Use of Advanced Neuroimaging Techniques in the Evaluation of Pediatric Traumatic Brain Injury

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Abstract
Advanced neuroimaging techniques are now used to expand our knowledge of traumatic brain injury, and increasingly, they are being applied to children. This review will examine four of these methods as they apply to children who present acutely after injury. (1) Susceptibility weighted imaging is a 3-dimensional high-resolution magnetic resonance imaging technique that is more sensitive than conventional imaging in detecting hemorrhagic lesions that are often associated with diffuse axonal injury. (2) Magnetic resonance spectroscopy acquires metabolite information reflecting neuronal integrity and function from multiple brain regions and provides sensitive, noninvasive assessment of neurochemical alterations that offers early prognostic information regarding the outcome. (3) Diffusion weighted imaging is based on differences in diffusion of water molecules within the brain and has been shown to be very sensitive in the early detection of ischemic injury. It is now being used to study the direct effects of traumatic injury as well as those due to secondary ischemia. (4) Diffusion tensor imaging is a form of diffusion weighted imaging and allows better evaluation of white matter fiber tracts by taking advantage of the intrinsic directionality (anisotropy) of water diffusion in human brain. It has been shown to be useful in identifying white matter abnormalities after diffuse axonal injury when conventional imaging appears normal. An important aspect of these advanced methods is that they demonstrate that 'normal-appearing' brain in many instances is not normal, i.e. there is evidence of significant undetected injury that may underlie a child's clinical status. Availability and integration of these advanced imaging methods will lead to better treatment and change the standard of care for use of neuroimaging to evaluate children with traumatic brain injury.

Key Words
Diffusion tensor imaging · Diffusion weighted imaging · Neuroimaging techniques · Traumatic brain injury

Introduction
Advances in neuroimaging over the past two decades have greatly helped in the clinical care and management of children with traumatic brain injury (TBI). The advent of newer and more sensitive imaging techniques is now being used to better characterize the nature and evolution of injury and the underlying mechanisms that lead to progressive neurodegeneration, recovery or subsequent plasticity. These advanced imaging techniques have also begun to demonstrate that in many patients, 'normal-appearing' brain as examined with computed tomographic (CT) scanning or with conventional magnetic resonance imaging (MRI) may not adequately depict brain injury. This review will describe four advanced MRI techniques.
as related to their use in TBI. They include susceptibility weighted imaging (SWI), magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI), diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI). These techniques were selected as they are of value in the acute period after injury, in contrast to functional MRI that has been used for long-term evaluation. Several of these methods appear particularly useful for the assessment of diffuse axonal injury (DAI) that is responsible for a wide range of motor and cognitive impairments.

**Susceptibility Weighted Imaging**

In the past, neuropathological studies have emphasized that long-term sequelae are related to large structural lesions (e.g. contusions, intraparenchymal hemorrhages, as well as subdural and epidural hematomas), yet more recent studies have demonstrated that hemorrhagic and nonhemorrhagic shearing lesions associated with DAI occur in up to 40% of children with TBI [Blackman et al., 2003; Cordobes et al., 1986; Gentry et al., 1988; Mittl et al., 1994]. Additionally, more subtle microscopic injury, which may not be visible with routine neuroimaging techniques such as CT scanning or T1, T2, fluid-attenuated inversion recovery (FLAIR) and gradient recalled echo (GRE) MRI may contribute to significant functional impairments [Meythaler et al., 2001]. The pathology of DAI is characterized histologically by widespread damage to axons in several brain regions including the corpus callosum, parasagittal white matter and gray-white matter junctions near the cerebral cortex and brainstem [Adams et al., 1982, 1989; Graham et al., 2000; Meythaler et al., 2001]. Recent immunohistochemistry studies have also shown that the extent and distribution of axonal injury is similar in children and adults [Gorrie et al., 2002].

Considering the widespread consequences of DAI, its detection is important for the evaluation, treatment and prognosis of TBI patients, particularly in those with moderate injuries where damage and/or repair may currently go unrecognized. MRI has provided substantial improvement in the ability to detect hemorrhagic and nonhemorrhagic lesions [Gentry et al., 1988; Levin et al., 1987; Orrison et al., 1994]. However, little is known about the true size, number, volume and distribution of DAI lesions in children who survive the acute injury and therefore do not undergo autopsy. There also remains scant literature regarding DAI imaging and outcome prediction in children. Several small case series of DAI in children have found varying outcomes but could not correlate the extent of injury with prognosis [Chiaretti et al., 1998; Gleckman et al., 1999; Vowles et al., 1987].

Newer gradient echo imaging methods have further improved the detection of susceptibility-related effects of hemorrhagic shearing injury [Grados et al., 2001; Scheid et al., 2003; Tong et al., 2003, 2004; Yanagawa et al., 2000]. One such sequence is SWI, which can be performed on conventional scanners and was originally designed for MR venography, utilizing the paramagnetic property of intravascular deoxyhemoglobin [Reichenbach et al., 1997]. Most blood products are also paramagnetic, making it possible to exploit magnetic susceptibility effects on SWI in order to increase the visibility of hemorrhages by accentuating signal loss from rapid spin dephasing. In particular, SWI allows improved detection of paramagnetic hemorrhagic blood products, such as extravascular deoxyhemoglobin and methemoglobin, based on their magnetic susceptibility effects related to phase dispersion [Haacke et al., 2005; Sehgal et al., 2005].

SWI has been shown to be much more sensitive in detecting hemorrhagic DAI lesions after TBI in children compared with conventional MRI. In a previous study, we examined 7 children with TBI (age 14 ± 4 years; SWI obtained 5 ± 3 days after injury) and demonstrated that the number of hemorrhagic DAI lesions seen on SWI was six times greater than on conventional T2*. A comparison of SWI with 2-dimensional GRE in a TBI patient is seen in figure 1. SWI can visualize smaller and thus more numerous hemorrhages than previous MRI, and by inference, much more than CT.

In an expanded SWI study, 40 children and adolescents with mild to severe TBI and DAI (mean age 12 years; SWI 7 ± 4 days after injury) were examined [Tong et al., 2004]. The number and volume of hemorrhagic lesions were compared with long-term neurologic outcome, assessed using the Pediatric Cerebral Performance Category Scale score which is modified from the Glasgow Outcome Scale score and quantifies the overall functional neurologic morbidity and cognitive impairment of infants and children [Fiser et al., 2000]. We found that children with lower Glasgow Coma Scale (GCS) scores (≤8, n = 30) or prolonged coma (>4 days, n = 20) had a significantly greater average number and volume of hemorrhagic lesions. Also, children with normal outcomes or mild neurologic disability at 6–12 months after injury had a significantly lower number and volume of hemorrhagic DAI lesions than those who were moderately or severely dis-
Fig. 1. Improved detection of small hemorrhages using SWI. Axial CT image (A) is normal. Corresponding FLAIR image (B) shows small hyperintense lesions in the left frontal white matter. Conventional GRE (fast imaging with steady-state precession, 500/18, 15° flip angle, 78 Hz per pixel, two signals acquired, 4-mm-thick sections) image (C) shows faint matching hyperintensity. However, the SWI (3-dimensional fast low-angle shot, 57/40, 20° flip angle, 78 Hz per pixel, 64 partitions, one signal acquired, 2-mm-thick sections reconstructed over 4 mm) image (D) demonstrates multiple tiny hypointense foci consistent with small hemorrhages within the area of injury.

Fig. 2. Extent of hemorrhagic lesions within individual outcome groups. The mean volume (A) and number (B) of hemorrhagic lesions tend to increase with worsening severity of outcomes. N = Normal (n = 14); MI = mild disability (n = 16); MOD = moderate disability (n = 7); S = severe disability (n = 2); V = vegetative state (n = 1). When the outcome groups were dichotomized, the mean volume and number of lesions were significantly higher in the poor outcome group (MOD, S, V) compared with the good outcome group (N, MI). Data are based on Tong et al. [2004].
abled or in a vegetative state (fig. 2). We also determined that there were regional differences in DAI injury. Over 90% of patients had lesions in the parietotemporal occipital gray matter (PTOGM), parietotemporal occipital white matter and frontal white matter. Four regions were less commonly affected (i.e. <65% of patients), including the thalamus, brainstem, cerebellum and basal ganglia. Twelve of 40 patients (30%) had lesions in all 9 of the brain regions examined. Forty-two percent of these patients had poor outcomes. There were 14 patients who had lesions in 6 or fewer regions and all had good outcomes at 6–12 months. Only patients with involvement of 7 or more regions had poor outcomes. In figure 3, we show examples of hemorrhagic DAI lesions detected in TBI patients that illustrate that SWI allows better detection of these lesions, even in brain close to the skull and in regions such as the brainstem, which are not as well visualized with conventional MRI. Because SWI is much more sensitive in detecting hemorrhagic DAI, more accurate data can be obtained to objectively assess the severity of acute injury, and the extent of detected hemorrhage can provide long-term neurological and neuropsychological prognostic information. Studies correlating the abnormalities seen on SWI with conventional neuropathology need to be done to better define the neuroimaging correlates of injury with pathology as well as clinical symptoms.

**Magnetic Resonance Spectroscopy**

MRS is a noninvasive neuroimaging tool that allows in vivo analysis of neurochemicals and their metabolites in humans. MRI uses the strong signals from proton nuclei of water and their spatial location to reconstruct anatomically.
ical images. In contrast, $^1$H-MRS focuses on protons located on neurochemicals other than water that are present in much lower concentrations within tissues, and thus necessitates the use of water suppression techniques and reduced spatial resolution compared with imaging in order to measure them. $^1$H-MRS is the most widely used application of in vivo MRS in humans and will be discussed in this review; other atoms that are used include $^{31}$P, $^{13}$C, $^{14}$N, $^{19}$F and $^{23}$Na.

**Principles of MRS**

Several key brain metabolites are measured with $^1$H-MRS using both short (20–40 ms) and intermediate to long (135–270 ms) echo delay time MRS techniques. Each metabolite resonates at a particular frequency dependent on the structure of the molecule and the strength of interaction between the nucleus and the electronic cloud within the particular molecule. The size of the change in frequency is known as the chemical shift (measured in parts per million). After Fourier analysis, the plot of signal amplitude versus frequency in parts per million is known as the MR spectrum (fig. 4). N-acetylaspartate (NAA; 2.01 ppm), an amino acid synthesized in mitochondria, is a neuronal and axonal marker that decreases with neuronal loss or dysfunction [Danielsen and Ross, 1999]. In white matter, the NAA peak includes a greater contribution from N-acetylaspartylglutamate than in gray matter. Total creatine (Cr; 3.0 ppm) comprised of phosphocreatine and its precursor Cr are markers for intact brain energy metabolism. Total choline (Cho; 3.02 ppm) primarily consisting of phosphoryl and glycerophosphoryl Cho is a marker for membrane synthesis or repair, inflammation or demyelination. Lactate (Lac; 1.33 ppm) accumulates as a result of anaerobic glycolysis and, in the setting of TBI, may be a response to the release of glutamate [Alessandri et al., 2000]. Short echo delay time acquisitions allow for measurement of additional metabolites not seen with long echo delay time acquisitions because the metabolites have short T$_2$ relaxation times. Specifically, glutamate and immediately formed glutamine (Glx; 2.1–2.4 ppm) are excitatory amino acid neurotransmitters released to the extracellular space after brain injury and play a major role in neuronal death [Bullock et al., 1998]. Myo-inositol (Ins; 3.56 ppm), an organic osmolyte located in astrocytes, increases as a result of glial proliferation [Garnett et al., 2000].

Several techniques are commonly used to acquire spectroscopic data. Single voxel spectroscopy (SVS) allows acquisition of a single spectrum from one volume element (voxel), typically 8 cm$^3$ or more, whereas 2- or 3-dimen-

![Fig. 4. Single voxel $^1$H-MRS (stimulated echo acquisition mode; TR/TE/TM = 3,000/20/13 ms) from OGM of a normal 12-year-old male.](image-url)
Following acquisition, spectral processing identifies metabolites according to their chemical shift resonance, measures the area under each peak corresponding to their concentration and reports the findings as peak area metabolite ratios such as NAA/Cr or Cho/Cr. The distribution of metabolite levels or ratios acquired with MRSI displayed as signal intensities is known as metabolite maps or images. Previously, it was thought that Cr is maintained at a constant level in the brain and was therefore used in many early studies as an internal standard. Although it is known that Cr levels can change in certain conditions, ratios continue to be useful for reporting and comparing serial measurements or data between institutions using similar acquisition techniques. Methods to quantitate metabolite levels are being used routinely, and can use water as an internal reference [Barker et al., 1993] or phantoms containing known metabolite concentrations to quantify peak areas and report absolute or relative metabolite concentrations rather than ratios [Danielsen et al., 1995; Provencher, 1993].

**MRS and Development**

Metabolite levels vary by anatomic region [Frahm et al., 1989] and change rapidly as the brain develops [Kreis et al., 1993] (fig. 5), requiring the use of normal age-matched reference data for interpreting MR spectra from children. During early brain development, NAA reflects active myelination and is expressed early in the thalamus and later in parieto-occipital and periventricular white matter [Cady et al., 1996; Huppi, 2001]. Metabolite concentrations in babies change nonlinearly with age, with changes occurring most rapidly in premature newborns. Detailed assessments of the normal distribution of metabolites in preterm and term neonates report significant spectral differences between anatomic locations and postconceptual age, with premature neonates showing lower NAA/Cho and NAA/Cr ratios in the thalami and basal ganglia than term neonates [Vigneron et al., 2001]. Other studies have found that the absolute brain metabolite content in premature neonates at term was not substantially different from neonates born at term, suggesting that prematurity did not substantially affect biochemical brain maturation [Kreis et al., 2002]. Metabolite changes associated with brain maturation continue rapidly through the first year of life [Holshouser et al., 1997; Pouwels et al., 1999] and, to a lesser degree, through adolescence [Horska et al., 2002; McLean et al., 2000].

![Fig. 5. Spectra illustrating rapid metabolite changes that occur during normal brain maturation from birth through adolescence. All spectra were acquired with single voxel $^1$H-MRS (stimulated echo acquisition mode; TR/TE/TM = 3,000/20/13 ms) from OGM. Figure from Ashwal et al. [in press].](image)
MRS in the Evaluation of TBI

MRS provides a sensitive, noninvasive assessment of neurochemical alterations after brain injury and has shown potential for providing early prognostic information regarding the clinical outcome in pediatric patients with head injury [Ashwal et al., 2000; Brenner et al., 2003; Holshouser et al., 1997]. Several MRS studies have shown their utility in detecting DAI. Elevated Cho detected in white matter may be a breakdown product after shearing of myelin and cellular membranes, and reduced NAA probably results from neuronal or axonal injury [Ross et al., 1998]. Increased Cho following TBI may be an indication of cell membrane shearing injury or astrocytosis [Garnett et al., 2001]. Studies specifically looking at the splenium of the corpus callosum in brain-injured patients showed decreased NAA [Cecil et al., 1998; Sinson et al., 2001].

MRS has been used to study children with accidental and nonaccidental trauma (NAT) [Ashwal et al., 2000]. Short echo delay time SVS from normal-appearing OGM and parietal white matter measured at a mean of 5 ± 3 days after injury in 26 infants (1-18 months) and 8 ± 6 days after injury in 28 children (≥18 months) found lower NAA/Cr or NAA/Cho and higher Cho/Cr in poor outcome patients. Lac was present in 91% of infants and 80% of children with poor outcomes; none of the good outcome patients had Lac. Using a logistic regression model, clinical variables alone predicted the outcome in 77% of infants and 86% of children, whereas Lac presence alone predicted the outcome in 96% of infants and children. These findings showed that MRS acquired early after injury was more accurate than clinical variables in predicting the outcome. The strong correlation between Lac and outcome was observed primarily in infants who had NAT rather than after accidental trauma. Of great interest was that spectra from brain areas that did not appear visibly injured showed altered metabolite ratios that correlated with injury.

Quantitation of short echo delay time MRS using a time-domain fitting routine (LCModel) [Provencher, 1993] was performed in one study in children and facilitated the measurement of Ins and Glx levels along with NAA, Cr, Cho and Lac. In this study of 38 children (MRS at 7 ± 4 days after injury), Ins levels from occipital gray matter (OGM) were increased in children with TBI [Ashwal et al., 2004a]. Patients with poor outcomes had higher Ins levels compared to patients with good outcomes. It was postulated that increased Ins in TBI patients with a poor long-term neurologic outcome might be due to astrogliosis or to a disturbance in osmotic function. In addition, Glx from OGM was significantly increased in children with TBI compared to controls, but there was no difference between children with good compared with poor outcomes [Ashwal et al., 2004b]. This finding was attributed by the authors to the delay from the time of injury to imaging in severe TBI patients compared with mild-moderate TBI patients, because the former need to be medically stabilized before transport to the scanner. According to the literature, Glx levels most likely peak early after injury and fall rapidly [Schumann et al., 2000; Zhang et al., 2001]; therefore, Glx differences may have been comparable between outcome groups if the timing of the measurements was the same for all patients.

Other investigators have used 2D-MRSI to study TBI. Macmillan et al. [2002] studied normal and abnormal areas of the brain, as seen on T2-weighted images in patients with TBI with and without subarachnoid hemorrhage, and found low NAA levels in both areas compared with controls [Macmillan et al., 2002]. They also found higher Cho and Cr levels in patients with subarachnoid hemorrhage but no Lac that would have suggested ischemic neurochemical changes. Another study demonstrated a uniform global reduction in NAA in head-injured patients that returned to normal values in those patients who made a good recovery [Signoretti et al., 2002]. A recent publication using volumetric 3D-MRSI to study 14 subjects with mild TBI found significant reductions in NAA/Cr and NAA/Cho and increases in Cho/Cr ratios compared with controls in brain regions that appeared normal on conventional MRI, further illustrating the high sensitivity of noninvasive MRS for evaluating diffuse brain injury [Govindaraju et al., 2004].

Multivoxel MRSI has also been used to study TBI in children. In one study, 2D-MRSI in normal-appearing occipital and frontal regions of school-aged children 6 weeks after TBI showed that NAA/Cho ratios were lower in TBI patients than in control subjects, but no group differences were present for Cho or Cr [Hunter et al., 2005]. In a recent study, we used 2D-MRSI in children to examine whether metabolite ratios from visibly injured (lesions seen on SWI) or normal-appearing brain (no abnormalities on SWI or MRI) were more accurate in predicting long-term outcome and to examine regional differences in injury between TBI patients and controls [Holshouser et al., 2005]. Proton MRSI in 40 pediatric TBI patients was acquired in a transverse plane through the level of the corpus callosum within 1–16 days after the injury. T2-weighted imaging, FLAIR and SWI were used to identify voxels as normal appearing or with nonhemorrhagic or hemorrhagic injury. Metabolite ratios for global (all voxels in-
cluded), normal-appearing and hemorrhagic brain were compared and used in a logistic regression model to predict long-term neurologic outcome. A significant decrease in NAA/Cr and an increase in Cho/Cr (evidence of DAI) were observed in normal-appearing and visibly injured (hemorrhagic) brain compared with controls. NAA/Cr was further decreased in normal-appearing brain for poor outcome patients compared with patients with good outcomes or controls, whereas ratios were altered similarly for all TBI patients in visibly injured brain. Reduction in NAA in visibly injured brain is most likely caused by the primary impact, whereas reduction in NAA in normal-appearing brain may reflect DAI and Wallerian degeneration [Garnett et al., 2000]. Ratios from normal-appearing brain predicted the outcome with 85% accuracy compared with 67% using ratios from visibly injured brain.

Shown in figure 6 are examples of SWI and MRSI in a patient from this study (see legend for detailed description). These figures show the exquisite localization that can be accomplished with these techniques, the superior sensitivity of SWI in detecting hemorrhagic DAI lesions and that a spectrum from normal-appearing brain has decreased NAA which indicates neuronal injury or dysfunction.

These findings emphasize that additional information is detected by MRSI that is not seen by current conventional neuroimaging or SWI. For quantitative estimation, we analyzed MRSI voxel data from TBI patients in the above study [Holshouser et al., 2005]. In patients with good outcomes, an average of 8.2% of the voxels contained hemorrhagic lesions and 1.6% contained nonhemorrhagic DAI lesions. This is compared with patients with poor outcomes in which a larger percentage contained hemorrhagic (27.6%) and nonhemorrhagic lesions (2.2%). We also determined the percentage of voxels from normal-appearing brain in which NAA/Cr ratios were below two standard deviations of normal for age in each patient. Figure 7 is a plot of these percentages grouped by neurologic outcome assessed at 6–12 months after injury. Approximately, 60% of voxels from normal-appearing brain taken at the level of the corpus callosum in children who have normal or mild long-term outcomes have decreased NAA/Cr ratios early after injury. The percentage of abnormal voxels from normal-appearing brain increases with increasing severity of the outcome. This demonstrates that proton MRSI is extremely sensitive for detecting neuronal injury in brain that appears normal on neuroimaging. This is also an excellent demonstration of the diffuse

![Image](Fig. 6. T2-weighted MRI (A) and corresponding SWI (B) of a 15-year-old female adolescent ejected from a car showing hemorrhagic lesions in the body of the corpus callosum and bifrontal extraxial collections. The patient had a good outcome (i.e. normal) at 12 months after the injury. A Grid overlay shows the 160-mm field of view and 54 (6 × 9) voxel volume of interest (rectangle). Boxes indicate corresponding voxels in C. C Spectral map from 54 voxels in the volume of interest shows (1) a spectrum from normal-appearing brain in the anterior corpus callosum with decreased NAA (2.0 ppm), (2) a spectrum with reduced metabolite signal intensity due to a small hemorrhagic lesion in the mid-corpus callosum, and (3) a spectrum from parietal white matter with normal metabolite ratios. Figure from Holshouser et al. [2005].)
nature of TBI and helps explain why global neuropsychological deficits are often seen in patients with normal imaging findings.

Using currently available MRI sequences such as T2-weighted imaging and FLAIR with SWI and MRSI should allow clinicians to categorize DAI into two radiographic groups – ‘visibly injured’ and ‘normal-appearing’ brain. Visibly injured brain consists of the hemorrhagic lesions that we can more sensitively detect with SWI, as well as the nonhemorrhagic lesions seen with T2 and FLAIR. Normal-appearing brain consists of those areas that appear normal on MRI but in which we see evidence of abnormal MRSI metabolites (e.g. reduced NAA, increased Cho). Developing a much more sensitive method to detect DAI and to identify the brain regions involved has the potential of being extremely important for clinical use. It should allow us to identify lesions that are currently being undetected. This has significant implications for the care of children with TBI, especially if we can continue to correlate areas of injury with functional outcomes. A much better estimation of the location and severity of injury will allow better implementation of focused treatment strategies that are likely to be studied and used in the future.

**Diffusion Weighted Imaging**

DWI has allowed exploration of the function and physiology of the brain [Huisman, 2003], and its general use in infants and children has recently been reviewed [Beaulieu et al., 1999]. Because DWI uses fast (echo-planar) imaging technology, it is highly resistant to patient motion, and imaging time ranges from a few seconds to 2 min [Schaefer et al., 2000].

Diffusion represents the random thermal movement of molecules (i.e. Brownian motion) and is determined by several variables, including the nature of the molecules present in the local tissue environment, temperature and the local structural architecture in which diffusion takes place. Image contrast on DWI is related to differences in the diffusion rate of water molecules rather than to changes in total tissue water. DWI can differentiate between lesions with decreased and increased diffusion compared with normal brain tissue. Restricted diffusion is believed to reflect cytotoxic edema in contrast to increased diffusion that typically occurs with vasogenic edema. DWI has proven to be sensitive in the early detection of acute cerebral ischemia and seems promising in the evaluation of TBI, potentially revealing pathology when conventional MRI is normal. Technical aspects of DWI are beyond the scope of this review but have been described by Huisman [2003] and by Schaefer et al. [2000].

**DWI and TBI**

Experimental studies in rodents and piglets and human clinical studies have demonstrated that DWI is useful and sensitive in detecting lesions due to TBI, although the results are variable. An example of DWI in a child with TBI and DAI is shown in figure 8.

**Animal Studies**

In rats, moderate fluid percussion injury results in increased diffusion up to 4 h after injury, reflecting increased extracellular water in the cortex and hippocampus [Hanstock et al., 1994]. Moderate fluid percussion injury does not reduce cerebral blood flow enough to induce ischemia, suggesting that DWI abnormalities are not related to ischemia [Yuan et al., 1988]. In other rodent studies, impact acceleration trauma alone was not associated with a change in apparent diffusion coefficient (ADC) values measured up to 4 h after injury, unless hypoxia and hypotension were present [Ito et al., 1996]. Reversibility of ADC changes was also found to be dependent on the severity of hypotension [Barzo et al., 1997]. Although some variability in the findings may reflect differences in mechanisms in injury, there are several

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studies which show that changes are related to time. One study in rats subjected to impact acceleration injury showed that ADC values transiently increased in the first 60 min, which was followed by a continuing decrease in ADC up to 7 days [Barzo et al., 1997]. In contrast, another study of rats also subjected to impact acceleration injury showed that ADC values at 2 and 24 h were reduced but were increased at 7 days [Assaf et al., 1997]. A third study, using fluid percussion injury in rats, confirmed the early decrease in ADC values in the ipsilateral cortex and hippocampus 1–2 h after TBI [Albensi et al., 2003].

DWI has also been examined in a piglet developmental model of TBI. Using cortical contusion at 5 days (‘infants’), 1 month (‘toddlers’) and 4 months (‘early adolescence’), serial studies were performed at 24 h, 1 week and 1 month after injury [Duhaime et al., 2003]. Despite similar injury, the youngest animals had lesions whose volumes peaked earlier and resolved more quickly than in the older animals. Intermediate-aged piglets had the most pronounced swelling and the oldest piglets had the largest peak in lesion volume. These findings demonstrate age-dependent differences in the response to injury, both in magnitude and the time course.

**Human Studies**

DWI can be used to show shearing injuries not visible on spin echo or FLAIR $T_2$-weighted images but is less sensitive than $T_2^*$ imaging to detect hemorrhagic lesions [Huisman, 2003]. The potential usefulness of DWI was analyzed in a study by Hergan et al. [2002]. DWI was obtained in 98 adult TBI/DAI patients and lesions were classified into three categories depending on their DWI and ADC signal characteristics [Hergan et al., 2002]. Type 1 lesions were DWI and ADC hyperintense, most likely rep-
resisting lesions with vasogenic edema. Type 2 lesions were DWI hyperintense and ADC hypointense, likely reflecting cytotoxic edema. Type 3 lesions were central hemorrhagic lesions surrounded by an area of increased diffusion. In addition, lesions were classified into three groups according to the size and extent of the lesions: group A, focal injury; group B, regional/confluent injury; group C, extensive/diffuse injury. This was a retrospective review that did not evaluate time-dependent changes or correlation with outcomes.

Another study by Huisman et al. [2003] of 25 adult patients with TBI/DAI found that the ADC values of DWI hyperintense lesions were reduced in 64% of lesions, elevated in 24% and similar to the ADCs of normal brain tissue in 12%.

As reviewed by Hergan et al. [2002], cytotoxic and vasogenic edemas have been observed in multiple studies involving experimental and clinical TBI, although the time course may differ. In addition, associated conditions such as hypoxia or ischemia may worsen the development of cytotoxic edema. Restriction of water diffusion associated with cytotoxic edema is most likely related to a graded failure of energy metabolism that results in membrane pump failure, and then a net translocation of water from the extracellular space to the intracellular compartment, where water mobility is relatively more restricted [Hergan et al., 2002]. Cell swelling also results in a reduction in the volume of the extracellular space, in increased tortuosity of the extracellular space and is believed to contribute to restricted diffusion [Sykova, 2004].

Some studies have reported that DWI identifies the largest number of overall lesions as well as the largest volume of trauma-related signal abnormalities in DAI compared with conventional MRI sequences that include T2-weighted fast spin echo, FLAIR and T2*-weighted gradient echo sequences [Huisman et al., 2003]. The total volume of DWI signal abnormalities encountered in DAI correlates better than other imaging variables with the acute GCS score and the subacute Rankin scale score [Schaefer et al., 2004].

Although less is known about DWI in pediatric TBI, recent studies have suggested that DWI may be a sensitive indicator of TBI, particularly in the setting of NAT [Field et al., 2003]. In one study, 89% of 18 children with presumed NAT showed abnormalities on DWI and ADC maps, and in 81% of the positive cases, DWI revealed more extensive injury than conventional MRI or showed injuries when MRI appeared normal [Bioussé et al., 2002; Suh et al., 2001]. Studies by Geddes et al. [2001a, 2001b] have suggested that hypoxia and ischemia are common mechanisms of intraparenchymal injury in children with NAT and this may be due to reactive vasospasm adjacent to hemorrhagic lesions, strangulation, cervicomedullary injuries and apnea. All of these mechanisms, alone or in combination, could likely cause cerebral ischemic injury that would be manifest by changes in DWI.

Other case reports have also demonstrated DWI changes in white matter after NAT, suggesting that DWI is more sensitive than conventional MRI and more likely to detect lesions earlier in the evolution of injury [Chan et al., 2003; Parizel et al., 2003]. These reports also noted large areas of dramatic diffusion restriction, which support the belief that ischemia is a major component of brain injury in NAT, probably more so than DAI.

Diffusion Tensor Imaging

DTI allows evaluation of white matter fiber tracts by taking advantage of the intrinsic directionality of water diffusion in human brain, and has been helpful in studying myelination during maturation [McGraw et al., 2002]. In adults, it is being used to evaluate neurological disorders, including multiple sclerosis, epilepsy, Alzheimer’s disease and brain tumors. Although less studied, several reports have described DTI in adult and pediatric patients with TBI.

Principles Underlying DTI

DWI and DTI incorporate pulsed magnetic field gradients into a standard MRI sequence, resulting in images that are sensitive to the small displacements of water molecules [Rugg-Gunn et al., 2001]. DTI is a more complex form of DWI for which the resulting diffusion parameters, including a quantitative measure of anisotropy, are insensitive to subject positioning and fiber tract alignment within the diffusion gradients of the scanner.

Diffusion is considered isotropic when motion is equal and unconfined in all directions. Brain tissue forms physical boundaries that restrict diffusion, and in white-matter tracts, diffusion of water mobility is restricted perpendicular rather than parallel to the fiber tracts. This form of diffusion restriction is termed ‘anisotropic diffusion’ [Klingberg et al., 1999].

As described by Sundgren et al. [2004], diffusion anisotropy can be measured in several ways. A common way to summarize diffusion measurements is to calculate parameters for overall diffusivity and anisotropy. The ADC serves for overall diffusivity and is derived from the trace of the diffusion tensor, while anisotropy is represented by fractional anisotropy (FA), relative anisotropy, volume ra-

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tio or lattice index. FA is a measure of the portion of the diffusion tensor due to anisotropy, relative anisotropy is derived from a ratio between the anisotropic and isotropic portions of the diffusion tensor, volume ratio expresses the relation between the diffusion ellipsoid volume and that of a sphere or radius, and lattice index characterizes the anisotropy of the fiber structure [Arfanakis et al., 2002]. Technical aspects are beyond the scope of this article and are considered in several recent papers [Mukherjee et al., 2002; Sundgren et al., 2004].

In fiber tractography or fiber tracking, white matter tract directions are mapped on the assumption that in each voxel, a measure of the local fiber orientation is obtained using DTI. Because fiber tractography requires more extensive computer calculations and manpower than DWI or DTI, it remains more of a research tool, and so far has limited application [Sundgren et al., 2004]. As technology improves, use of tractography will be more feasible in child neurology, particularly in the study of acquired brain injuries that result in disorders such as cerebral palsy, and in the study of congenital and genetic disorders that affect white matter development.

**DTI and Development**

DWI, particularly DTI, has been applied to assess myelination in the developing nervous system [Bydder et al., 2001; McGraw et al., 2002; Prayer and Prayer, 2003] and can demonstrate changes associated with white matter maturation from premyelination to postmyelination stages. It is also of use to assess the function of developing white matter tracts and the sequelae of disruption of white matter tracts after injury [McKinstry et al., 2002]. These features are demonstrated in the results of one study that examined 30 children ranging in age from 1 day to 17 years and reported that apparent anisotropy in compact white matter was higher than that in the noncompact white matter structures of the corona radiata and centrum semiovale [Morriss et al., 1999]. There were also age-related increases in anisotropy in all white matter structures with adult values reached by 3 years of age. Numerous other reports have described the regional and temporal course of myelination development [Miller et al., 2002; Mukherjee et al., 2001; Neil et al., 1998].

DTI studies in children have shown that the diffusion tensor $D^\omega$ decreases with age in gray and white matter and that spatial anisotropy, i.e. $A_{\sigma}^\omega$, increases with age, especially in white matter [Morriss et al., 1999; Mukherjee et al., 2002; Neil et al., 1998]. Lower FA values have also been found in neonates compared with adults [Sundgren et al., 2004]. As reviewed by Mukherjee et al. [2002], the presumed mechanisms of these maturational changes in water diffusivity are a decrease in brain water content, the formation of new barriers to water mobility, such as cell membranes associated with the outgrowth of axons and dendrites as well as glial processes, and white matter myelination. Several studies have examined the regional maturational changes in preterm infants as young as 28 weeks of gestation as they matured to term [Huppi et al., 1998]. It has been suggested that the diffusion tensor $D^\omega$ values reflect overall brain water content whereas the spatial anisotropy $A_{\sigma}^\omega$ values are more sensitive to tissue microstructure associated with white matter packing and myelination [Neil et al., 1998].

**DTI and TBI**

Most DTI studies in TBI have focused on the adult population. Huisman et al. [2004] studied 20 adults within 7 days and found that FA was reduced in the internal capsule and splenium of the corpus callosum and correlated better with the GCS and Rankin scores (measures of injury severity) than ADC values. As DAI most commonly affects white matter, it was suggested that DTI could serve as a sensitive marker of early white matter injury and that changes seen with DTI most likely represented changes in axonal microstructure. Examples of DTI in children with TBI are shown in figures 9 and 10.

Ptak et al. [2003] evaluated 15 patients within the first 7 days after TBI and developed a composite score (i.e. C-FAST score) based on measurements of FA from 6 white matter regions. They found good correlation between the C-FAST score and death, hospital stay greater than 10 days, and intensive care unit stay greater than 5 days. Additionally, the correlation with discharge to a rehabilitation facility was good when adjusted for age and sex. The GCS score, revised trauma score and the Abbreviated Injury Scale also showed good correlation as predictors of a critical C-FAST. This study, which incorporated measurement of FA from multiple areas, was interesting and unique in that the authors assumed that focal injury affects function throughout the entire axon and that inclusion of the injury site was not required. Because focal injuries affect membrane function of the entire axon, altered anisotropy should be apparent throughout the entire axon, and therefore, the white matter region measured need not necessarily include the injured site.

In another study, DTI data were acquired in 5 adult TBI patients with traumatic focal contusions or hematomas [Jones et al., 2000]. A reduction in mean diffusivity in gray and white matter without an associated increase in $T_2$- weighted signal intensity was observed in 4 patients. This
change was interpreted as indicating either a partial redistribution of water from the extra- to intracellular compartment, or a reduction in the diffusivity of water in the intracellular or cytosolic environment. These diffusion changes with normal $T_2$-weighted characteristics can be found early after ischemia, suggesting that such regions could represent salvageable tissues.

In two recent studies of DTI in patients with TBI, diffusion anisotropy was found to be decreased in normal-appearing cerebral white matter on conventional MRIs, whereas mean diffusivity was described as either normal [Arfanakis et al., 2002] or increased [Rugg-Gunn et al., 2001]. Several mechanisms were suggested to explain the DTI changes including axoplasmic transport impairment.

**Fig. 9.** DTI of cerebellar white matter injury of a 16-year-old boy 11 days after mild head trauma (GCS score 13–14). Axial $T_2$-weighted images of the posterior fossa (top row) demonstrate only fluid within the right mastoid sinuses due to temporal bone fracture. No cerebellar abnormality is identified. However, FA images derived from DTI (bottom row) show asymmetrically reduced anisotropy in the white matter of the right cerebellar hemisphere. Note that the images are displayed using radiological convention, where the right side of the patient corresponds to the left side of the image. Figure by courtesy of Dr. Pratik Mukherjee from the University of California, San Francisco.

**Fig. 10.** Three-dimensional coronal (left) and oblique (right) projections of DTI fiber tractography of the superior cerebellar peduncles (A) and the middle cerebellar peduncles (B) show decreased number and length of tracks extending into the right compared with the left cerebellar hemisphere. The fiber tracks are overlaid on a directionally encoded color FA map, where red indicates left-right, green indicates anteroposterior and blue indicates up-down fiber orientation (see color compass at top right). Figure by courtesy of Dr. Pratik Mukherjee from the University of California, San Francisco.
or axolemmal disruption, misalignment or increased permeability.

In the study by Arfanakis et al. [2002], DTI was acquired in 5 patients (mean age 35.6 years) within the first 24 h after mild TBI. In all patients, images of diffusion anisotropy (FA, lattice index) revealed regions of reduced anisotropy compared with contralateral brain regions as well as with control subjects. These regions differed from lesions associated with hemorrhage or edema and did not show abnormalities on other MRIs. Reduction in diffusion anisotropy was less evident 1 month after injury in several patients. The mechanism of reduced anisotropy was attributed to misalignment of the cytoskeletal network, which is believed to be an early neuropathological abnormality seen with DAI [Arfanakis et al., 2002]. Misalignment of axonal membranes was believed to increase restriction in diffusion parallel to the main axis of the neurons as well as increase diffusion in directions perpendicular to the axons. The overall effect of this misalignment of the axonal membranes in DAI could be responsible for reductions in anisotropy. As described by these authors, a second phase of DAI that includes impaired axoplasmic transport, local accumulation of organelles and local swelling and expansion of the axonal cylinder could increase diffusion restriction parallel to the main axis of the fibers and decrease local diffusion anisotropy. As neurons further degenerate, diffusion restriction along directions perpendicular to the axon may occur, reducing anisotropy. Additionally, for moderate and severe TBAs, an increase in permeability may take place in injured axons. This may increase diffusivity in directions perpendicular to axons and reduce anisotropy.

In the second report, 2 adult patients were studied 11 and 18 months after injury [Rugg-Gunn et al., 2001]. Both patients, despite having a normal nonacute MRI, showed regions of significantly increased mean diffusivity as well as other regions of decreased anisotropy. In contrast to the patients reported by Arfanakis et al. [2002], these 2 patients had suffered severe TBI. When the DTI studies were done, the first patient had mild pyramidal signs and sensory loss affecting the right arm and leg, and mild frontal lobe dysfunction. The second patient had only moderately increased left lower limb reflexes but severe frontal lobe dysfunction and personality change. The findings of increased mean diffusivity suggested that there was an expansion of the extracellular space, caused by neuronal or glial cell loss, which was not identified by conventional MRI. In addition, the reduction in anisotropy in the internal capsule of the second patient suggested that there was structural disorganization and a loss of the parallel fiber arrangement of major white matter tracts within the internal capsule. Serial DTI and fiber tracking (at 4 days, 24 days and 2 months) have been reported in 1 adult patient after TBI and have documented
changes in the evolution of axonal injury over time [Naganawa et al., 2004].

To date, there has been only one case report of a child with TBI in whom DTI was performed [Field et al., 2003]. This case involved a 14-month-old male infant with suspected NAT who underwent DTI within 24 h of injury. His initial CT scan, performed on admission, revealed a minimally depressed right occipital fracture and a thin (2–3 mm) right hemisphere convexity subdural hematoma that also involved the interhemispheric fissure and tentorium, with a 5-mm right-to-left midline shift. No evidence of intraparenchymal hemorrhage or contusion was noted. MRI at 18 h after admission showed similar findings without evidence of intraparenchymal injury. DWI was normal. However, DTI revealed transient changes in relatively large areas of the cortical and subcortical right hemisphere with markedly increased anisotropy, and mildly increased mean diffusivity in regions of the right frontal, temporal, parietal and occipital lobes existed (fig. 11). On day 3, he developed left focal seizures and hemiparesis, and follow-up CT scans at 69 and 93 h after admission showed parenchymal edema and decreased size of the subdural hematoma. Follow-up MRI (at 135 h) showed diffuse right hemisphere swelling, and DWI and ADC maps revealed markedly restricted diffusion throughout most of the right hemisphere. Diffusivity had returned to normal, but subtle increased anisotropy in the right frontal lobe remained. At discharge, a right hemiplegia was still present. The mechanisms for the DTI changes in this infant were considered to possibly be related to development over different time courses of cytotoxic and vasogenic edema. Cytotoxic edema has been associated with reduced mean diffusivity, possibly due to shrinking, and increased tortuosity of the extracellular space engendered by water shifting from extra- to intracellular compartments [van der Toorn et al., 1996]. Vasogenic edema has been shown to increase mean diffusivity and to decrease anisotropy [Mukherjee et al., 2001].

Conclusions

The neuroimaging techniques described in this review have significant potential to assist in the early evaluation of children with TBI. All will require careful evaluation to assess the effects of age and development on the characteristics patterns of injury and in correlation with long-term studies of neurological, neuropsychological and behavioral function.

References


References


