Posttraumatic Epilepsy: A Major Problem in Desperate Need of Major Advances

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This brief review is meant to provide an update on the data from clinical and laboratory studies that have provided insight into the mechanisms underlying the development of epilepsy following traumatic brain injury (TBI). The link between severe brain trauma and epilepsy in humans is well recognized. However, we have yet to identify an effective intervention to prevent the development of epilepsy in patients who are at risk after TBI. Laboratory studies, which have relied primarily on the fluid-percussion model, have documented long-term hyperexcitability associated with TBI, and recent studies are shedding light on the structural and electrophysiological abnormalities that may underlie epileptogenesis in this setting. Nonetheless, given the extent of the clinical problem and our current state of knowledge, this area of epilepsy research deserves far more attention.

Traumatic brain injury (TBI) accounts for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy (1). Posttraumatic epilepsy can occur soon after injury or may develop months to years later. Studies of civilian and military populations have assessed the basic epidemiology of this condition. A number of population-based studies, both prospective and retrospective, have been aimed at identifying risk factors for development of a first seizure and recurrent seizures following TBI. In addition, a series of large clinical trials have looked at whether or not antiepileptic drug prophylaxis can reduce the risk of developing early and late seizures after TBI.

Several animal models have been used to elucidate the structural, chemical, and physiologic changes that are associated with TBI and that may contribute to seizures and epilepsy. Disease heterogeneity makes it difficult to simulate all aspects of human TBI with any single animal model. Also, until recently,

none of the animal models have shown spontaneous clinical or electrographic seizures over long-term follow-up.

Here we review the human and animal data that have provided insight into the potential mechanisms linking TBI to posttraumatic epilepsy. An important take-home message is that, despite a considerable amount of research in this area, our understanding of the pathophysiology of trauma-induced seizures and epilepsy is very rudimentary. Much work remains to make headway with a clinical problem that is of great importance.

Insights from the Clinical Setting

A few definitions are necessary to insure common terminology. Early seizures generally include those occurring within 1 week of the brain injury, although some studies exclude the first 24 hours and others include up to 30 days after the injury. Late seizures are those occurring 1 week or more after the injury. Definitions for severity of head injury vary, but one of the most established paradigms is that proposed by Annegers et al. (2), in which head injury is classified as mild, moderate, or severe. Mild injuries are defined by lack of skull fracture and a period of posttraumatic amnesia or loss of consciousness that is 30 minutes or less. Moderate injuries may or may not be associated with skull fractures, but there is a period of 30 minutes to 24 hours of posttraumatic amnesia or loss of consciousness. Severe injuries are characterized by brain contusion, intracranial hematoma, or 24 hours or more of either unconsciousness or posttraumatic amnesia.

A MEDLINE search of all prospective, civilian cohort studies that were published in English since 1965, and that evaluated risk factors for developing at least one seizure after TBI, yielded eight studies (2–9). Among the studies identified (see Table 1), the incidence for seizures ranged from 2% to 25%, with higher frequencies seen with more severe injury. Some studies took all patients with any history of brain injury, whereas other investigations selected patients admitted to the hospital or admitted specifically to the intensive care unit. Presumably, among patients in the latter group, seizure incidence would be higher as a result of increased severity of injury. Table 1 summarizes the incidence of early and late seizures as well as predisposing risk factors found to have statistical significance in these studies.

In addition to the trials summarized in Table 1, Haltiner et al. (10) looked at the risk of a second seizure after a first late posttraumatic seizure in patients with moderate to severe head injury. All patients ($N = 63$) were started on antiepileptic drugs after the first seizure, but only 55 patients remained on

TABLE 1. *Incidence of Early and Late Posttraumatic Seizures in Civilian Populations*

Study	Feature	N	Early Seizure %	Risk Factors	Late Seizure %	Risk Factors
Jennett and Lewin (3)	Admitted	896	4.2	PTA >24h, age <5y, skull fracture, intracranial hemorrhage	10.2	Early seizure, PTA >24h, depressed skull fracture, intracranial hematoma
Annegers et al. (2)	Population	2747	2.1	Age <15 y, severe injury	1.9	Severe injury, early seizure
Desai et al. (4)	Admitted, pediatric	702	4.1	Age <16 y, focal neuro deficits, LOC/PTA >30 min, skull fracture, intracranial hematoma	N/A	N/A
Annegers et al. (5)	Population	4541	2.6	Not evaluated	2.1	Severe injury, brain contusion, subdural hematoma, LOC/PTA >24h
Hahn et al. (6)	Admitted, pediatric	937	9.8	GCS 3–8, diffuse cerebral edema, acute subdural hematoma	N/A	N/A
Angeleri et al. (7)	Admitted	137	8		13.1	GCS 3–8, early seizures, single brain CT lesions, EEG focus
Asikainen et al. (8)	TBI Rehab Center	490	16.3	Age <8 y	25.3	Early seizures, depressed skull fracture
Englander et al. (9)	Admitted with CT findings or GCS 3–10	647	3	N/A	10.2	Multiple or bilateral cortical contusions, dural penetration, multiple intracranial operations, midline shift >5mm, evacuated SDH

PTA, posttraumatic amnesia; LOC, loss of consciousness; GCS, Glasgow coma scale; TBI, traumatic brain injury; SDH, subdural hematoma.

treatment. They found that the rate of seizure recurrence at year 2 was extremely high (86%) in all patients, but slightly lower (73%) in patients who were taking antiepileptic drugs. Within the subgroup taking antiepileptic drugs, 8 patients (13%) had recurrent seizures while not fully complying with therapy. For this reason, the investigators suggested that a single late seizure is a strong indication to initiate antiepileptic drug treatment. In two series involving military personnel (11,12), the total combined incidence of early and late posttraumatic seizures ranged from 33% to 53% and was highest with penetrating head injuries. Factors that correlated with higher incidence of seizures in a series of patients who served in Vietnam (12) included higher total brain volume loss, presence of initial or residual focal neurological deficits, retained metal fragments, and intracerebral or subdural hematomas. Thus, in both the civilian and military studies, severe brain injuries with focal intracranial lesions, fractures, or prolonged alteration in consciousness are the most important risk factors for development of posttraumatic seizures.

Traditionally, TBI patients have been treated with prophylactic antiepileptic drugs, with the expectation that treatment will reduce the incidence of posttraumatic epilepsy. However, a number of studies have shown that antiepileptic drugs are only effective in preventing early posttraumatic seizures (13–15). No beneficial effect of antiepileptic drugs has been demonstrated for patients with late posttraumatic seizures, and phenytoin may have negative cognitive effects in this population (16). On the basis of these data, it is recommended that patients with severe traumatic brain injury receive prophylactic treatment with phenytoin as soon as possible after injury, but not routinely beyond the first 7 days after injury (15). Watson et al. retrospectively evaluated the effects of corticosteroids on late seizures after TBI using a cohort from a phenytoin prophylaxis trial (17). They found that treatment was not associated with any decrease in late posttraumatic seizures, and treatment within the first day of trauma was associated with increased seizure activity.

Insights from the Laboratory

Long-standing recognition of the clinical importance of TBI has led to a substantial amount of translational and basic

investigation. An extensive and fairly rich literature concerning the pathology and imaging of TBI in humans as well as more limited information on the physiological and biochemical changes observed in the nervous system of victims of TBI exists. The pathological consequences of TBI are many, including primary damage from direct laceration or contusion of brain tissue by bone fragments or foreign bodies, hemorrhage, and diffuse axonal and vascular injury. Secondary damage from hypoxia–ischemia, edema, and breakdown of the blood–brain barrier may also occur (18).

Given the tremendous variation in the nature of TBI, it is not surprising that many different models (ranging from acceleration–deceleration injury in nonhuman primates to mechanical trauma to individual neurons in culture) have been developed to study basic mechanisms of head injury. For the purposes of studying epileptogenesis after TBI, however, there is some rationale to focusing on models involving the neocortex or temporal lobe. For instance, in two retrospective case series of human patients with intractable epilepsy after TBI, it was found that 24% to 35% of patients had foci in the mesial temporal lobe, while 12% to 48% had neocortical foci (19,20).

Fluid percussion in the rodent is the most commonly used model in the field of epileptogenesis and TBI. In this model, lateral or rostral parasagittal injury to the cortex and underlying structures is induced by delivering a very brief fluid pressure pulse to the intact dura through a burr hole. Numerous studies have documented the many anatomical and biochemical changes observed with the fluid percussion model and have shown that the model reproduces many features of head injury observed in other models and species (21,22). In 1992, Lowenstein et al. found that lateral fluid percussion injury causes a selective loss of hilar interneurons in the dentate gyrus and that this effect is associated with abnormal hyperexcitability of the dentate granule cells, as measured by extracellular field potentials in response to paired-pulse stimulation of the perforant path (23). Subsequently, Coulter and colleagues conducted in vitro electrophysiological recording studies using combined hippocampal–entorhinal cortical slices from TBI rats (24). They demonstrated that slices from TBI rats showed greater disinhibition in the dentate gyrus compared with those from control rats and that most slices generated self-sustaining epileptic activity after stimulation of Schaeffer collaterals, the main afferent input from CA3 to CA1 pyramidal neurons.

A study by Toth et al. (25) confirmed that weeks to months after fluid percussion injury, specific subclasses of dentate interneurons supplying inhibitory innervation of granule cells were decreased. However, Santhakumar et al. (26) later showed that hilar interneuron loss was not preferential. The investigators proposed that survival of glutamatergic mossy cells of the dentate hilus were involved in creating hyperexcitable responses from dentate granule cells (the irritable mossy cell hypothesis). This finding provided yet more fuel to the ongoing (and still unresolved) debate as to whether relative survival or loss of hilar mossy cells is the basis of persistent granule cell hyperexcitability after damage to the dentate gyrus (27).

Although these studies documented clear anatomical changes in the hippocampus and other brain structures, along with abnormal excitability of specific networks, it was not until 2001 that investigators discovered persistent electrophysiological changes that might be considered more direct evidence for TBI-induced epileptogenesis. Santhakumar et al. (28) demonstrated an increase in excitability of CA1 pyramidal cells in response to Schaeffer stimulation 3 months after fluid percussion injury. At the same time, Golarai et al. (29) found that animals had an enhanced susceptibility to pentylenetetrazole-induced convulsions 15 weeks after TBI (created with a weight-drop) as well as persistent D,L-2-amino-5-phosphovaleric acid (APV)-sensitive hyperexcitability in the granule cell and molecular layers of the dentate gyrus.

Somewhat parallel to the studies involving the fluid percussion model, other investigators have utilized models of direct cortical injury to explore the mechanisms underlying TBI-induced seizures. Prince and colleagues have produced an important body of work using the "cortical undercut" or "cortical island" technique. In this approach, a small region of neocortex is partially isolated by using a needle bent at 90° and transecting the underlying white matter. Electrophysiological characterization of brain slices prepared from the injured region has shown epileptiform potentials arising from layer V (30,31). Furthermore, layer V pyramidal neurons display increased input resistance and membrane time constants, and they appear to be the source of sprouted axons that are associated with an increased number of excitatory connections (32). There is good evidence that at least some of these changes are activity-dependent, since they can be blocked when tetrodotoxin is introduced into the injured region early after injury (33).

The work using the cortical undercut or cortical island techniques has provided some potential insights into the cellular and network properties that are altered by TBI. However, a critical, missing element has been evidence that the models actually cause posttraumatic epilepsy; that is, the emergence of spontaneous seizures in the intact animal. Fortunately, evidence of the association between TBI and spontaneous seizures has come out very recently in studies by D'Ambrosio and colleagues (34). Using the lateral fluid percussion injury model and chronic electrocorticography, they demonstrated that a single episode of severe fluid percussion injury caused spontaneous partial seizures that originate from the neocortex at the site of injury. Furthermore, the seizures were chronic and became progressively worse (electrographically and behaviorally) over time. In a follow-up study, the investigators provided very convincing

evidence for a progression of the phenotype from a predominance of frontal parietal seizures (at or near the site of injury) to a predominance of mesial temporal seizures at later time points (35). It is important to note that in both these studies, the investigators used an impact force that is significantly higher than what has been typically used in other studies of fluid percussion injury and epileptogenesis. Nonetheless, given that epilepsy following head trauma in humans is most strongly associated with severe brain injury, these experimental findings can certainly be considered relevant to the clinical setting.

Conclusions

Posttraumatic epilepsy is a serious clinical problem. Clinicians involved in the regular care of patients with epilepsy know that posttraumatic epilepsy is an extremely disabling condition. These patients are frequently pharmacoresistant and are often not good surgical candidates. Clinical research to date has defined a clear relationship between the severity of TBI and the development of posttraumatic epilepsy, but results of trials with antiepileptic drugs have been very disappointing. Although some very interesting work has come from the laboratory regarding the nature of hyperexcitability after experimental TBI, it is remarkable how little has been accomplished relative to the magnitude of the clinical problem and how little is understood about the biology of this phenomenon. Research into the nature of posttraumatic epilepsy deserves a far more robust and concentrated effort.

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