2 may appear in the absence of large tissue tears, microhemorrhage, or focal edema (Adams et al., 1989). Therefore, the damage produced by milder forms of diffuse brain injury may not be easily discerned with standard imaging techniques. Without evidence of diffuse damage on CT or MRI images, diagnosis of mild to moderate DAI is often dependent on physical examination, and may be confirmed only by postmortem histopathologic analysis. Due to the deficiencies of current imaging techniques, the application of more sophisticated MRI techniques has been proposed, which may identify brain damage with higher precision and more acutely than previous MRI procedures.

NEW DIAGNOSTIC IMAGING TECHNIQUES

Standard imaging techniques are not only limited in their ability to adequately diagnose diffuse brain injury, but also in their ability to detect acute posttraumatic metabolic and/or neurochemical changes. Several new MRI techniques have been developed that may enhance the detection of tissue damage and may noninvasively monitor metabolic changes following brain injury. We will describe two new MRI techniques, magnetization transfer imaging (MTI) and diffusion-weighted imaging (DWI), which have been evaluated for their abilities to detect brain tissue damage and pathophysiologic changes. Although these two techniques are based on completely different principles, they have both shown promise in their initial application for the diagnosis of traumatic brain injury.

Magnetization Transfer Imaging (MTI) and Diffuse Brain Injury

MTI has been shown to be very useful in demonstrating white matter abnormalities, due to its sensitivity in diagnosing demyelination in the early stages of multiple sclerosis, both clinically and in at least one experimental model (Dousset et al., 1992). This technique appears sensitive enough to differentiate edema from demyelination in the white matter that are not observable with standard MRI techniques. The physical principle of MTI is based on the interaction of immobile protons with free protons following a magnetic pulse (Wolff and Balaban, 1989). While immobile protons are associated with macromolecules (such as myelin), free protons are found in bulk water. The signal obtained to produce a magnetic resonance image is derived from measuring the magnetic spins (fields) of the protons only in the free water. Magnetization transfer contrast is introduced by apply-

ing an off-resonance radio-frequency pulse, saturating the energy level of immobile protons without affecting the signal of free protons. Exchange of this saturated magnetization from immobile protons to protons in free water, termed "cross-relaxation," will affect the signal intensity observed on the subsequent magnetic resonance image. It has been previously established that the magnetization transfer ratio (MTR) calculated in normal white matter is between 41 and 43%, and that a decrease in MTR may be observed following damage to the white matter. In particular, the extent of MTR loss has been shown to be commensurate with the severity of white matter damage (Dousset et al., 1992). Since the loss of MTR in the white matter may be dependent on disruption of macromolecules and not on a potential increase in free water, a decreased MTR value has been proposed to serve as a specific indicator of tissue damage and not generalized cytotoxic edema. Separation of edematous lesions from tissue damage, such as axonal injury, may be of important prognostic value, since edema may be reversible, while extensive tissue damage may suggest a poor prognosis.

We have recently reported initial findings evaluating the utility of MTI as a diagnostic tool to demonstrate DAI in the posttraumatic setting. We applied the MTI technique to a new model of nonimpact rotational acceleration brain injury in miniature swine. This brain injury model is similar to a previous model of brain rotational acceleration, extensively characterized in nonhuman primates, which produced diffuse axonal damage in a distribution similar to that observed following human brain injury (Gennarelli et al., 1982). The miniature swine model of rotational acceleration brain injury was developed through the use of physical models, and has been shown to produce mild DAI in a relatively consistent pattern (Meaney et al., 1993; Ross et al., 1994). In brief, using a HYGE pneumatic impactor, the head is rapidly rotated 105° about the rostra-caudal axis over 4–6 ms. Four animals were used for the initial evaluation with peak coronal plane rotational accelerations in the range of 0.6–1.7 $\times$ 10^5 rad/s^2. MRI procedures were performed in anesthetized animals 1 day preinjury, immediately following injury (20–60 min), and 3 and 7 days following injury using a General Electric Sigma 1.5 T clinical MR scanner. MTI was performed by employing a 3D volume gradient echo pulse sequence (TR 106 msec; TE 5 msec; flip angle 20°) with and without a saturation pulse applied 2000 Hz off resonance from water. As reported earlier, MTI abnormalities, identified as decreases in MTR, were observed in specific white matter regions of brain-injured minipigs (Lenkinski et al., 1993; Kimura et al., 1994). Importantly, several regions of decreased MTR, subsequently shown not to be hemorrhagic, were not apparent with conventional MRI (T2-weighted images). In general, these abnormalities appeared to correspond anatomically with the histopathologic evidence of DAI (terminal clubbing and swelling of axons). It is important to note that these preliminary studies have yet to be examined in a quantitative manner and a correlation between loss of MTR and DAI has not been established. Nevertheless, these promising results, coupled with the results from the multiple sclerosis studies, suggest that MTI may have improved sensitivity over standard MRI techniques in identifying white matter abnormalities.

Diffusion-Weighted Imaging (DWI) and Contusional Brain Injury

DWI has recently been extensively evaluated in several models of experimental cerebral ischemia (Moseley et al., 1990; Minematsu et al., 1992; Mintorovitch et al., 1991). In these models, this technique has been shown to be more sensitive than conventional MRI techniques in demonstrating the early appearance and evolution of pathologic changes in regions of injury. In addition, DWI has been used to evaluate the efficacy of pharmacologic compounds in the treatment of cerebral ischemia (Minematsu et al., 1993; Lo et al., 1994). The basic principle of DWI is the detection of a change in diffusion of freely moving protons in water. Following ischemia, the swelling of neurons and glia (cytotoxic edema) is thought to restrict the interstitial space. Because of the shifting of water from the extracellular space to intracellular compartments, it has been hypothesized that there is a decrease in the translational movement or diffusion of free protons. This is thought to be due to the greater interaction of protons with abundant intracellular macromolecules, thus restricting movement or diffusion. Although a decrease in the regional diffusion coefficient of protons has been shown to correspond with regions of pathologic changes following ischemia (Sevick et al., 1992), there is debate as to the exact mechanism(s) responsible for this decrease.

Recently, DWI was evaluated in a model of experimental lateral (parasagittal) fluid-percussion (FP) brain injury in the rat (Hanstock et al., 1994). In this extensively characterized model, brain injury is induced by rapidly injecting a bolus of saline (21 ms) through a craniectomy into the closed cranial space (McIntosh et al., 1989). This injury induces reproducible damage to cortical, hippocampal, and thalamic structures (Cortez et al., 1989; Hicks et al., 1992), with associated deficits in cognitive and neurologic motor function (McIntosh et al., 1989; Smith et al., 1991). Although lateral FP brain injury in the rat is generally considered a model of focal contusion, recent studies have found diffuse effects, in-

cluding the diffuse appearance of axonal damage. Since the rat has relatively little white matter compared to higher species, and due to the small brain size, brain MRI studies are typically restricted to the evaluation of significant changes in gray matter.

In the rat FP brain injury model, Hanstock and colleagues (1994) evaluated the DWI technique using a Varian 7T horizontal bore magnet. Diffusion-weighted images were acquired with a spin echo pulse sequence TR 2 s, TE 100 ms, b 0, 544, and 1110 s/mm^2. These investigators found that unlike a decrease in the diffusion coefficient observed in models of ischemia, by 4 h following injury of low severity, there appeared to be an increase in the diffusion coefficient in the injured cortical and hippocampal tissue. These changes were not observed in the T2-weighted images. These authors suggested that posttraumatic vasogenic edema formation may have accounted for this increase, potentially by increasing the fluid volume in the extracellular space.

Our laboratory has also recently reported an initial evaluation of DWI in the identical rat FP brain injury model, using a 4.7T GE magnet (Alsop et al., 1994). Diffusion-weighted images were acquired with a spin echo sequence, TR 2 s, TE 60 ms, b 0, 1000 s/mm^2. We found that within 1 h of injury of moderate severity, the diffusion coefficient *decreased* in the injured cortical, hippocampal, and thalamic regions. These regions of decreased diffusion were unremarkable in T2-weighted images. Although the cause for the difference in results between the two brain injury studies described above is not clear, it may be related to differences in the severity of injury and to the postinjury timing of DWI evaluation. Nevertheless, in both studies DWI techniques revealed abnormalities in regions previously shown to undergo histopathologic damage. Also, in both studies changes observed with DWI were not visible in T2-weighted images. Taken together, the results from these studies suggest that DWI may be more sensitive than conventional MRI techniques in demonstrating acute pathologic changes following focal brain trauma.

At present, the utility of DWI for diagnosing DAI is not known. Although changes in the diffusion of protons most likely occur following traumatic diffuse white matter damage, the application of DWI to the evaluation of white matter injury necessitates special consideration. Restriction of protons by macromolecular barriers may not be the same for different directions of motion. This is particularly true of white matter, which has alignment of myelin fiber tracts in varying planes. "Anisotropic diffusion" of brain white matter has been observed with DWI, demonstrated as differing diffusion coefficients according to the direction or plane of measurement (Moseley et al., 1991). Therefore, to adequately evaluate potential white matter damage with DWI, the diffusion gradient may need to be applied along four to six planes. Nevertheless, this technique may prove useful for detecting abnormalities in brain white matter following trauma, since a decrease in anisotropy of white matter has been observed in a model of spinal cord injury (Ford et al., 1994).

DISCUSSION

Recent technologic advances with MRI techniques, including MTI and DWI, may ultimately help to sharpen our abilities in the diagnosis of traumatic brain injury. Although CT remains the most common first line of diagnostic imaging following brain injury, clinical availability of more sophisticated and higher field strength MRI capabilities is rapidly increasing.

Characterization of promising new MRI techniques may prove essential for the full utilization of these new devices.

ACKNOWLEDGMENTS

A portion of this work was supported by NIH Grants NS08803 and AG12527.

REFERENCES

ADAMS, J.H., DOYLE, D., FORD, I., GENNARELLI, T.A., GRAHAM, D.I., and McCLELLAN, D.R. (1989). Diffuse axonal injury in head injury: Definition, diagnosis, and grading. Histopathology **15,** 49–59.

ALSOP, D.C., LENKINSKI, R.E., DETRE, J.A., GROSSMAN, R., McINTOSH, T.K., GENNARELLI, T.A., and SMITH, D.H. (1994). Assessment of diffusion weighted MRI for evaluation of acute traumatic brain injury in a rat model. Soc. Magn. Reson. Med. **3,** 1370.

CORTEZ, S.C., McINTOSH, T.K., and NOBLE, L. (1989). Experimental fluid percussion brain injury: Vascular disruption and neuronal and glial alterations. Brain Res. **482,** 271–282.

DOUSSET, V., GROSSMAN, R., RAMER, K.N., et al. (1992). Experimental allergic encephalomyelitis and multiple sclerosis: Lesion characterization with magnetization transfer imaging. Radiology **182,** 483–491.

FORD, J.C., HACKNEY, D.B., ALSOP, D.C., JARA, H., JOSEPH, P.M., HAND, C.M., and BLACK, P. (1994). MRI characterization of diffusion coefficient in a rat spinal cord injury model. Magn. Reson. Med. **31,** 488–494.

GENNARELLI, T.A. (1993). Mechanisms of brain injury. J. Emerg. Med. **11(suppl 1),** 5–11.

GENNARELLI, T.A., THIBAULT, L., ADAMS, J.H., GRAHAM, D.I., THOMPSON, C., and MARCINCIN, R.P. (1982). Diffuse axonal injury and traumatic coma in the primate. Ann. Neurol. **12,** 564–574.

GRAHAM, D.I., ADAMS, J.H., and GENNARELLI, T.A. (1988). Mechanisms of non-penetrating head injury. Prog. Clin. Biol. Res. **234,** 159–168.

GRAHAM, D.I., ADAMS, J.H., DOYLE, D., et al. (1993). Quantification of primary and secondary lesions in severe head injury. Acta Neurochir. **Suppl. 57,** 41–48.

HANSTOCK, C.C., FADEN, A.I., BENDALL, R.M., and VINK, R. (1994). Diffusion-weighted imaging differtiates ischemic tissue from traumatized tissue. Stroke **25,** 843–848.

HICKS, R.R., SAINT MARIE, R.L., and McINTOSH, T.K. (1992). Temporo-spatial mapping of neuronal degeneration after lateral fluid-percussion brain injury in rats. J. Neurotrauma **9,** 388.

KIMURA, H., SMITH, D.H., LENKINSKI, R.E., GROSSMAN, R., and GENNARELLI, T.A. (1994). Magnetic transfer imaging of diffuse axonal injury in pig brain: Characterization by magnetization transfer ratio with histopathologic correlation. Radiology **193P,** 461.

LENKINSKI, R.E., SMITH, D.H., McINTOSH, T., ROSS, D.T., GENNARELLI, T.A., and GROSSMAN, R.I. (1993). An integrated MRI/MRS study of a minipig model for shearing injuries in the brain. Proc. Soc. Magn. Res. Med. **3,** 1491.

LEVI, L., GUILBURD, J.N., LEMBERGER, A., SOUSTIEL, J.F., and FEINSOD, M. (1990). Diffuse axonal injury: Analysis of 100 patients with radiological signs. Neurosurgery **27,** 429–432.

LEVIN, H.S., WILLIAMS, D., CROFFORD, M.J., et al. (1988). Relationship of depth of brain lesions to consciousness and outcome after closed head injury. J. Neurosurg. **69(6),** 861–866.

LEVIN, H.S., WILLIAMS, D.H., VALASTRO, M., EISENBERG, H.M., CROFFORD, M.J., and HANDEL, S.F. (1990). Corpus callosal atrophy following closed head injury: detection with magnetic resonance imaging. J. Neurosurg. **73,** 77–81.

LO, E.H., MATSUMOTO, K., PIERCE, A.R., GARRIDO, L., and LUTTINGER, D. (1994). Pharmacologic reversal of acute changes in diffusion-weighted magnetic resonance imaging in focal cerebral ischemia. J. Cereb. Blood Flow Metab. **14,** 597–603.

McINTOSH, T.K., VINK, R., NOBLE, L., YAMAKAMI, I., FERNYAK, S., and FADEN, A.I. (1989). Traumatic brain injury in the rat: Characterization of a lateral fluid percussion model. Neuroscience **28,** 233–244.

MEANEY, D.F., SMITH, D.H., ROSS, D.T., and GENNARELLI, T.A. (1993). Diffuse axonal injury in the miniature pig: Biomechanical development and injury threshold. *Crashworthiness and Occupant Protection in Transportation Systems ASME,* AMD-Vol. 169/BED-Vol. 25, pp. 169–175.

MINEMATSU, K., LI, L., FISHER, M., SOTAK, C.H., DAVIS, M.A., and FIANDACA, M.S. (1992). Diffusion-weighted magnetic resonance imaging: Rapid and quantitative detection of focal brain ischemia. Neurology **42,** 235–240.

MINEMATSU, K., FISHER, M., LI, L., et al. (1993). Effects of a novel NMDA antagonist on experimental stroke rapidly and quantitatively assessed by diffusion-weighted MRI. Neurology **43,** 397–403.

MINTOROVITCH, J., MOSELEY, M.E., CHILEUITT, L., SHIMIZU, H., COHEN, Y., and WEINSTEIN, P.R. (1991). Comparison of diffusion- and T2 weighted MRI for the early detection of cerebral ischemia and reperfusion in rats. Magn. Reson. Med. **18,** 39–50.

MOSELEY, M.E., COHEN, Y., MINTOROVITCH, J., et al. (1990). Early detection of regional cerebral ischemia in cats: Comparison of diffusion- and T2-weighted MRI and spectroscopy. Magn. Reson. Med. **14,** 330–346.

MOSELEY, M.E., KUCHARCZYK, J., ASGARI, H.S., and NORMAN, D. (1991). Anisotropy in diffusion-weighted MRI. Magn. Reson. Med. **19,** 321–326.

ROSS, D.T., MEANEY, D.F., SABOL, M., SMITH, D.H., THIBAULT, L.E., and GENNARELLI, T.A. (1994). Distribution of diffuse axonal injury following inertial closed head injury in miniature swine. Exp. Neurol. **126,** 1-10.

SEVICK, R.J., KANDA, F., MINTOROVITCH, J., et al. (1992). Cytotoxic brain edema: Assessment with diffusion-weighted MR imaging. Radiology **185,** 687–690.

SMITH, D.H., OKIYAMA, K., THOMAS, M., CLAUSSEN, B., and McINTOSH, T.K. (1991). Evaluation of memory dysfunction following experimental brain injury using the Morris Water Maze. J. Neurotrauma **8,** 259–269.

TEASDALE, E., CARDOSO, E., GALBRAITH, S., and TEASDALE, G. (1984). CT scan in severe diffuse head injury: Physiological and clinical correlations. J. Neurol. Neurosurg. Psychiat. **47,** 600–603.

WOLFF, S.D., and BALABAN, R.S. (1989). Magnetization transfer contrast (MTC) and tissue water proton relaxation *in vivo.* Magn. Reson. Med. **10,** 135–144.

ZIMMERMAN, R.A., BILANIUK, L.T., and GENNARELLI, T.A. (1978). Computed tomography of shearing injuries of the cerebral white matter. Radiology **127,** 393–396.

Address reprint requests to:
Dr. Douglas H. Smith
Division of Neurosurgery
University of Pennsylvania
105 Hayden Hall
240 South 33rd Street
Philadelphia PA 19104-6316