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Epilepsy after head injury

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Abstract

Purpose of review—The purpose of this short review is to provide an update on the epidemiology of posttraumatic epilepsy, associated risk factors, data from prevention studies, and recent breakthroughs in experimental research.

Recent findings—There is increasing evidence that neuroimaging findings, stratification by neurosurgical procedures performed, and genomic information (e.g. apolipoprotein E and haptoglobin genotypes) may provide useful predictors of the individual risk of developing posttraumatic epilepsy. While antiepileptic drug prophylaxis can be effective in protecting against acute (provoked) seizures occurring within 7 days after injury, no antiepileptic drug treatment has been found to protect against the development of posttraumatic epilepsy and therefore long-term anticonvulsant prophylaxis is not recommended. Glucocorticoid administration early after head injury also has not been found to reduce the risk of posttraumatic epilepsy. At the basic research level, there have been advances in the understanding of pathophysiological changes in posttraumatic excitatory and inhibitory synapses, and the critical period for epileptogenesis after head injury has been better defined. Finally, the development of a novel animal model, which mimicks more closely human posttraumatic epilepsy, may facilitate efforts to characterize relevant epileptogenic mechanisms and to identify clinically effective antiepileptogenic treatments.

Summary—Despite the continuing lack of clinically effective agents for posttraumatic epilepsy prophylaxis, recent advances in basic and clinical research offer new hope for success in the development of new strategies for prevention and treatment.

Keywords

posttraumatic epilepsy; partial seizures; head trauma; epileptogenesis; antiepileptic drugs; microdialysis

Introduction

Every year, about half a million people in the US sustain head injuries severe enough to require hospitalization [1^{*}]. These injuries are a major health problem in terms of acute morbidity and mortality as well as long-term neuropsychological [2^{*}] and neurological sequelae, including posttraumatic epilepsy (PTE). In the last decade, a number of randomized trials have failed to identify a protective effect of antiepileptic drug (AED) prophylaxis against the development of PTE [3^{*}]. The reasons for these failures are unclear, and may include suboptimal dosing, initiation time or duration of the treatments attempted, inadequate knowledge of patho-

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physiological mechanisms of traumatic brain injury (TBI), or absence of intrinsic antiepileptogenic properties of the few compounds tested to date.

Definitions

In this review, PTE will be defined as one or more unprovoked seizures occurring late (e.g. at least 1 week) after TBI, the latter being defined as head trauma requiring some degree of medical attention [4^{*}]. Although in a strict sense a diagnosis of epilepsy should be limited to patients with at least two unprovoked seizures, a broader definition is justifiable because many PTE studies limited their follow-up to occurrence of only one seizure. In one population-based study, 86% of patients with one late posttraumatic seizure had a second seizure within 2 years [5]. Early posttraumatic seizures are defined as seizures occurring within 7 days of trauma. Seizures occurring within minutes of the impact are not usually included in studies of early posttraumatic seizures.

The epidemiology of posttraumatic epilepsy: incidence data

The frequency of TBI varies with age, gender, geographical, social and professional factors. In the US, the overall incidence is estimated at 1.8–2.5 per 1000 persons per year, and higher rates have been reported for Europe and South Africa [1^{*}]. The incidence of epilepsy after TBI, in turn, ranges from 1.9% to over 30%, the magnitude of risk being dependent on the severity of trauma and the duration of follow-up [4^{*},6]. In civilian populations, the overall risk has been estimated at 2–5%, increasing to 7–39% for subgroups with cortical injury and neurologic sequelae [3^{*}]. In what is probably the best population-based study conducted to date [6], the cumulative 5-year probability of seizures was 0.5% in patients with mild injury (loss of consciousness or posttraumatic amnesia for <30 min, and no skull fracture), 1.2% for those with moderate injuries (loss of consciousness or posttraumatic amnesia for 30 min to 24 h, or skull fracture), and 10.0% in those with severe injuries (brain contusion or intracranial hematoma or loss of consciousness or posttraumatic amnesia for >24 h). Not surprisingly, the highest incidence has been reported in military series, due to a higher proportion of injuries that involve dural penetration and widespread brain damage.

In most cases of PTE, the risk of seizures is highest in the first year after trauma, and decreases progressively thereafter. How long an increased risk persists is a matter of controversy. In a population-based study, persons with moderate injury continued to have an increased risk for up to 10 years, whereas those with severe injuries had an increased risk for over 20 years after injury [6].

The epidemiology of posttraumatic epilepsy: risk factors

Important independent risk factors for PTE include acute intracerebral hematoma (especially subdural hematoma), brain contusion, increased injury severity (as reflected by loss of consciousness or posttraumatic amnesia lasting >24 h), occurrence of early posttraumatic seizures, and being older than 65 years at the time of injury [4^{*}]. Because risk factors for early seizures overlap with those for PTE, the importance of early seizures as an independent risk factor has not been univocally demonstrated in studies conducted to date. Early seizures, in particular, may not be a significant risk factor in pediatric populations [4^{*}], and were not identified as an independent risk factor in multivariate analysis in a population-based study [6]. Early seizures, however, were an independent risk factor in a Cox regression model analysis of high-risk patients recruited in seizure-prophylaxis studies [7]. Additional independent risk factors in the latter analysis were duration of coma over 1 week, dural penetration by injury rather than by surgery, depressed fracture not surgically treated rather than surgically elevated, and at least one nonreactive pupil. In a prospective multicenter study which enrolled 637 patients with moderate to severe TBI, factors associated with the highest cumulative probability

for PTE over a 2-year follow-up included biparietal contusions (66%), dural penetration with bone and metal fragments (62.5%), multiple intracranial operations (36.5%), multiple subcortical contusions (33.4%), subdural hematoma with evacuation (27.8%), midline shift greater than 5 mm (25.8%), or multiple or bilateral cortical contusions (25%) [8^{**}]. In another study, hypoperfusion in temporal lobes, degree of hydrocephalus, evidence of intracerebral hematoma, and operative brain injury were also identified as risk factors for PTE [9^{**}]. These data suggest that stratifying by neuroimaging findings and neurosurgical procedures can be useful to define individual risk for PTE.

Given the evidence that the apolipoprotein E (apoE) $\epsilon 4$ allele and a specific pattern of G-219T promoter polymorphism are associated with an unfavorable outcome after TBI [10,11^{*},12^{*}], there has been interest in genetic markers for the risk of PTE. Preliminary evidence does indicate that the apoE $\epsilon 4$ allele is a risk factor for PTE, independently of its effect on functional outcome [13^{**}]. Similarly, preliminary evidence suggests that the haptoglobin Hp2-2 allele is a risk factor for PTE because it has the lowest hemoglobin-binding activity, thus not preventing iron loss and related peroxidation damage [14^{*},15].

Can epilepsy after head trauma be prevented?

Most AED studies of seizure prophylaxis after TBI were uncontrolled or nonrandomized studies [3^{*}]. Although these studies have major inherent biases which do not allow meaningful conclusions, many have claimed a long-lasting protective effect, leading many clinicians to prescribe long-term anticonvulsant prophylaxis in high-risk patients. Unfortunately, this practice goes against the best scientific evidence provided by randomized trials. In a Cochrane systematic review of 890 patients from 10 randomized trials assessing phenytoin or carbamazepine, there was clear evidence for a reduction in the risk of early seizures (pooled relative risk 0.33, 95% CI 0.21–0.52), with 10 patients being kept seizure free in the first week for every 100 patients treated [3^{*}]. However, there was no indication of effectiveness in the prevention of late seizures (relative risk 1.28, 95% CI 0.90–1.81). Likewise, in a recent systematic review [16^{**}], phenytoin prophylaxis was confirmed to protect against early posttraumatic seizures (relative risk 0.37, 95% CI 0.18–0.74), but no significant differences in the risk of late seizures were found for patients given AED prophylaxis compared with untreated or placebo-treated controls (relative risk 1.05, 95% CI 0.82–1.35). Although agents other than AEDs have not been assessed in prevention trials, analysis of a prospectively collected database found no evidence that glucocorticoids given in the early (<1 week) posttraumatic period can prevent PTE [17^{**}]. Early glucocorticoid administration was actually associated with increased seizure activity, although this could be a spurious finding resulting from the nonrandomized allocation to therapy.

In conclusion, based on available data, phenytoin can be justified as a short-term treatment option to prevent seizures occurring in the first week after trauma in high-risk patients [16^{**}], but not in low-risk patients [18^{*}]. Because pharmacological prophylaxis has not been found to be efficacious and is associated with significant adverse effects, long-term prescription of AEDs for the prevention of PTE is not recommended.

Why has antiepileptic drug prophylaxis failed to protect against late posttraumatic seizures?

The observation that AEDs failed to prevent the development of PTE in randomized trials may have various explanations: (1) the AEDs tested were intrinsically devoid of antiepileptogenic properties; (2) the modalities of treatment (e.g. dosing regimens, onset and duration of treatment) were sub-optimal; or (3) other aspects in the trial design prevented identification of a drug effect. Indeed, many factors could have been simultaneously at play. The AEDs most

frequently investigated in PTE trials, for example phenytoin and carbamazepine, show little or no protective activity in animal models of epileptogenesis [19], and would not represent the best choice if a human trial were to be set up today. However, valproic acid does display antiepileptogenic activity in a variety of experimental models, including kindling, and yet it tended to increase rather than decrease the risk of PTE and mortality, although without reaching statistical significance, in a large randomized trial [20]. In many studies, the possibility of inadequate AED dosing and erratic compliance cannot be excluded, given that the serum AED levels were mostly sub-optimal [16**]. In addition, previous trial designs did not utilize potentially useful information from clinical pharmacology studies. One example is the use of microdialysis to assess drug brain penetration and acute changes in neurotransmitter release in TBI patients, a technique recently applied to document the lowering effect of topiramate on glutamate release after severe head injury [21**]. Another important aspect is that in most trials treatment was initiated many hours after injury, missing a possibly short time window of opportunity for neuroprotection [22*]. Finally, many studies had inadequate power to detect clinically important effects, although for valproic acid power was sufficient to exclude a greater than 25% reduction in the risk of late seizures [23]. Additional complicating factors include the heterogeneity of the enrolled populations, potential differences in therapeutic response associated with neuroimaging patterns [24*], the difficulty of classifying correctly a first seizure event (particularly partial onset seizures), and the large differences in trial design, including duration of follow-up [3*].

All these limitations should not be viewed as a justification to continue the ill-fated practice of prescribing long-term anticonvulsant prophylaxis after TBI. Rather, it should serve as a stimulus for the design of better clinical trials in the future, and for the development of improved animal models to assist in drug discovery and trial design.

Perspective from experimental research

A potential explanation for the failure of clinical trials to detect antiepileptogenic activity of compounds effective in animal models may be that the models employed did not reproduce the predominant and relevant epileptogenic mechanisms of human PTE or a suitable therapeutic window to target them. There is indeed concern that the epilepsy models used to screen for AEDs may not be optimal [25-29]. A truly relevant PTE model would give reasonable confidence that the modeled epilepsy arises via mechanisms similar to those operating in humans, and would help in optimizing pharmacological interventions (doses, onset and duration) that target those mechanisms. Since human PTE presents with partial seizures of cortical and limbic origin, efforts to control and prevent PTE should also advance the broader search for better treatments of partial seizures, which are often resistant to current AEDs and represent a major source of disability.

Recently, there have been important advances in developing animal models of PTE, identifying novel mechanisms of posttraumatic epileptogenesis, and characterizing the temporal window during which it occurs.

Animal models of posttraumatic epilepsy

Two laboratories have independently discovered that a single event of fluid percussion injury (FPI), a well characterized and relevant model of closed head injury, is sufficient to induce PTE in the rat [30**,31,32]. While the epilepsy features described by the two groups differ somewhat, common findings are that FPI-induced PTE is robust and manifests as chronic spontaneous recurrent partial seizures that worsen over time. D'Ambrosio and colleagues [30**,31] studied PTE in rats following rostral (bregma -2 mm) parasagittal FPI and demonstrated the development of two epileptic foci: one in the frontal-parietal neocortex near the injury site, and one in the hippocampus. The neocortical focus played a greater role in

defining the epileptic manifestations in the early months after injury, while the hippocampal focus became increasingly dominant over time. Seizures were predominantly brief and focal in the first weeks following injury and were associated with behavioral arrest and facial automatisms. At later time points, seizures were associated with ictal loss of posture, contralateral limb dystonia, or atonia [33]. Nissinen *et al.* [32] described, in abstract form, the effect of a more posterior (bregma –4 mm) parasagittal FPI, and identified a hippocampal focus responsible for tonic–clonic convulsions months after injury. The latter study was not designed to detect possible cortical foci. The divergent behavioral correlates of PTE reported by the two laboratories are likely to reflect differences in site and severity of the injuries. In particular, brainstem injury resulting from the more posterior FPI may account for the appearance of tonic–clonic seizures.

FPI-induced PTE represents a significant departure from traditional models of epilepsy. The initiating insult, a transient compression of the dura mater without penetration, is mechanically very similar to human closed head injury. FPI-induced epilepsy also reproduces cortical and hippocampal partial seizures that are commonly associated with human PTE and are often pharmacoresistant. Moreover, this PTE model possesses all the features identified by White [25] as ideal for an animal model of epileptogenesis: (1) pathology consistent with human epilepsy, (2) a ‘seizure-free’ latent period between the initiating injury and the onset of epilepsy, (3) spontaneous seizures following this latent period. Further work is needed to optimize the use of FPI, and similar head injury models in the rat, for AED discovery and testing.

Cellular mechanisms of posttraumatic epileptogenesis and its critical period

Novel epileptogenic mechanisms have been recently identified in the injured neuron. Using an in-vitro model of stretch injury, which reproduces a mechanical component of concussive head injury, Goforth and colleagues [34**] have identified alterations in glutamatergic transmission mediated by AMPA receptors. Previous work from the same group had shown that stretch injury results in loss of desensitization of the AMPA receptor, with consequent potentiation of AMPA-mediated synaptic transmission in cultured cortical neurons. The more recent findings indicate that such potentiation occurs within 15–30 min following injury, persists for around 24 h, and is dependent on N-methyl D-aspartate (NMDA) receptor activation [34**]. In addition, evidence indicates that stretch injury of cortical neurons in culture also results in modification of GABA_A transmission as early as 15 min–7 h after the injury [35**]. The potentiation of GABA_A transmission also seems to be dependent on NMDA receptor activation, possibly through phosphorylation of the GABA_A channel itself. These findings are important for two reasons. First, they demonstrate that specific changes in both excitatory and inhibitory synapses occur after stretch injury and may represent novel therapeutic targets to be investigated in in-vivo models. Second, they indicate a temporal window during which these synaptic changes occur and are maintained, and therefore suggest the duration of the critical period during which antiepileptogenic prophylaxis may be attempted. Indeed, another possible reason for the failure of clinical trials of antiepileptogenic interventions after TBI is that the drugs were not delivered soon enough. Graber and Prince [36], using the cortical-island model of PTE, showed that chronic treatment with TTX, a selective voltage-operated Na⁺-channel inhibitor that blocks neuronal excitability, prevented epileptogenesis when started immediately after injury. Recently these authors have suggested that this critical period may be as short as 3 days following injury [37**]. Their observations are important because they indicate that an antiepileptogenic treatment in TBI may be possible. However, the clinical relevance of the cortical-island model is questionable because it does not closely reproduce the focal and diffuse mechanical injury, the pathophysiology (i.e. immediate cellular and axonal disruption, massive glutamate and K⁺ release, and Ca²⁺ influx), the time course and the severity of concussive human TBI. By deafferentiating the cortex, the cortical-island model may emphasize slower inflammation-based epileptogenic mechanisms and, therefore, overestimate the duration of the

critical period. These observations, together with the time course of synaptic changes observed following stretch injury, suggest that the critical period following human concussive injury may be quite short – minutes to hours. Further experiments with more clinically relevant models are, however, needed to better define the critical period.

Conclusion

Recent studies have improved our understanding of the risk factors for PTE and of the mechanisms involved. A better definition of the critical period of epileptogenesis and of the epileptic changes at excitatory and inhibitory cortical synapses has emerged from in-vivo and in-vitro work. Moreover, a promising novel FPI model of PTE has been developed, which could be highly valuable in further characterizing epileptogenic mechanisms and, hopefully, in identifying clinically efficacious agents in the future.

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Abbreviations

AED, antiepileptic drug; FPI, fluid percussion injury; NMDA, N-methyl d-aspartate; PTE, posttraumatic epilepsy; TBI, traumatic brain injury.

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