Traumatic Brain Injury

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Abstract
Traumatic brain injury (TBI) is the leading cause of death and disability with a wide spectrum of pathologies, severity, mechanisms and outcomes that are age-dependent. This review covers this spectrum with emphasis on severe TBI and recent advances in diagnostic and prognostic tests.

Keywords: Traumatic brain injury; Prognosis; EEG; Evoked potentials; Event-related potentials

Definition and Classification
Traumatic brain injury (TBI) is the disruption of brain function due to externally applied forces either causing acceleration or deceleration of the brain or direct physical contact of an object with the brain or head.

TBI can be classified into primary and secondary injuries. Primary injuries occur at the moment of injury, while secondary injuries occur after the moment of impact, often causing additional damage to an already injured brain. Another classification divides TBI into focal injuries (e.g., contusions or lacerations) or diffuse injuries (as with concussions or diffuse axonal injury.) TBI can also be graded by severity: mild, moderate and severe, with severe TBI usually defined as a Glasgow Coma Score for 8 or less with a mental status change exceeding 6 hours. A mild head injury is defined as a mental status change lasting less than 30 minutes from the time of the injury; a moderate TBI has an associated mental status change lasting 30 minutes to 6 hours.

Epidemiology and Etiologies
In the United States alone, about 1.7 million people have medical care for varied types and severities of head injury annually [1].

The predominant mechanism is dependent on the population studied. For school aged children, sports injuries predominate, while in the elderly falls are very important. In young-middle aged adults motor vehicle accidents, assaults and alcohol-related injuries are common in Western societies. In the military working in war-torn countries blast and penetrating brain injuries are prominent.

Concussions and Minor Head Injury
Concussions are at the mildest end of the mild TBI continuum. Concussion has been described as “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces” [2]. The concussive force can be applied either by a direct blow to the head face or neck or elsewhere with an “impulsive force” transmitted to the head, usually resulting in acceleration-deceleration type of head displacement, e.g., football helmets colliding or a blow in boxing). The displacement usually has both linear and rotational components. The underlying pathogenesis probably involves ionic transmembrane shifts, altered brain blood flow, abnormal energy metabolism and altered neurotransmitter release. In mild cases homeostatic mechanisms correct these derangements in the days or weeks following concussion.

“Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously” [2]. The alteration is primarily functional rather than structural. Concussion can be graded in severity; some features may last for a prolonged period of time. No abnormality on standard neuro-imaging should be seen.

Features that are common in mild TBI, including concussion include
1. Loss of consciousness/alertness: this occurs in fewer than 10% of cases of concussion but is more common in more severe TBI cases and is usually only seconds in duration.
2. Confusion: this is commonly manifest by disorientation, problems concentrating usually with a memory lapse.
3. Amnesia: most commonly this is anterograde (moving forward from the time of the injury) but can also include retrograde memory loss, usually for a few seconds before the injury. The duration of amnesia is probably the best marker for the severity of the mild TBI. Amnesia for more than 24 hours indicates a significant head injury and carries an increased risk of residual cognitive deficits and post-traumatic seizures.
4. Balance and co-ordination defects.
5. Cognitive problems: these usually recover within 2 weeks in concussions, but can last longer in more severe TBI cases. Younger individuals, e.g., high school students, may suffer longer duration of cognitive problems than mature adults, although the elderly may again have longer lasting residua.

Multiple Mild TBIs
Residua from repeated TBIs are often cumulative and linger for longer time periods [3]. Not all patients respond in the same way and much more research is needed in this area.

Second Impact Syndrome
This is a controversial entity, but cases have been described in which a second minor TBI can be followed by a malignant course [4,5]. The second injury typically occurs during the recovery period from

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the first injury. There is a loss of cerebral autoregulation resulting in increased blood flow coupled with vasogenic edema. Most cases have been reported in children. The mortality is greater than 50%.

**Traumatic Encephalopathy**

Traumatic encephalopathy (TE) is a chronic static or progressive decline in neurological or neurobehavioral status after exposure to head injury [6]. Most reported cases follow repeated head injuries, but there are some cases in which a single head injury is followed by TE. Some cases can follow repeated subconcussive type injuries, e.g., in football (soccer) or martial arts. Victoroff recently developed criteria for the diagnosis of TE [7]. In his careful analysis of reported cases, most of whom were boxers [6], the onset of symptoms occurred at or beyond the end of the career and there was often a delay of a decade or more before the diagnosis was made, often in the late 30s or 40s of age. Symptoms and signs were progressive in more than half the cases. Key features included:

1. History of head injury either concussive or repeated subconcussive injuries.
2. Symptoms following traumatic exposure: headache, speech disturbance, tremor, deterioration in stance or gait or falls, cognitive changes such as memory loss and getting lost, anxiety, paranoia, personality changes, ethanol abuse or sensitivity to intoxication, and anger and aggression.
3. Signs: nystagmus, ataxia, reduced facial expression, hypertonia or rigidity, hyper-reflexia, hemiparesis, tremor and disorders of stance and gait.
4. Neurobehavioral signs: memory loss, other cognitive changes (including frank dementia), mood disturbance (lability, depression, euphoria), thought disorders (e.g. paranoia), pathological personality traits (irritability, impulsivity, apathy) anger and aggression.

The above should be persistent without a suitable alternative diagnosis.

**Severe Traumatic Brain Injury**

In this review we shall concentrate on severe TBI, which is the leading cause of death and disability among patients under 45 years of age [8,9]. Mortality ranges from 30-40%, with most patients dying after withdrawal of life support in ICUs [8]. Thirty per cent of survivors have major neurological sequelae [8,9]. The decision to withdraw is usually based on the projected neurological prognosis. A recent survey of Canadian ICUs revealed that there was tremendous variation in the timing and percentages of such withdrawals among hospitals, with many occurring within the first three days of care [8]. This is worrisome, as it is acknowledged that prediction of outcome in TBI patients is imprecise. Better predictive guidelines for favorable and unfavorable outcomes need to be established.

TBI is heterogeneous in mechanisms (ranging from penetrating brain injuries to acceleration-deceleration) and pathology (including diffuse axonal injury [DAI], contusions and lacerations) [10]. This complicates the formulation of uniform guidelines for prognosis.

Universal prognostic guidelines for TBI have not been formulated. However, we shall review the best evidence from clinical, electrophysiological and neuro-imaging perspectives, referring to specific types of injury when appropriate.

**Diffuse Axonal Injury**

Patients diagnosed with DAI have an immediate loss of consciousness and remain with a GCS of 8 or less for a variable amount of time, from a few hours to a few months, or may never regain awareness. The impact of the trauma causes the axons to become stretched or disrupted by the sudden acceleration-deceleration or rotational forces [11,12]. Typically DAI is maximal in frontal and temporal regions and in severe cases involves the corpus callosum and the upper brainstem [13].

Ommaya and Gennarelli proposed that TBI followed a centripetal model with the periphery of the brain being more prone to damage with a less severe trauma, while deeper structures need more force to be damaged [14]. It was found that the depth of the parenchymal lesions seen on MRI were directly related to the duration of impaired consciousness, and that deeper lesions (corpus callosum or brainstem) also correlated with a greater degree of impaired consciousness [15]. These findings are consistent with the grading system for DAI introduced by Adams et al., with impact on the hemispheres (Grade I), the corpus callosum (Grade II) or the brainstem (Grade III) [16].

There is evidence that in DAI, as with concussion, neurons develop delayed injury after the initial impact, probably due to biochemical cascades that are more marked in their activation than in less severe injuries [17,18]. Neuronal damage is followed by the appearance of secondary lesions that were not seen on the first images due to loss of white matter overtime. PET studies using [18F] fluorodeoxyglucose (FDG) and [18F] flumazenil in DAI patients also showed focal damage mostly in the medial frontal gyrus, the cingulate gyrus and the thalamus [19].

**Focal Lesions**

In focal brain lesions, i.e., subdural and epidural hematomas and contusions (see Figure 1), the decreased level of consciousness is due to the mass effect exerted by the lesion directly on the diencephalon, mesencephalon or brainstem, and/or by the increased intracranial pressure due to the volume of the lesion leading to herniation. Midline displacement with supratentorial mass lesions is most closely correlated with the degree of obtundation [20,21]. This precedes the

**Figure 1**: There is a large, acute right-sided, supratentorial, subdural hematoma with massive shift of midline structures from right to left and entrapment of the left lateral ventricle.
Clinical Features

There are often external signs of trauma, e.g., facial bruising or lacerations, Battle’s sign (bruising over the mastoid or hematympanum, indicating a fracture through the petrous temporal bone) or "raccoon eye" (evidence of a fracture through the orbital roof). The history is valuable: loss of consciousness that immediately follows the injury often indicates DAI, while loss of consciousness after an initial "lucid interval" or the "talk and die" syndrome raises the possibilities of delayed brain edema (more common in children or young adults) or intraparenchymal or extracerebral hemorrhage (subdural or epidural hematoma) with increasing mass effect.

Patients with DAI do not have raised intracranial pressure unless there is accompanying intracranial bleeding or cerebral edema. Very severe cases may show "brainstem findings", including Horner’s syndrome, gaze palsies or 6th nerve palsies, but most cases show coma related to bicerebral injury. Patients without obvious brainstem injury may show either decerebrate or decorticate posturing, either spontaneously or following stimulation. Patients with supratentorial mass lesions who develop coma will often show initial pupillary changes indicative of herniation unless they are bilateral.

Imaging

Advances in technology have greatly facilitated the recognition of various pathologies. For example, diffuse axonal injuries were not seen on CT-scan, resulting in patients being diagnosed on the bases of history, clinical symptoms, and the absence of lesions on CT. The final diagnosis was therefore usually made at autopsy. With MRI technologies (T1 and T2 sequences), axonal tears with subsequent edema were discovered. Newer sequences such as fluid-attenuated inversion recovery (FLAIR) made the lesions more apparent, but with the study of water diffusion through diffusion tensor imaging (DTI), more precise images of tracts were obtained.

While CT is still the imaging modality of choice in the acute setting of a trauma, when the patient is unconscious, other imaging techniques are emerging. CT causes exposure to radiation, and has a relatively poor resolution for small lesions. While essential to rule out a large hemorrhagic lesion needing an adequate treatment, CT does not detect diffuse axonal injuries [22].

Standard MRI sequences (T1-, T2-weighted and FLAIR images) can reveal small contusions as well as some diffuse axonal injuries and allow for better discrimination of the structural lesions than using CT. While not usually indicated when the neurological status is normal after a concussion, some MRI studies have shown subacute and chronic changes with brain atrophy in more severe injuries (decrease in white matter and ventricular enlargement) [23,24].

The study of fiber tracts with diffusion tensor MRI, tacking advantage of the anisotropic motion of water within the axons (fractional anisotropy, FA), has enabled the identification of white matter tract disruption, and therefore the detection of smaller areas of DAI. Maps of FA would be disturbed when the sheaths of myelin are disrupted or when there is edema around the axons. Studies of mild traumatic brain injuries have shown abnormalities in the genu of the corpus callosum (reduction of FI) [25-27]. Diffusion tensor imaging (DTI) is progressively being used clinically in the traumatic brain injuries [12,28,29]. It is useful assessing the prognosis for consciousness recovery after TBI and support the possible use of DTI as a biomarker for early classification of patients [30].

Proton magnetic resonance spectroscopy (MRS) is a non-invasive way of looking at brain metabolites. Differences in ratio of metabolites as well the presences of some metabolites are the signature for neuronal or other cell injuries. Disruption of neurons will also lead to changes in metabolite regulation (e.g., impaired mitochondrial energy production will reduce N-acetyl-aspartate (NAA), a neuronal marker, and membrane degradation might increase choline (Cho). The presence of lactate indicates some degree of anaerobic metabolism. After trauma, a decrease in NAA/Cr (creatinine) ratio, which is the signature for neuronal damage, has been shown in the corpus callosum [31,32], in the brainstem, in basal ganglia [33], and in and near contused areas [34-36]. In concussion, changes in the NAA/Cr ratio have been shown [37,38], but such changes are usually transient, coming back to baseline within a few days [37,39] to months [37,39]. However they may remain abnormal in more severe trauma. The Cho/Cr ratio, which is seen in membrane disruption, increases after TBI and remains high up to 6 months after the injury [38], even in some concussed patients. This could be reflective of glial proliferation or inflammation in the perilesional region. Lactate/creatine (Lac/Cr) ratio was elevated during the first week after TBI [40]. Absolute peak value for Glutamate/glutamine (Glx) and Cho were found to be significantly elevated in the occipital gray and parietal white matter early after injury in patients with poor long-term (6-12-month) outcomes of one study [41] which showed that Glx and Cho values predicted long-term outcome with 94% accuracy and when combined with the motor Glasgow Coma Scale score provided the highest predictive accuracy (97%), while somatosensory evoked potentials were not as accurate. Previous research suggests that MRS might be helpful by showing the true extent of axonal damage especially when combined with MRI (T2, FLAIR and diffusion) images [42].

Functional MRI (fMRI) has been used to study a variety of brain injuries, of varying severity. In concussion in athletes, studies have found different patterns of activity in patients versus controls [43-45] in tasks involving working memory [45]. For example, in patients with a severe TBI, those with a better recovery showed a near normal activation pattern when completing a Tower of London task (prefrontal and parietal activation), while the patients with a worse recovery had an inconsistent pattern of activation and poor behavioral performance. For the time being, fMRI is used mostly as a research tool, but it has great promise clinically.

Single photon emission computed tomography (SPECT) has been used in trauma in the study of regional cerebral blood flow and has shown abnormalities in the medial temporal lobe circulation [46]. The exposure to radio-isotopes is a disadvantage. Furthermore, the qualitative or, at best, semiquantitative, nature of SPECT is not sensitive to changes in global blood flow, but it can be useful in compares regions of the brain to each other.

Positron emission tomography (PET): is used to observe the metabolism of the brain, usually using FDG. Some studies have shown that there are differences in patients who have had a concussion as...
compared to controls with a reduced mesial temporal metabolism, as well as more globally in the frontal and temporal cortex. Some studies have also shown a decrease in the global glucose metabolism for up to 4 weeks post-injury, without correlation with the GCS. PET also is currently used only as a research tool and not clinically in TBI.

**Electrophysiological Assessment**

**EEG**

EEG has several roles in the assessment of the patient with TBI:

- **Seizure detection:** Vespa and colleagues monitored 84 patients with moderate-severe TBI from the time of their admission to the ICU for up to 14 days post-injury. Seizure occurred in 20% of the patients, half of which were nonconvulsive. The six patients with status epilepticus died, compared with a mortality rate of 24% in the nonepilepsy patients [47].

- Seizures, typically focal in origin with variable spread, are more likely in patients with greater severity of TBI and in patients with contusions than in those with DAI. The occurrence of seizures after the drainage of subdural hematoma has also been noted. Seizures are reduced in frequency but not completely prevented by prophylactic phenytoin, now given to patients with a Glasgow Coma Scale score (GCS) of 8 or less and an abnormal CT head scan. Such therapy reduces seizure frequency in the first week only, but does not alter outcome or the incidence of post-traumatic epilepsy [48]. Thus, it is advisable to perform continuous EEG monitoring (CEEG) in patients at risk for seizures and to treat accordingly. It remains to be shown, however, that treatment of early post-traumatic seizures improves outcome or shortens ICU length of stay.

- **Prognosis:** Conventional EEG has not been of great assistance in prognostication, although this has been insufficiently explored [49]. Simple reactivity and the presence of normal-appearing spindles are relatively favorable features, especially when combined with clinical and neuro-imaging results [50].

- **Sedation monitoring:** CEEG monitoring can also be used to guide sedation monitoring. Sedation with propofol and midazolam are commonly used to control agitation, to facilitate assisted ventilation and to help lower intracranial pressure (ICP). It has been our experience that sedation is often overdone or is erratic; this probably prolongs time on the ventilator and ICP stay overall, in addition to contributing to delirium on less severely injured patients. Monitoring for sedation is optimal with automated/quantitative EEG, but raw EEG at the bedside, even with 2 or more channels, can still be helpful in avoiding having excessive suppression.

**Quantitative EEG (QEEG)**

QEEG has the advantage of condensing the EEG temporally so that slowly evolving changes can be readily seen. QEEG usually uses fast Fourier transforms to convert the EEG into amplitude and frequency changes over time, with frequency on the x-axis and the power (amplitude squared) on the y-axis. Separate epochs are “stacked” with the most recent on the bottom as a compressed spectral array. More recently, color-coded displays with frequencies of different colors and amplitude displayed vertically and with time in hours on the x-axis.

Although some good work has been published on the application of QEEG in TBI, this technology has not been widely adopted and tends to be used mainly in the academic units that developed it, except perhaps for amplitude-integrated EEG for seizure detection.

Seizures usually produce a significant change in background amplitude and frequency that can be readily seen on QEEG display. It is a good policy to confirm that such “blips” are seizures by examining the raw EEG. Reliable criteria exist for recognizing seizures with standard criteria [51].

QEEG has been shown to be effective in the rough separation of mild from severe head injury. Thatcher and colleagues, using discriminant analysis, were able to differentiate these two categories with >90% sensitivity and specificity [52,53].

QEEG also lends itself to assessing the severity of brain injury by examining spectral content including the phase and amplitude coherence between cortical areas. Low scores indicate disruption of interconnectivity of cortical regions [54]. Thornton has shown abnormal connectivity in frontal regions by examining beta frequency coherence in an auditory memory task [55]. Independent component analysis has also been applied to detect differences in coherence in multiple channels [56].

**Polysomnography:** Polysomnography has been used to assess prognosis in TBI [57]. The closer sleep staging and arousability the better the outcome. There are some patterns such as the cyclic alternating pattern that are associated with an unfavorable prognosis [57].

**EEG and cognitive assessment**

More recently EEG changes during commanded motor tasks have been explored by Cruse et al. [58]. Patients, most with TBI, who were clinically diagnosed as being in VS were given commands to move their right hand and toes while being recorded. Three of 16 patients could generate EEG responses (a shift in power of various frequency bands in electrodes over the motor cortices) similar to control subjects.

**Evoked potentials**

Evoked potentials (EPs) are recorded electrical responses from the nervous system that are produced by a stimulus and occur at a fixed interval from the stimulus. This allows for computer averaging techniques to sum these time-locked responses and then divide the summated responses by the number of stimuli. Non time-locked signals approach zero, while the evoked response remains.

The most prognostically useful EP is somatosensory (SSEP), usually produced by stimulation of the median nerve at the wrist [59].

A systematic review of 25 studies of high grade TBI patients showed that SSEPs provide a more reliable prediction of poor outcome than the GCS, EEG, CT scan or clinical examination [60]. The bilateral absence of the cortical component of the SSEP was associated with an outcome no better than vegetative state. Unilateral absence or contralateral delay was still associated with significant impairment. Combining the SSEP results with GCS, pupillary and motor responses enhanced the predictive value for intermediate degrees of SSEP abnormalities [59,60]. In applying SSEPs for prognosis it is best to record along the sensory pathway, to ensure that the problem lies intracranially. Although SSEPs are not affected as much by sedation as EEGs are, it is wise to minimize anesthetic drugs when applying this test.

Auditory and visual evoked responses have not been very useful, except in examining the integrity of those pathways, respectively.
Event-related potentials

Event-related potentials (ERPs) are responses that are of a higher order than EPs in that they rely on discriminative functions or advanced processing of signals. Because of this the latencies from the stimuli are longer in duration. In contrast to short latency EPs, which when absent are useful in determining a poor prognosis, ERPs when present give support to return of conscious awareness. Examples are:

Mismatch negativity (MMN)

MMN is defined as a negative shift in the averaged EEG recording occurring within a time window of 100-300 msec in response to variant sounds that are presented randomly but infrequently compared to standard sounds [61]. Fischer et al. [62] studied patients in coma and found that MMN was useful in predicting recovery from coma and an outcome better than Wijnen et al., studied patients who shifted from coma to VS and found that the improvement in amplitude of the MMN to >2 microvolts predicted an ultimate outcome better than the minimally conscious state (MCS) [61].

P300 response (P3)

The P3 response is a positive wave appearing about 300 msec after an “oddball” or variant stimulus, and is analogous to the MMN. Its presence was originally thought to require the patient to be awake and attentive, but P3 can be generated in comatose patients [23]. Reuter and Linke, found the TBI patients who showed the P3 response in coma were able to function independently 6 months after the injury [63].

N400 response

Connolly and colleagues have tested semantic comprehension of speech/language in unresponsive but alert patients with ERPs [64,65]. The N400 response is generated when the last word of a sentence does not make sense, e.g., “The pizza was too hot to sing.” Auditory or visual presentations can be used in such testing. Patients who show the N400 responses can sometimes be rehabilitated and have a greater chance of recovering some independence.

Biomarkers

With brain trauma various glial and neuronal constituents are released into the blood and CSF. This release is time dependent and will vary depending on the predominant pathology, e.g. DAI vs. contusions. In group studies there are strong correlations between various biomarkers in the serum as well as CSF and outcomes with severe TBI both for children and adults [66-71].Some of the main contenders for useful serum biomarkers are the S100 glial protein, ubiquitin C-terminal hydroxase 1 (UCH-1), glial fibrillary acidic protein and pentraxin [67-69]. In the CSF there are more abundant potentially useful biomarkers including alpha-synuclein, various cytokines and neuronal specific enolase [66,70,71]. While biomarkers offer considerable prognostic promise, studies have been small, single centered and leave some uncertainties, such as optimal time for sampling and correlation with specific pathologies and age groups. In general, prognostication in the first hours or days from trauma is difficult and needs to be done with great care to avoid self-fulfilling prophecies. Further research and validation studies are needed for both severe and mild TBI [72].

Management

After a concussion, care should be taken to prevent a second impact injury. In returning to play, patients should refrain from practicing until completely asymptomatic, then slowly returning to play, gradually, depending on their symptoms (or lack of symptoms); non-athletes can gradually start their activity again when they are asymptomatic. Individuals with long-lasting symptoms can benefit from neuropsychological testing [73].

Patients with more severe injury should be scanned to assess the necessity of a neurosurgical intervention. When the GCS is lower than 8, and the imaging is abnormal, a pressure monitoring probe is usually inserted [74]. The intracranial pressure can therefore be monitored and treated if necessary. Lesions creating mass effect will need to be evacuated surgically. Hemispheric edema with raised intracranial pressure refractory to medical treatment (hypertonic saline, mannitol, etc.) might require a hemicraniectomy [75].

Abnormal cerebral autoregulation can also be monitored using continuous transcranial Doppler ultrasonography (using the pulsatility index), or pressure reactivity index monitoring [76]. The pressure reactivity index is the slope of the regression line relating MAP and ICP [77]. NIRS (Near InfraRed Spectroscopy) is progressively being investigated and used to monitor the cerebral blood flow or brain oxygenation. It is based on the different absorption characteristics of oxy- and deoxy-hemoglobin [78]. Those new techniques to monitor the patients are currently still research oriented, but could become clinical tools in a near future.

References


