31 Utility of Magnetic Resonance Findings in Elucidating Structural and Functional Brain Impairment in Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a major cause of death and disability in the United States, contributing to about 30% of all injury-related deaths. TBI survivors often develop clinical impairments and long-term disabilities. These include impaired thinking or memory, effects on movement and sensations such as vision, hearing, or emotional functioning including personality changes, depression, burst of anger, abnormal social behavior, and insomnia. These issues not only affect individuals but can have a deleterious impact on families and communities. The advances in computer software applied to a non-invasive acquisition of images containing digital data, provides us with objective examination of brain structure and function. Magnetic resonance (MR) imaging of the brain makes it possible to investigate morphological and functional connectivity without exposing the patient to ionizing radiations. In patients with TBI, computed tomography and conventional MR scans seldom show limited or no abnormalities to explain clinical symptomatology. For these reasons, we propose an "ad hoc" protocol that exploits advances in MR sequences to predict long-term outcomes including evaluation of cortical thickness, detecting hemosiderin

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deposits via magnetic susceptibility weighted images, to explore indemnity of fiber tracts using diffusion tensor with fractional anisotropy measurement, to assess metabolic changes in the frontal lobe and cingulate cortex by utilizing the properties of magnetic resonance spectroscopy, and lastly to detect abnormal connectivity in the brain networks via resting-state functional magnetic resonance imaging. Meticulous application of our protocol can potentially detect subtle abnormalities in patients with mild TBI such as detection of iron or mineral deposits, abnormal cortical thickness, abnormal metabolites, disruption of white matter tracts, and decreased or loss connectivity in brain networks. Application of special MR sequences as described in our protocol can optimize clinical outcomes, offer predictive capabilities of short and long-term prognosis, and aid in risk-stratification tailored upon individual comorbidities.

Keywords

Traumatic brain injury • Diffuse axonal injury • DTI • Rs-fMRI • Cortical thickness • Susceptibility imaging • DWI • MRS

Introduction

In technical parlance, traumatic brain injury (TBI) is described as "an alteration in brain function, or other evidence of brain pathology, caused by an external force." Synonymous with its nomenclature, TBI simply refers to structural and functional changes in the brain attributable to external trauma [1, 2]. The desideratum for an external force distinguishes TBI from various acquired brain injuries, including vascular insults, and neoplastic and degenerative pathologies [3]. Typical mechanisms leading to TBI, albeit heterogeneous in nature, include blunt trauma, penetrating injury, blast waves, and sudden acceleration or deceleration. Both the magnitude and transfer of impact to the scalp vault and its contents determine the severity of damage, presenting variably in the form of cerebral edema, focal contusions, hematomas, and shearing of white matter tracts leading to diffuse axonal injury (DAI).

Affecting population across all age groups, TBI has become one of the leading causes of mortality and disability in children and adolescents worldwide [4–8]. In the United States (US), TBI accounts for approximately 30% of all deaths resulting from injury, averaging 138 deaths per day [9]. The dramatic increment in the cumulative rates for TBI-related emergency department (ED) visits, hospitalizations, and mortality across the globe as witnessed during the previous decades have been concerning from a public health perspective. In the US, this upsurge translated from approximately 1.5 million cases in 2003 to 2.5 million in 2010, an increase in incidence to over 50%, from 538 per 100,000 at baseline to 823 per 100,000 in 2010 [4–10]. During the same period, the average mortality from TBI declined from 18.2 deaths per 100,000 to 17.1 per 100,000, a meager rate of 6% [4] Considering under-reporting of events and limited accountability for uninsured patients with non-fatal TBI without access to healthcare facilities and those seen at private clinics, the projected estimates far undervalue the actual magnitude of burden posed by TBI. The economic impact from these low estimates is equally colossal. In 2010 alone, healthcare spending including direct and indirect costs for management of patients with TBI stood at a staggering US$ 76.5 billion, [11] contributing to approximately 3% of the national health expenditures for that year [12]. A major proportion of this economic burden is attributed to long-term residual disability seen in patients with TBI, in the form of motor and sensory deficits, cognitive impairments, and emotional disturbances. Insomnia,

cognitive decline, post-traumatic headache, and depression are common factors limiting a patient's reintegration into the community and return to employment [13–18]. Post-traumatic depression following TBI contributes independently to cognitive decline [16–18], which affects quality of life over the long term. TBI has also been implicated in delayed-onset neurodegenerative syndromes such as Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE). Brain pathology following a single incident of severe TBI mimics closely that seen in AD during early amyloid pathology, whereas repetitive TBI can produce tauopathy with or without amyloidosis, which resembles the pathology of boxers' dementia [19–21]. Although clinical assessment of TBI severity based upon the Glasgow coma scale (GCS) [22] provides some insight into the extent of severity at the time of presentation, it is often under-predictive of the actual extent of structural and impending functional damage to the brain, and is often deemed unreliable for predicting acute prognosis or long-term sequelae. To this effect, neuroimaging, particularly the MR imaging, plays a crucial role in determining the extent of injury, providing guidance for surgical management, and predicting prognosis. In this article, we provide a comprehensive overview on the utility of magnetic resonance (MR) imaging in explaining anatomical and functional brain impairment in patients with TBI.

Neuroimaging in TBI

Integration of technological advancements in the digital world has led to development and enhancement of non-invasive neuroimaging modalities employed for objective assessment of anatomical, functional, and metabolic milieu of the brain. This has led to improved diagnosis and subsequent management for patients with TBI. Ability to assess these changes confers risk-stratification via gauging severity, predicting prognosis, and streamlining management for these patients. While head roentgenogram may have become obsolete in today's era, other neuroimaging modalities such as computed tomography, MR imaging, positron emission tomography (PET), and single-photon emission computed tomography (SPECT) provide valuable insights on brain abnormalities.

Conventional computed tomography (CT) is a routinely employed diagnostic procedure to assess acute head injury requiring observation or admission [23]. By using the degree of X-ray attenuation, CT scans can differentiate between normal brain with the presence of bleed, contusions, discontinuity in scalp or facial bones, edema, and ischemia. With the advent of high-resolution, multi-detector scanners, scanning duration has dramatically reduced, and offers selective re-scanning of slices affected by motion artifacts [24]. Three-dimensional (3D) reconstruction depicts bony injury and intracranial pathologies, if any [25]. Despite obvious advantages of CT in the initial detection of head injury with surgical guidance in management of acute cases and its cost-effectiveness, conventional CT scans have limitations in detecting the subtle neuronal damage and diffuse axonal injury seen in over 50% patients with TBI. These subtle changes form the basis of residual disability and cognitive impairment from TBI [26–29]. Most of these limitations in detecting these neuronal changes can be mitigated through the use of specialized magnetic resonance (MR) sequences. Structural MR sequences in conjunction with functional MR imaging can potentially provide accurate assessment of extent and severity of brain injury in these patients.

Magnetic Resonance Imaging: An Overview

Of the various available neuroimaging modalities, developments in MR technology have been remarkable. It is based upon the principle of nuclear magnetic resonance. In the presence of a static magnetic field, nuclei of atoms (mainly protons) resonate when varying electromagnetic fields are applied at a fixed frequency. The MR machine computes an image based on the "resonance" signals to compute spatial orientation based on processing the frequency and phase in these signals. Diverse MR sequences exploit the physical properties of the target tissue (protons) to provide information on morphological and functional integrity. MR signals are obtained from several parameters such as T1, T2, proton

density and flow, chemical shift, and molecular diffusion [30]. Unlike CT scans, MR imaging neutralizes the risk of being exposed to ionizing radiation, thus eliminating the risk of radiation-induced DNA damage that has been implicated as a potential risk factor for carcinogenesis [31, 32]. With increasing availability in emergency settings, MR imaging constitutes a valuable tool for baseline assessment in practically all patients with TBI, albeit with some contraindication. An absolute contraindication for brain MR is for patients with cardiac pacemakers, penile implants, cochlear implants, and ferromagnetic materials, and relative contraindications are metallic implants including, but not limited to, vascular clips, coronary and peripheral arterial stents, prosthetic heart valves, cardiac devices, aortic stent grafts, vena cava filters, hemodynamic monitoring, and pacing devices [23]. Claustrophobic patients and those with tattoos are some relative contraindications for MR scans. Some MR scans utilize contrast agents, therefore those with renal insufficiency or hypersensitivity, or are pregnant or breastfeeding may not be eligible candidates [33].

Structural MR Imaging

In contrast to CT scans, conventional MR scans are more sensitive in depicting minute areas of petechial hemorrhages, contusions, or extra-axial hematomas, axonal injury [34–37], and white matter abnormalities [38]. In patients with mild TBI, conventional MR scans depict abnormal findings in approximately one third of patients with normal CT scans [35–39]. T1-weighted MR scans provides descriptive overview of anatomic affection of the brain, if any, such as midline shift, ventricular distortion, or mass effect. Although gadolinium-based contrast may offer few advantages over non-contrast scans in regards to structural anatomical changes in mild TBI, special MR sequences such as fluid attenuation inversion recovery (FLAIR) and gradient echo have shown particularly high sensitivity for appreciating axonal injury, and in predicting outcomes [40, 41].

- *FLAIR*: The FLAIR technique permits detection of periventricular and superficial cortical lesions [42]. By diminishing the signal from CSF while concurrently amplifying the intensity of lesions that are non-fluid-containing, FLAIR is of utility in identifying lesions in close proximity to the CSF-filled subarachnoid and ventricular spaces. Areas of T2 prolongation appear as bright, while normal CSF signals are depicted dark [42]. FLAIR is helpful in detecting non-hemorrhagic DAI and sub-arachnoid hemorrhage.
- *Gradient echo sequence* (*GRE*): T2-weighted gradient echo MR is sensitive to signal intensity loss that results from changes in magnetic susceptibility. GRE is sensitive in detecting the presence of blood breakdown products such as deoxyhemoglobin, intracellular methemoglobin, ferritin and hemosiderin. This is useful in detecting hemorrhagic DAI and contusions.
- *Susceptibility-weighted imaging* (*SWI*): This is a relatively newer contrast type of MR that differs from T1- or T2-weighted imaging that exploits magnetic susceptibility differences across various tissues such as calcium and iron, and uses phase image signals to detect these differences. It is sensitive in detecting microbleeds in the form of paramagnetic hemoglobin or intracellular hemorrhages [43]. It is also used to image venous blood via the blood-oxygen-level-dependent (BOLD) technique.
- *Short tau inversion recovery* (*STIR*): STIR signals attenuate fat signals, and provide distinction of water-containing lesions in areas with relative fat abundance such as the orbit, head and neck, or spine. STIR improves T1 or T2 lesion conspicuity, and is useful in avoiding chemical shift artifacts. While its utility as a diagnostic tool is limited in TBI, STIR is often used to differentiate between lipomas and hemorrhage, evaluation of optic nerve injury, and vertebral body compression fractures in patients with head trauma.
- *Diffusion-weighted imaging* (*DWI*): DWI processes information based upon differences in water molecule diffusion rate by employing echo-planar or line-scan spin echo MR technique. The measure of mobility of water molecules is reflected via the apparent diffusion coefficient (ADC). Regions with relatively higher degree of diffusion such as

that of the CSF appear hypo-intense with a high ADC value, while areas with restricted diffusion, such as protons within grey or white matter, appear hyper-intense with low ADC value. A distinction between cytotoxic and vasogenic edema can be made using DWI. While the former depicts characteristics of restricted diffusion, vasogenic edema demonstrates signs of increased diffusion. In patients with mild TBI, focal areas of restricted diffusion associated with cerebral edema or DAI are often seen. In contrast to FLAIR and T2-weighted imaging, DWI demonstrates a greater degree and extent of abnormalities in patients with TBI. Regions with acute DAI brighten up and appear dark in ADC due to restricted pattern of diffusion from plausible cellular death.

- *Diffusion tensor imaging* (*DTI*): DTI is an extension of DWI that senses diffusion of water molecules across several directions, along the course of nerve fibers, with a tensor applied to describe diffusion in an anisotropic system. This forms the basis for the 3D reconstruction of the fiber tracts (white matter), thus enabling the possibility of exploring broken connections [44]. Key approaches to assess microstructural damage include whole-brain voxel-based analysis, region-of-interest (ROI) analysis and in-vivo tractography. A quantified estimate of DTI data is derived from the functional anisotropy (FA) value, which ranges from 0 to 1. An FA value of zero depicts an isotropic diffusion occurring in all directions, while FA value of 1 indicates a unidirectional diffusion. A standardized color coding is applied in 2D representation to depict direction of fibers; red representing lateral commissural pathways, green for anterior–posterior pathways, and blue indicating cranial–caudal pathways. In patients with mild TBI with normal CT scans and GCS 15, DTI is regarded as a potential biomarker as it detects micro-structural changes in white matter, even in patients with mild TBI, as opposed to other MR sequences [45–49].

A decreased FA value corresponds to axonal degradation and fiber discontinuity owing to intertract or perivascular accumulation of water, and can be detected as early as 24 h after TBI [50–53].

DTI studies have confirmed decreased FA value in the corpus callosum, which sustains a high degree of deformation [53, 54]. Structural abnormalities in the corpus callosum as shown by DTI indices correlated clinically with cognitive, somatic, and affective disorders as seen post injury in these patients. An association between quantitative measures of gait function and DTI findings demonstrate white matter integrity in the genu of corpus callosum to be an important marker of gait [55]. Other common brain regions affected in mild TBI detected on DTI include anterior and posterior cingulum, middle cerebellar peduncles, and inferior longitudinal (ILF) and uncinate fasciculi (UF). As cingulum is the fiber tract related to the limbic system, any structural abnormality is associated clinically with depression, memory loss, lack of social restraint, aggressiveness, heightened sexuality, and bulimia [56]. The anterior cingulum is linked to emotion, especially apathy and depression, while the posterior cingulum is more related to cognitive functions [57, 58]. Structural abnormalities as detected in the ILF bundle using DTI can explain functional impairments such as thought disorders, visual emotion, and cognitive impairment [59]. Studies have demonstrated abnormalities in DTI to correlate with symptom severity, and with predicting long-term cognitive impairments [48, 52, 60, 61]. Disruption of the UF may cause problems with expression of memory, decision making, and acquisition of certain types of learning and memory. Additionally, uncinate involvement in TBI often extends beyond memory to include social–emotional problems and low motivation [62].

- *Magnetic resonance angiography* (*MRA*): This is a specialized form of MR imaging that visualizes blood vessels as opposed to brain tissues. It can detect bleed or patency of blood vessels, and is often used to screen for evidence of vascular injury in the head and neck region in patients with TBI [63].
- *Cortical thickness*: Using high-resolution T1 anatomical MR images, evaluation of cortical changes using an automated, vertex-based reconstruction for measurement of thickness

of the brain cortex can be performed [62–77]. This provides baseline assessment of cortical integrity. Cortical thinning occurs in TBI, and correlates with measures of PTSD, depression, executive functioning, declarative memory loss, and post-concussive symptoms [68, 78–80]. Precuneus thickness is correlated to acute traumatic stress symptoms in TBI survivors. Recent evidence suggests structural changes in frontal cortex over 3 months following mild TBI [81].

Functional Imaging

- *Magnetic resonance spectroscopy* (*MRS*): MRS is similar to conventional MR that uses properties of magnetism. As opposed to MR that utilizes time domain to obtain T1 and T2 relaxation times that are processed as images, MRS data uses frequency-domain information to display a spectrum of signal intensity from different brain metabolites [82]. The main metabolites are N-acetyl aspartate (NAA) related to neurons, creatine (Cr) related to energetic metabolism, choline (Cho) representing membrane metabolism, and myoinositol (mI) representing glial cells. Data is quantified as a ratio of all metabolites with respect to creatinine. In children with TBI, a disturbance in brain metabolites is predictive of overall outcomes relating to behavioral and cognitive functions both in acute and long-term phase [83–86].
- *Resting-state fMRI*: Several studies have demonstrated that damage to white matter alters structural integrity, which leads to impairment in functional connectivity across regions of the brain. Structural and functional disruptions are implicated in cognitive impairment in TBI [87–90]. Resting-state fMRI assesses functional connectivity in the brain following severe TBI and even in patients with mild TBI during the initial phase [90–96]. As it processes brain connectivity in the absence of any task or activity, this modality of MR permits functional evaluation irrespective of severity and cognitive functions. Using advanced neuroimaging processing tools, functional connectivity during resting state can be studied effectively. The most commonly studied functional connectivity network during resting state is the default mode network (DMN) [97]. Although commonly related to the cognitive process, DMN can be affected in a broad range of disorders affecting the brain [98]. Resting-state fMRI assesses changes in oxygen delivery to various centers that are synchronously connected within a time duration of 8 min while the patient is at rest (not performing any task). The data processed and reconstructed to depict any synchrony across various regions is compared to a pool of normal controls. This generates a brain map with areas of abnormally decreased connectivity or increased connectivity within target centers.

Findings in Traumatic Brain Injury

In our protocol to study morphological, metabolic, and functional characteristics of the patients with TBI, we routinely employ T1-weighted images, T2 and proton density, diffusion-weighted sequence, tensor sequence, SWI, FLAIR sequence, magnetic resonance spectroscopy, and resting-state fMRI.

With no likely abnormality being seen on CT scans and conventional MRI in most patients with TBI, an "ad-hoc" protocol is recommended for unanimous implementation across centers for complete MR evaluation for patients with TBI. This should mandate cortical thickness reconstruction, magnetic susceptibility weighted sequences for detecting any hemosiderin deposits, DTI for measurement of FA values for structural integrity of white matter tracts, and lastly resting-state fMRI for functional regional connectivity across the brain. The protocol is viable even for patients with mild TBI, as they present a pattern with one or more of the following:

(a) Hemosiderin deposits in temporal and frontal poles that could be picked up with magnetic susceptibility weighted sequences.
(b) Cortical thickness or abnormal integrity in frontal dorsomedial and central decreased

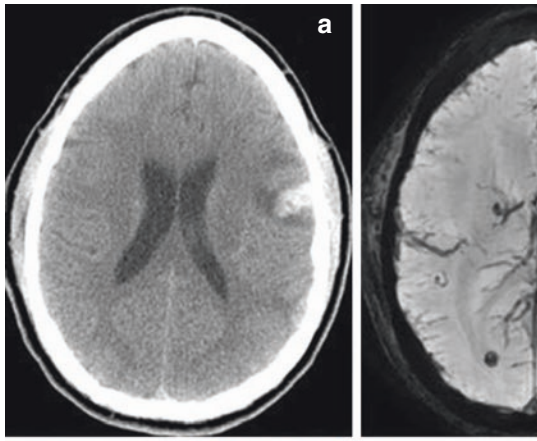
cortical thickness which may extend to the parietal, depending on the power of the impact, as well as in the ventral surfaces of the brain such as the orbitofrontal cortex, temporal poles and temporo-occipital areas [99–105].

(c) Abnormal fractional anisotropy values in the genu of the corpus callosum and cingulum fibers [106–120].

(d) Decreased NAA in magnetic resonance spectroscopy indicating neuronal loss, mostly in frontal lobes [121, 122].

(e) A decrease in or loss of connectivity to the frontal cortex from anterior and posterior cingulum on rsfMRI [92, 123–125].

Implementation of the aforementioned protocol at presentation, short- and long-term follow up can help unveil microstructural changes to explain and predict long-term outcomes. These findings may intuitively form the basis of rehabilitation, and an octagonal approach for long-term care, and plausibly attenuate residual disability (Figs. 31.1, 31.2, 31.3 and 31.4).



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WM tract	Patient FA	Normal	SD
Genu cc	0.539396	0.74	0.04
Splenium cc	0.525055	0.78	0.03
cing R	0.465562	0.45	0.02
cing L	0.482117	0.45	0.02
ILF R	0.35729	0.41	0.03
ILF L	0.322366	0.41	0.03
UF R	0.277559	0.33	0.02
UF L	0.305373	0.33	0.02
SLF R	0.549114	0.42	0.02
SLF L	0.51181	0.42	0.02

Fig. 31.1 Patient is a 20-year-old male admitted to the hospital for 30 ft. fall from oil rig. Patient was helicoptered in from the field and intubated due to low GCS 4–5. Presented with subarachnoid hemorrhage, brain laceration in the left frontal lobe, multiple skull fractures. *After* 3 *years the patient showed cognitive decline, depression, bursts of anger, decreased capacity for planning, bad social interaction*. Never returned to work. (**a**) Computed tomography in transverse view showing laceration and hematoma in left frontal lobe. (**b**) Magnetic resonance with susceptibility sequence depicts the frontal hemorrhage and blood deposits in the ventricles. (**c**) Hemosiderin deposits in microglia appear 3 years after first magnetic resonance in the susceptibility sequence. (**d**) Decreased cortical thickness (*blue*) in the frontal lobe in the same patient pinpointing Brodmann's areas involved. (**e**) Diffusion tensor imaging performed in the same patient with decreased fractional anisotropy values in corpus callosum and inferior longitudinal fasciculus

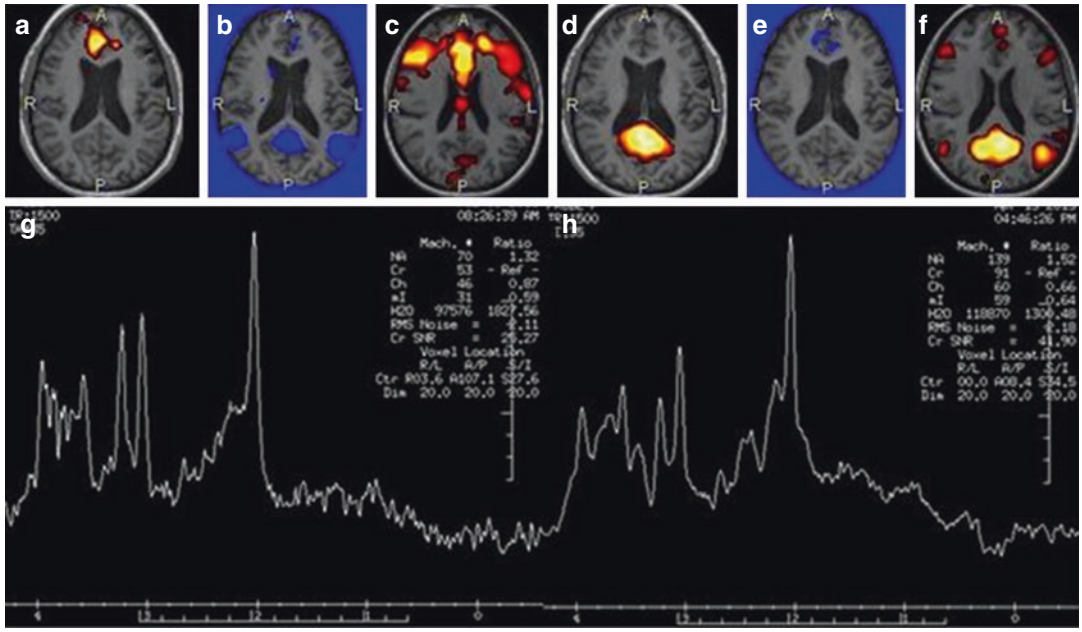

Fig. 31.2 Resting-state functional magnetic resonance. (**a**) Functional connectivity. A seed was placed in the anterior cingulum. No connectivity with posterior cingulum and dorsal frontal cortex compared with normal in (**c**). (**b**) Z-test, patient compared to 20 normal individuals depicting decreased connectivity in the posterior cingulum. (**d**) Normal frsfMRI with seed in anterior cingulum. (**e**) Resting-state functional magnetic resonance. Compared to normal in (**f**), there is no connectivity with posterior cingulum, frontal cortex, angular cortex. (**f**) Z-test showing decreased connectivity in the patient's anterior cingulum. (**f**, **g**) Magnetic resonance spectroscopy. Decreased n-acetyl aspartate in the frontal lobe. NAA is a marker for neurons, indicating decreased neuronal content in the frontal lobe. There is also an increase in myoinositol, a marker for glia. This correlates with increase in scarring and fibrillary content

ROI	FA	Normal	SD
genucc	0.375139	0.74	0.04
spleniumcc	0.419388	0.78	0.03

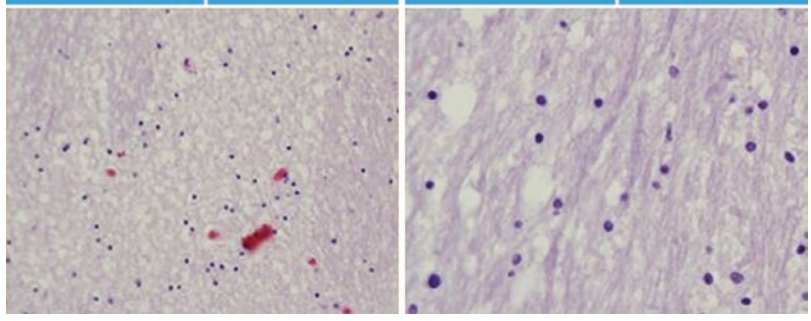

Fig. 31.3 Autopsy in a patient who died from TBI. MR was obtained before death. Correlation of abnormal fractional anisotropy with pathology. Swollen and disrupted fibers in genu and splenium of corpus callosum correlate with fractional anisotropy (FA) abnormal values

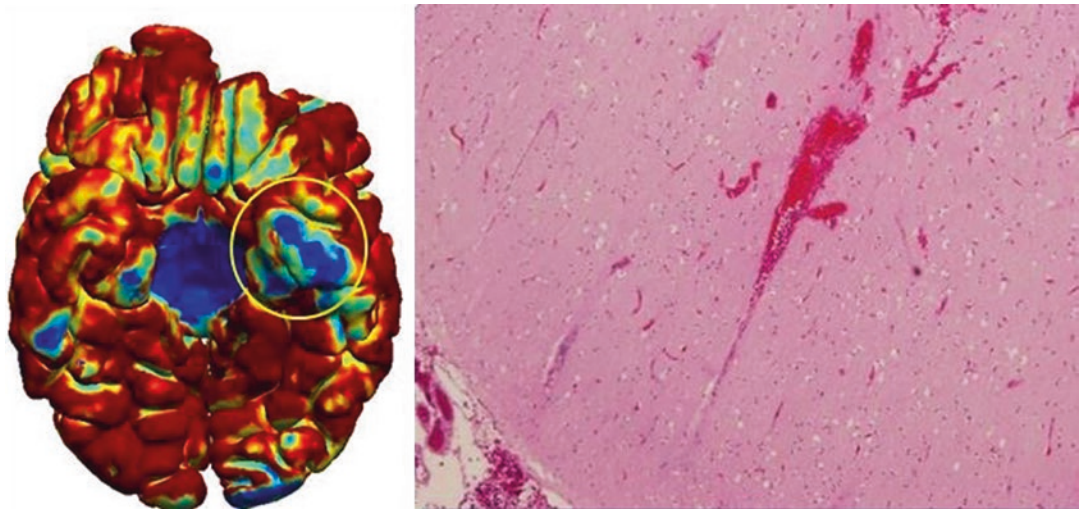

Fig. 31.4 Autopsy case. Patient with encephalomalacia in frontal pole after surgery for resection of a meningioma. He sustained a seizure while driving. MR obtained before death. Correlation between abnormal cortical thickness (*blue*) and contusion demonstrated by pathology

Conclusions

Neuroimaging has increasingly become a vital tool for management of patients with head injury. While conventional CT and MR modalities offer rapid structural assessment ensuring prompt institution of surgical management for selective cases, functional modalities allow accurate prediction of overall functional and clinical outcomes in patients with TBI. With easy accessibility to MR technology, complex MR sequences entailing deeper insights into structural and functional impairments should routinely be employed in assessment of patients with TBI. MR imaging techniques additionally enhance our knowledge base relating to anatomic abnormalities and functional outcomes. Higher resolution scans, integration of digital software for data processing, and technical advancements offer a viable solution for automation in image processing and interpretation.

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