

## [ Imaging ]

# Imaging in Chronic Traumatic Encephalopathy and Traumatic Brain Injury

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**Context:** The diagnosis of chronic traumatic encephalopathy (CTE) can only be made pathologically, and there is no concordance of defined clinical criteria for premorbid diagnosis. The absence of established criteria and the insufficient imaging findings to detect this disease in a living athlete are of growing concern.

**Evidence Acquisition:** The article is a review of the current literature on CTE. Databases searched include Medline, PubMed, JAMA evidence, and evidence-based medicine guidelines Cochrane Library, Hospital for Special Surgery, and Cornell Library databases.

**Study Design:** Clinical review.

**Level of Evidence:** Level 4.

**Results:** Chronic traumatic encephalopathy cannot be diagnosed on imaging. Examples of imaging findings in common types of head trauma are discussed.

**Conclusion:** Further study is necessary to correlate the clinical and imaging findings of repetitive head injuries with the pathologic diagnosis of CTE.

**Keywords:** CTE; chronic traumatic encephalopathy; concussion; concussion in sports; traumatic brain injury (TBI); head trauma; tauopathy

The term *chronic traumatic encephalopathy* (CTE) was historically used in the 1950s and 1960s to describe progressive dementia in boxers.<sup>25,69</sup> More recently, the neuropathologic diagnosis of CTE has been made in athletes, war veterans, and people with self-injurious behavior.<sup>23,36,41,63,65,74-76,85,86</sup> Currently, the diagnosis of CTE can only be made pathologically, and there is no concordance of defined clinical criteria for premorbid diagnosis. Establishing criteria and defining sufficient imaging findings to detect this postmortem diagnosis in a living athlete are research priorities. The absence of established criteria and the insufficient imaging findings to detect this disease in a living athlete are of heightened concern. This article will review the pathophysiology and clinical syndrome associated with CTE as well as traditional imaging of traumatic brain injury (TBI) and investigational imaging techniques that have potential future clinical utility.

## CLINICAL SYNDROME

In 1928, Martland<sup>58</sup> described “punch drunk” syndrome, which occurred in boxers who had sustained multiple head injuries. This syndrome consisted of leg weakness, vertigo, gait difficulties, and episodes of confusion that later progressed to parkinsonism and dementia.<sup>58</sup> In 1937, Millsbaugh<sup>70</sup> described a similar syndrome in boxers that he termed *dementia pugilistica*. The term *chronic traumatic progressive encephalopathy* was first used by Critchley<sup>25</sup> in 1957. He described a progressive euphoric dementia in boxers that was accompanied by a combination of pyramidal, extrapyramidal, and cerebellar signs and symptoms. Recently, there has been recognition that CTE may affect more athletes than just boxers.<sup>63,75,76</sup>

Several recent retrospective clinical analyses have been performed, with the assistance of family members, on athletes

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who donated their brains to the VA CTSE Brain Bank.<sup>9,94,95</sup> Although defined clinical criteria for CTE currently do not exist, these studies reported a consistent constellation of symptoms. The clinical symptoms can be divided into 3 categories: cognition, mood, and behavior. Cognitive symptoms consist of memory, speech, and executive dysfunction. Mood changes include depression, apathy, and suicidality. Behavior changes include aggression, increased violence, and disinhibition.<sup>9</sup> More recently, in a study published in 2013 with 36 patients, there was a suggestion of 2 major clinical presentations of CTE based on age; the younger group had a predominance of mood and behavioral symptoms and the older group had a predominance of cognitive symptoms.<sup>94</sup> Parkinsonism and speech changes may accompany the other symptoms.<sup>63</sup> A small subset of cases have been reported with a syndrome that mimics amyotrophic lateral sclerosis (ALS).<sup>64</sup>

There is overlap of the above clinical syndromes with the criteria of well-established neurodegenerative disorders, especially frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD).<sup>9,31</sup> Although not described in mild TBI, moderate to severe TBI has been found to be a risk factor for AD and other dementias.<sup>78</sup>

## PATHOPHYSIOLOGY

The first neuropathologic description of CTE in 1973 was in boxers.<sup>23</sup> The first case of CTE-type pathology in a former National Football League (NFL) player was reported in 2005, with a second case reported a year later.<sup>75,76</sup> CTE-like pathology has since been described in athletes involved in multiple other sports including boxing, hockey, soccer, and wrestling.<sup>41,63,74-76,84,86,94</sup> There have also been cases described in war veterans exposed to blast injury and in some with self-injurious behavior such as head banging.<sup>36,41,65,94</sup> On gross pathology, advanced CTE is characterized by generalized atrophy, more pronounced in the frontal and medial temporal lobes, thalamus, hypothalamus, and mamillary bodies; thinning of the corpus callosum; enlargement of the lateral and third ventricles; and pallor of the substantia nigra and locus coeruleus. Cavum septi pellucidi is also a frequently described finding.<sup>23,32,41,63,74-76,84,86</sup>

The microscopic appearance of CTE is characterized by the accumulation of phosphorylated tau neurofibrillary tangles (NFT), neurites, and glial tangles (GT) throughout the frontal, temporal, and insular cortices; diencephalon; brainstem; dentate nucleus; and spinal cord. Accumulations of transactive response DNA binding protein 43 Da (TDP-43), also found in frontotemporal dementia and amyotrophic lateral sclerosis, are characterized as neuronal and glial inclusions, neurites, and intranuclear inclusions in cases with more severe tau pathology. There is significant neuronal loss seen in the hippocampus, entorhinal cortex, and amygdala.<sup>36,41,63,84,86</sup>

The tau-immunoreactive NFTs are irregular and primarily affect the superficial cortical layers with focal epicenters at the depths of sulci and surrounding small blood vessels.<sup>32,36,63</sup>

Although this tau is the same as that found in AD and other tauopathies, this specific distribution is the main distinguishing feature.<sup>36,63,86</sup> Also, the density of NFT and GT is much greater than in other tauopathies.<sup>32,84,86</sup>

The current theory on the cause of CTE is that it arises from repetitive head trauma, in keeping with the historical descriptions.<sup>36,63,100,104</sup> The degree of head trauma reported ranges from mild TBI to more severe TBI. There are anecdotal reports of subconcussive injuries leading to CTE.<sup>6,7,32,63,94,95</sup> The NFTs usually cluster in areas associated with direct mechanical trauma. Ischemia may be the cause of tau in the depths of the sulci, and the tau surrounding blood vessels may be associated with breakdown of the blood-brain barrier after brain injury.<sup>19</sup>

However, to date, there are no prospective, cross-sectional, or epidemiologic studies to confirm that mild traumatic brain injury or any other condition causes CTE. There are confounding factors in the current published cases, such as the contribution of age-related changes, comorbid illness, alcohol and drug use, other neurodegenerative disorders, and a family history of neurodegenerative diseases.<sup>6,24,49,62,100</sup> It is also unknown what threshold of impact, rotational, or deceleration forces are needed to generate a concussion.<sup>6</sup> There are cases with documented repetitive head trauma without neuropathologic evidence of CTE, so head trauma alone may not be sufficient to cause CTE.<sup>9</sup> It has yet to be established whether a certain number of concussive or subconcussive injuries predisposes an individual to developing this disease and what role genetic or environmental factors may play.<sup>23,93</sup>

## IMAGING OF TRAUMATIC BRAIN INJURY

Chronic traumatic encephalopathy cannot be diagnosed by imaging, but structural imaging findings in acute and chronic head trauma are well established. This section reviews imaging findings in acute and chronic brain injuries and briefly discusses investigational techniques such as magnetic resonance spectroscopy (MRS), single-photon emission computed tomography (SPECT), diffusion tensor imaging (DTI), and positron emission tomography (PET). These techniques are currently being evaluated for their utility in the detection, classification, and prognostication in the setting of traumatic brain injury, including CTE.

### Acute Traumatic Brain Injury

Imaging in acute TBI is designed to detect injuries that require emergent intervention and is used to detect lesions that may cause long-term disability.<sup>35</sup> Both computed tomography (CT) and magnetic resonance imaging (MRI) are used in the acute traumatic setting. However, CT is the primary imaging modality because of short scan times, ability to tolerate life support equipment, and ability to accurately detect neurosurgical emergencies.<sup>79</sup> CT has a 99.7% negative predictive value in excluding neurosurgical emergencies.<sup>54</sup> Multiple criteria have been developed to determine the necessity of CT scans in mild TBI such as the Canadian CT head rule, New Orleans criteria,

Table 1. New Orleans criteria

**Computed tomography is required for patients with minor head trauma and any one of the following factors<sup>a</sup>**

Headaches

Vomiting

Older than 60 years

Drug or alcohol intoxication

Persistent anterograde amnesia (deficits in short-term memory)

Visible trauma above the clavicle

Seizure

<sup>a</sup>Criteria only apply to patients who have a Glasgow coma scale score of 15. Reproduced from Stiell et al.<sup>96</sup>

and the national emergency X-ray utilization study. The New Orleans criteria recommend a noncontrast head CT in cases of very mild TBI (Glasgow Coma Score [GCS] of 15) with one of the following findings present: short-term memory deficit, drug intoxication, physical evidence of trauma above the clavicles, age greater than 60 years, seizure, headache, or vomiting (Table 1).<sup>39,96</sup> The New Orleans criteria have been shown to be 100% sensitive for detecting injuries that require neurosurgical intervention.<sup>92</sup> Emergent CT can also be used to evaluate clinical outcomes depending on the severity of imaging findings in moderate to severe brain trauma according to various classifications, including the Marshall score, Rotterdam score, International Mission for Prognosis and Clinical Trial (IMPACT) model, and Traumatic Coma Databank (TCDB) model.<sup>57</sup>

Magnetic resonance imaging may be used in cases where CT results do not correlate with the clinical findings in the acute setting, as MRI has a much higher sensitivity for detecting diffuse axonal injury (DAI) and small contusions.<sup>80</sup> Additionally, MRI is preferred over CT to further evaluate patients with persistent symptoms in the subacute or chronic setting. MRI techniques such as diffusion-weighted imaging (DWI), T2\*-weighted gradient recalled echo (GRE), susceptibility-weighted imaging (SWI), and T2-weighted fluid attenuated inversion recovery (T2W FLAIR) are routinely used in clinical practice to identify primary and secondary lesions related to trauma. Several studies have shown that T2W FLAIR has increased sensitivity in detecting subarachnoid hemorrhages, brain contusions, and brainstem injuries when compared with noncontrast CT.<sup>3</sup> T2\*GRE and SWI have been shown to be better than CT for detecting microhemorrhages, diffuse axonal injuries, and subacute/chronic hemorrhages.<sup>88</sup> SWI, which

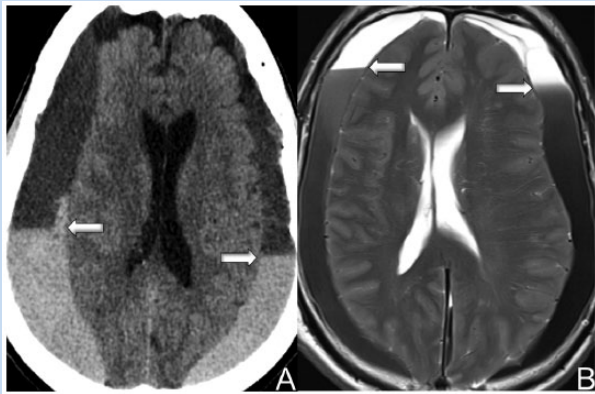
increases signal loss secondary to rapid spin dephasing, has been shown to be more accurate and sensitive in detecting microhemorrhages when compared with T2\*GRE.<sup>18</sup> While conventional SWI imaging can potentially overestimate the extent of hemorrhage since mineralization also causes rapid signal loss, newer techniques such as quantitative susceptibility mapping (QSM) can differentiate between the 2.<sup>12,17</sup>

### Subdural and Epidural Hematomas

While subdural hematomas (SDH) can occur from multiple etiologies, they are most commonly associated with trauma. The mechanism that commonly produces an SDH is rapid deceleration, such as from a motor vehicle accident, fall, or assault, particularly in the elderly because of brain atrophy.<sup>15,33</sup> The rapid deceleration causes injuries to either the bridging dural veins, the cortical veins, or less likely, the superficial cortical arteries. SDHs are crescent-shaped, extra-axial fluid collections that do not cross the dural attachments but can cross the cranial sutures. Common locations for SDH are along the cerebral convexities, falx cerebri, and cerebellar tentorium.<sup>11</sup> The density of the collection on CT varies depending on the age of the collection and the baseline hematocrit. In the acute phase (<3 days), an SDH often appears uniformly hyperdense; however, acute SDH may have a mixed heterogeneous appearance secondary to clot retraction or rebleeding (Figure 1A). Over time, the subdural collection will become less dense and can become isodense to gray matter. A chronic subdural collection will become hypodense, similar to cerebrospinal fluid (CSF). Careful inspection on subdural windows is always recommended to exclude an isodense subdural collection.

On MRI, T2W FLAIR can be especially helpful for the detection of subdural hematomas since they are usually hyperintense in the acute and subacute phases, although the signal intensity may vary (Figure 1B).<sup>89</sup> On T1- and T2-weighted sequences, subdural hematomas are usually isointense to hyperintense in the hyperacute phases (<12 hours) and hypointense in the acute phase (12 hours-3 days). Subacute subdural hematomas are typically hyperintense on T1W sequences. During the chronic phase, subdural hematomas demonstrate signal characteristics similar to CSF. The degree of midline shift and herniation, size of the subdural hematomas, and presence of accompanying contusions have been shown to have a worse prognosis and increased mortality.<sup>87</sup>

Epidural hematomas (EDH) develop in approximately 2% of head trauma cases, and 85% are associated with a skull fracture.<sup>13,37</sup> The majority of epidural hematomas are supratentorial (90%), with a large percentage of supratentorial hematomas located in the temporoparietal region. Epidural hematomas usually result from a tearing injury to a meningeal artery, with the middle meningeal artery classically being affected. Rarely, epidural hematomas can be venous in origin from injury to the transverse sinus, superior sagittal sinus, or sphenoparietal sinus.<sup>105</sup> The hemorrhage occupies a potential space located between the outer endosteal layer of the dura and the calvarium. On imaging, a biconvex extra-axial fluid



**Figure 1.** Acute chronic subdural hematomas in an elderly patient. (A) Computed tomography and (B) magnetic resonance imaging demonstrate bilateral chronic convexity subdural collections with layering-dependent hematocrit levels (arrows) containing acute hemorrhage.



**Figure 2.** Epidural and subdural hematomas. (A) Axial computed tomography (CT) demonstrates a hyperdense lentiform extra-axial epidural hematoma (short arrow) overlying the right frontal lobe with depressed bone fragments from an overlying comminuted calvarial fracture. Mass effect from the epidural hematoma caused leftward subfalcine herniation (long arrow). (B) Axial CT in a different patient demonstrates a hyperdense left hemispheric convexity crescentic subdural hematoma (short arrows) causing ventricular effacement and rightward subfalcine herniation (long arrow).

collection is present and crosses dural attachments but not cranial sutures (Figure 2). Certain ancillary findings indicate a worse prognosis, including midline shift, mass effect, contra coup subdural hematomas, or a swirl sign.<sup>2</sup> A swirl sign on CT is hypodense material within the hyperdense epidural hematoma, suggesting active bleeding. Active bleeding can have a Hounsfield unit, a measure of density on CT, of 20 to 30 less than a formed clot.

## Subarachnoid Hemorrhage

The etiology of traumatic subarachnoid hemorrhage (SAH) includes the tearing of small pial vessels, transependymal flow from intraventricular hemorrhage, or extension of hemorrhage from a nearby intraparenchymal hematoma or contusion.<sup>50</sup> Traumatic SAH is most common along the cerebral convexities and less commonly seen within the Sylvian fissure and basilar cisterns.<sup>27</sup> CT findings include hyperdensities within the subarachnoid spaces and cisterns (Figure 3). Except for SAH within the basilar cisterns, T2W FLAIR has been shown to be more sensitive in detecting SAH than CT.<sup>97</sup> SWI and T2\*GRE also frequently demonstrate blood products within the subarachnoid space.<sup>103</sup> The complications of SAH include hydrocephalus and vasospasm, but these are seen more frequently with aneurysmal SAH.

## Brain Contusions

Cortical contusions result from either sudden rotation/deceleration or direct impact. A cortical contusion is predominantly a surface brain injury involving the gray matter that can extend into the subcortical white matter. The deep white matter is more commonly spared. Cortical contusions are most commonly supratentorial and frequently seen in the anterior temporal or anteroinferior frontal lobes, areas where the cerebral gyri impact on the irregular osseous surface of the calvaria (Figures 3 and 4A).<sup>34</sup> Commonly, cerebral contusions have a coup-contrecoup pattern, seen at the site of impact and also within the brain parenchyma opposite from the site of impact.<sup>38</sup> Involvement of the brainstem leads to a particularly poor prognosis.<sup>29</sup> MRI is far more sensitive than CT for detecting small contusions, contusions along the skull base, and chronic contusions (Figure 4B).<sup>42,51</sup> Hemorrhage, edema, and mass effect within a contusion may increase within the first 24 to 48 hours, often creating a need for serial CT surveillance.<sup>82</sup> Secondary complications, such as infarctions, herniation, and hydrocephalus also are evaluated on serial CT examinations.<sup>22</sup> Encephalomalacia from chronic cortical contusions is best demonstrated with MRI. Chronic hemorrhagic contusions will also demonstrate blooming artifact on SWI and T2\*GRE (Figure 5), not easily detected with CT.<sup>16,51</sup> Hemorrhagic contusions demonstrate variable signal on T1- and T2-weighted sequences depending on their age.

## Diffuse Axonal Injury

Diffuse axonal injury is thought to result from traumatic shearing forces seen with a rapid deceleration or change in angular force that stretches axons secondary to differences in densities and distances in axis of rotation from one another.<sup>50</sup> The shearing effect is greatest at the gray-white junctions. DAI is felt to be a harbinger of severe white matter injury and is associated with greater neurologic impairment when compared with cerebral contusions and extra-axial hematomas.<sup>67</sup> Conventional CT and MRI are thought to only detect a small percentage of DAI lesions.<sup>10</sup> The most common locations for DAI involve the gray-white junctions in the frontal and temporal lobes, splenium of corpus callosum, and brainstem. MRI is far more sensitive than CT for detecting axonal





Figure 3. Multicompartmental trauma in a patient with moderate traumatic brain injury. Multifocal hyperdense acute subarachnoid hemorrhages along the anterior frontal lobes and within the posterior right sylvian fissure (short arrow), small bifrontal convexity mixed density subdural hematomas (arrowheads), and a hypodense left frontal contusion (long arrow) are noted on this axial computed tomography scan.

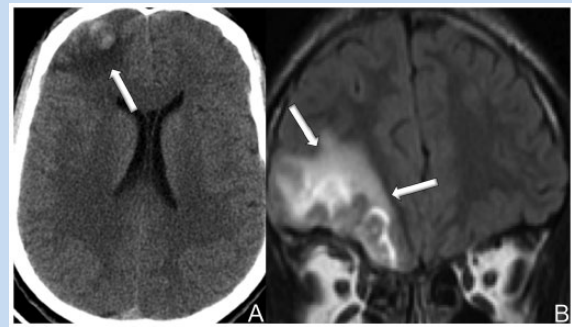


Figure 4. Acute cerebral contusion in a confused patient with severe traumatic brain injury. (A) Axial computed tomography (CT) scan demonstrates a right frontal cortical and subcortical hyperdense acute hemorrhagic contusion with surrounding hypodense vasogenic edema. (B) The coronal T2-weighted FLAIR (fluid attenuated inversion recovery) performed shortly after the CT scan better delineates the size and extent of this acute hemorrhagic brain contusion and the extensive surrounding vasogenic edema (arrows). The anteroinferior right frontal lobe, overlying the right orbital roof, is a common location for cerebral contusions.

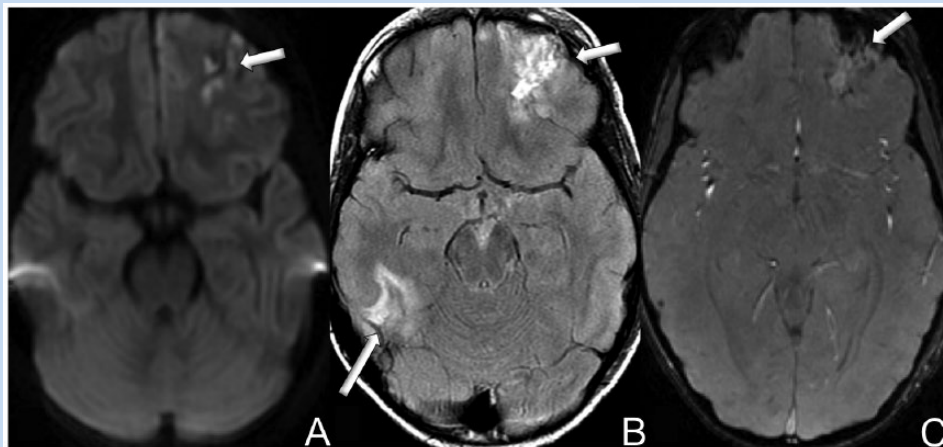


Figure 5. Multifocal acute cerebral contusions. (A) Diffusion-weighted imaging demonstrates foci of restriction diffusion within the left anteroinferior left frontal lobe (short arrow). (B) T2-weighted FLAIR (fluid attenuated inversion recovery) demonstrates associated abnormal parenchymal hyperintensity consistent with vasogenic edema within the left frontal lobe, site of the “coup” injury (short arrow), and within the right temporal lobe, site of the “contrecoup” injury (long arrow). (C) Susceptibility-weighted imaging demonstrates multiple foci of low signal intensity (short arrow) related to hemorrhage in the left anteroinferior frontal lobe.

injuries.<sup>51</sup> White matter lesions can be hypodense (edema) or hyperdense (hemorrhage) on CT scans (Figure 6). On MRI, SWI and T2\*GRE demonstrate low signal intensity blooming artifact, T2W FLAIR may show hyperintense at nonhemorrhagic foci, and acute lesions may demonstrate restriction on DWI (Figure 7).<sup>40</sup> Staging with the Adams and Genneralli

classification has demonstrated correlation with the severity of traumatic brain injury depending on location.<sup>1</sup> Stage 1 involves the frontal and temporal lobes, stage 2 extends into the corpus callosum, and stage 3 involves the dorsolateral midbrain and upper pons. Higher stage DAI corresponds with worse prognosis.<sup>1</sup>

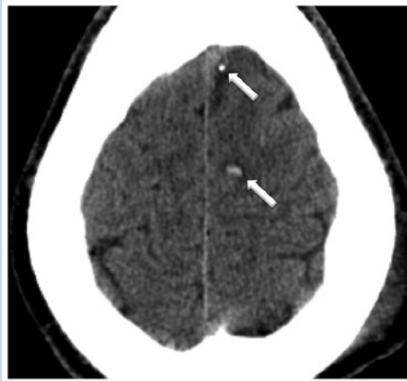


Figure 6. Diffuse axonal injury. Hyperdense left superior frontal hemorrhagic foci at the gray-white junctions (arrows) are consistent with acute axonal injuries on this noncontrast axial computed tomography scan.

### Acute Secondary Brain Injuries

Primary brain injuries and secondary brain injuries from infarction and edema can result in brain herniation. Subfalcine herniation, secondary to mass effect on the cingulate gyrus and consequent displacement, is the most common; this may result in compression of the anterior cerebral arteries and acute infarction. Compression of the ipsilateral ventricle and dilation of the contralateral ventricle due to entrapment at the foramen of Monro may also occur in this setting. In ascending transtentorial herniation, the cerebellum is displaced superiorly through the tentorial incisura. In downward transtentorial herniation, the frontal and/or temporal lobes herniate inferiorly through the tentorial hiatus with effacement of the supracellar cistern. With cerebellar tonsillar herniation, death may occur from cervicomedullary compression and infarction. The different types of herniation are associated with different clinical syndromes and are important to recognize, as there is potential for significant morbidity and mortality in the absence of urgent intervention.<sup>48</sup>

Primary and secondary brain injuries can cause diffuse cerebral swelling, with loss of gray-white differentiation and effacement of the sulci and cisterns, usually sparing the cerebellum.<sup>50</sup> Additionally, patients with TBI can develop noncommunicating hydrocephalus from ventricular compression and obstruction. Communicating hydrocephalus may also develop acutely or chronically in patients with intraventricular or subarachnoid hemorrhage.

Vascular injuries such as dissections, pseudoaneurysms, occlusions, and arteriovenous fistulas are rare complications of trauma occurring in 0.1% to 0.2% of all trauma patients.<sup>66</sup> Vascular injuries have an increased incidence in patients with complex skull fractures, basilar skull fractures, or cervical spine injuries.<sup>14</sup> The internal carotid artery is the most commonly affected vessel. In patients with a high clinical suspicion, CT angiography (CTA) is highly sensitive and specific in detecting vascular injuries.<sup>90</sup> Although not as commonly used, MR angiography (MRA) has also been shown to be efficacious in the

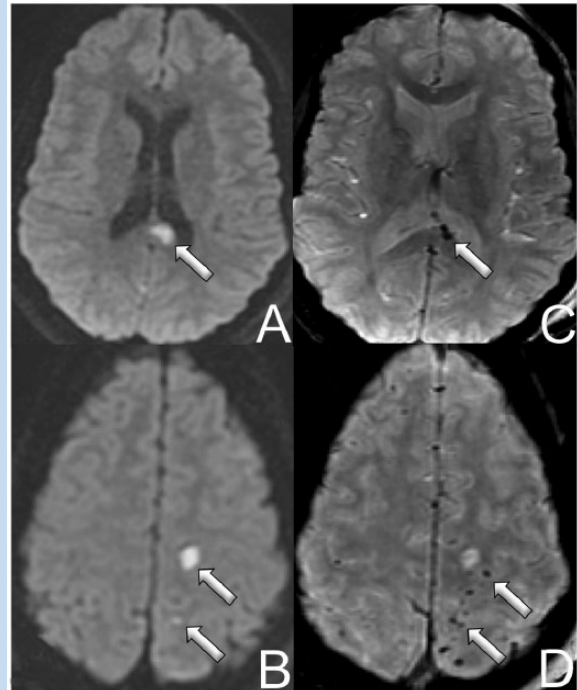


Figure 7. Diffuse axonal injury. Foci of restricted diffusion on diffusion-weighted imaging (DWI) are present within the splenium of the (A) corpus callosum and (B) at the gray-white junctions of the left frontal and parietal lobes on the DWI magnetic resonance image (arrows). Susceptibility-weighted imaging (SWI) demonstrates numerous associated foci of blooming artifact consistent with microhemorrhages within the (C) corpus callosum and (D) at the gray-white junctions (arrows). Axonal injuries identified on DWI and SWI do not always map to the same brain regions. Of note, the majority of these traumatic lesions were not appreciated on a computed tomography scan performed earlier the same day.

traumatic setting. Findings of an intramural hematoma, intimal flap, or occlusion of the vessel are seen on both CTA and MRA.

### Chronic Traumatic Brain Injury

Cerebral volume loss after TBI has been demonstrated in several studies.<sup>26,56,99,106</sup> Several longitudinal studies have correlated the degree of volume loss with the severity of the TBI.<sup>99</sup> Almost all of this research has been performed with moderate or severe TBI, although recent studies have demonstrated cerebral atrophy with mild TBI.<sup>106</sup> Volume loss has been seen as early as 3 weeks.<sup>99</sup> In a large study of 338 active professional boxers, atrophy was the most common abnormality, seen in 22 boxers.<sup>44</sup>

Encephalomalacia can be an indicator of prior trauma. However, encephalomalacia can also be seen with other etiologies such as prior infarctions or infections. The patient's history and the location of the encephalomalacia can indicate prior trauma as the more



**Figure 8. Chronic cerebral contusions. Noncontrast computed tomography demonstrates bifrontal gliosis and volume loss (arrows) related to remote cerebral contusions.**

likely etiology; common locations for prior trauma include the gyri recti and anteroinferior temporal lobes as previously discussed. On CT, hypodensity and volume loss are noted at this site of remote injuries (Figures 8 and 9A). On MRI, cystic encephalomalacia will be isointense to CSF, with surrounding gliosis appearing hyperintense on T2W sequences (Figure 9, B and C). Several studies have shown that patients with encephalomalacia have an increased rate of disability and seizure.<sup>46,68</sup> Chronic findings of DAI on MRI include gliosis on T2W FLAIR and susceptibility artifact on T2\*GRE and SWI sequences in the expected locations, as previously described (Figure 10).

### Investigational Techniques in TBI

Diffusion tensor imaging (DTI) is an MRI technique that quantifies the diffusional anisotropy (property of being directionally dependent) of water in white matter tracts (Figure 11).<sup>8</sup> Fractional anisotropy (FA) is a measure of diffusional anisotropy with a unitless scale from 0 to 1. An FA of 0 signifies that water freely diffuses in all directions, while an FA of 1 signifies that water uniformly diffuses in 1 direction.<sup>8</sup> Abnormalities in the anisotropy or the diffusion ellipsoid within white matter are hypothesized to be related to axonal disruption. Current research supports the theory that DTI detects microstructural abnormalities not detected by conventional MRI. Commonly studied white matter tracts include the corpus callosum, longitudinal fasciculus, cingulum bundle, and uncinate fasciculus.<sup>79</sup> Numerous recent studies suggest that DTI can help identify acute and chronic TBI and can be correlated to neurologic deficits.<sup>28,45,53,59,60,71-73,83</sup>

However, many of these studies conflict and are based on small case-control studies. Additionally, specific parameters to detect TBI in individual cases are lacking, and DTI methodology and analysis have not been standardized. Significantly decreased FA values in multiple white matter tracts have been described<sup>59,60</sup>; however, longitudinal analyses have been inconsistent regarding whether these DTI changes resolve over time.<sup>61,102</sup> Overall, DTI

has shown promise in many preliminary studies, but larger prospective standardized multicenter trials are needed to validate the technique for clinical practice.

Blood oxygenation level–dependent (BOLD) functional MRI (fMRI) can detect changes in the oxygenation of hemoglobin and correlates to brain function during the performance of a specific task.<sup>5</sup> As the metabolic demand increases in a region of the brain actively involved in the task, there is increased cerebral blood flow and thereby increased deoxygenated hemoglobin. The number of studies of BOLD fMRI is significantly smaller than studies with DTI, and there are smaller numbers of patients enrolled in each study. One challenge with BOLD fMRI is that TBI causes a decrease in cerebral blood flow (CBF) from the injury itself. Therefore, differentiating changes in CBF related to the injury versus a change in neuronal activity becomes problematic.<sup>43</sup> A few studies have demonstrated some promise, although these studies are limited by their small sample size. One fMRI study that involved 11 football players without a history of concussion, but with increased hits to the head measured via a device placed in the helmets to detect impacts, demonstrated decreased visual working memory and altered activation of the dorsolateral prefrontal cortex when comparing examinations from before and after a football season.<sup>98</sup> This finding is particularly interesting given the neuropsychologic deficits in both working memory and executive function that can accompany a postconcussive syndrome. Another case-control study involving 15 concussed youth athletes also demonstrated decreased activity in the dorsolateral prefrontal cortex.<sup>47</sup>

Magnetic resonance spectroscopy is used to evaluate certain neurometabolites such as choline, *N*-acetylaspartate (NAA), creatinine, and glutamine as a spectrum of resonance peaks. There have been numerous small studies using this technique in TBI.<sup>4,20,21,30,52</sup> One case-control study on 40 concussed athletes demonstrated a significant decrease in NAA at 3 days with normalization of NAA at 30 days.<sup>101</sup> Another small pilot study comparing 5 athletes with history of multiple concussions and suspected CTE compared with 5 matched control subjects demonstrated a 20% reduction in NAA in the frontal lobes compared with the control group.<sup>52</sup>

Several recent small studies using SPECT in TBI investigated changes in CBF, one of which demonstrated decreased CBF in 75% of subjects.<sup>55</sup> A few studies using fluorodeoxyglucose positron emission tomography (FDG-PET) for evaluation of metabolic changes in the brain have also been recently published; 1 recent study performed on professional boxers showed decreased uptake in the frontal lobe, cerebellum, and posterior cingulate cortex.<sup>81</sup> Another study performed in a cohort of 12 soldiers with a history of “blast injury” demonstrated regional areas of decreased FDG uptake in the cerebellum, pons, and medial temporal lobe.<sup>77</sup> Finally, 2-(1-[6-(2-[fluorine-18]fluoroethyl) (methyl)amino]-2-naphthyl)-ethylidene)malonitrile (FDDNP) is a new PET imaging probe that binds both tau and amyloid proteins. A preliminary FDDNP-PET study on 5 football players with clinical signs concerning for CTE compared with controls demonstrated



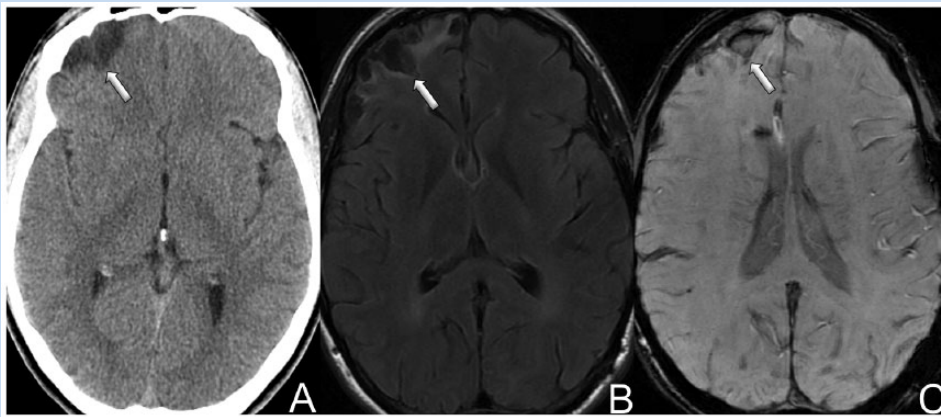


Figure 9. Chronic parenchymal contusion. (A) Axial computed tomography (CT) and (B) T2-weighted FLAIR (fluid attenuated inversion recovery) demonstrate volume loss and gliosis (short arrows) within the anteroinferior right frontal lobe at the site of a remote contusion. (C) Susceptibility-weighted imaging demonstrates loss of signal (short arrow) secondary to extensive hemosiderin deposition within this chronic contusion.

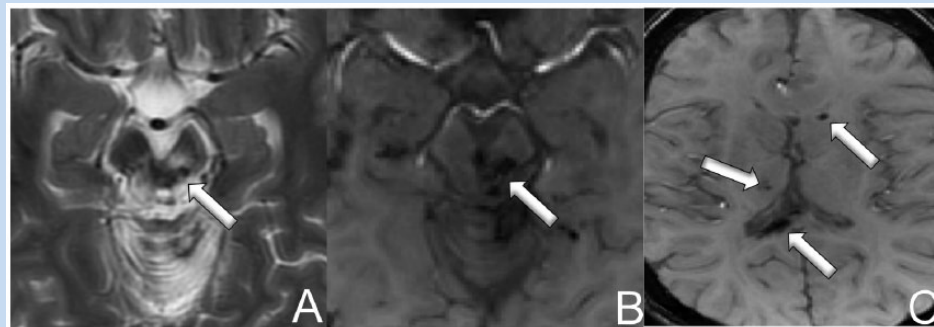


Figure 10. Chronic diffuse axonal injury. (A) Axial T2-weighted image demonstrates atrophy and gliosis of the midbrain and left cerebral peduncle (arrow). Susceptibility-weighted imaging demonstrates multiple foci of susceptibility artifact within the midbrain (arrow B), splenium of the corpus callosum, right thalamus, and left basal ganglia (arrow C) compatible with chronic microhemorrhages in locations typical for diffuse axonal injury.

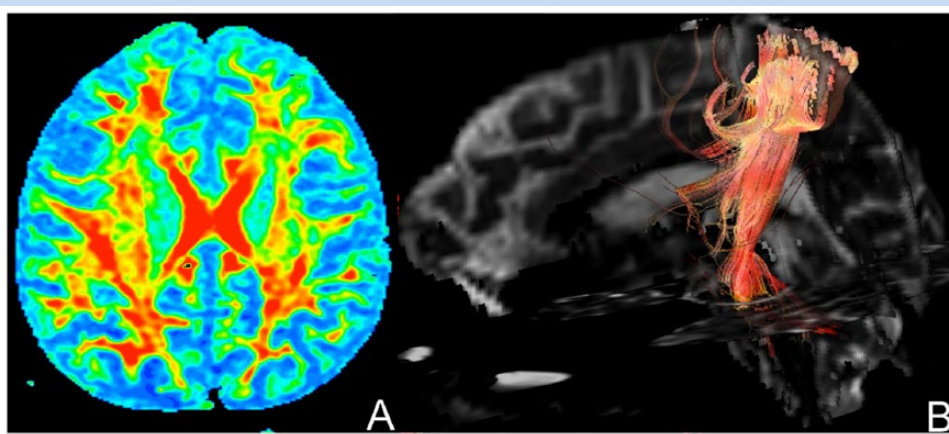


Figure 11. Diffusion tensor imaging. (A) Reconstructed fractional anisotropy (FA) map demonstrates regions of high-ordered water motion (high FA) as red and more random water motion (low FA) as blue. (B) Three-dimensional white matter tractogram of the intact corticospinal tract generated from the diffusion tensor imaging data.



increased signal in subcortical regions and amygdala in the symptomatic patients.<sup>91</sup>

## CONCLUSION

Chronic traumatic encephalopathy is described as a progressive tauopathy currently only diagnosed on neuropathologic examination. It has been found in athletes of various sports, war veterans, and in people with self-injurious behavior. No clear clinical syndrome has been determined at this time, but reviews of pathologically diagnosed cases indicate involvement of cognition, mood, and behavior. Pathology shows NFTs throughout the frontal, temporal, and insular cortices; diencephalon; brainstem; cerebellar dentate nucleus; and spinal cord, especially at the depths of sulci and around blood vessels. While it is believed that repeated head trauma might cause CTE, further research is needed to quantify the number, extent, and severity of injuries that render a person susceptible to developing these neuropathologic criteria. Imaging modalities such as CT and MRI are currently able to accurately depict the structural sequelae of TBI and triage acute TBI patients appropriately but are limited in assessing microstructural changes. DTI, BOLD fMRI, MRS, SPECT, and PET are under active investigation at research institutions as possible future clinical tools to detect the microstructural changes that are thought to occur in TBI. Further study is necessary to correlate the clinical and imaging findings of repetitive head injuries with the pathologic diagnosis of CTE.

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