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Epilepsy and Encephalopathy

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ABSTRACT

Background: Epilepsy encompasses more than the predisposition to unprovoked seizures. In children, epileptic activity during (ictal) and between (interictal) seizures has the potential to disrupt normal brain development. The term "epileptic encephalopathy (EE)" refers to the concept that such abnormal activity may contribute to cognitive and behavioral impairments beyond that expected from the underlying cause of the epileptic activity.
Methods: In this review, we survey the concept of EE across a diverse selection of syndromes to illustrate its broad applicability in pediatric epilepsy. We review experimental evidence that provides mechanistic insights into how epileptic activity has the potential to impact normal brain processes and the development of neural networks. We then discuss opportunities to improve developmental outcomes in epilepsy now and in the future.
Results: Epileptic activity in the brain poses a threat to normal physiology and brain development.
Conclusion: Until we have treatments that reliably target and effectively treat the underlying causes of epilepsy, a major goal of management is to prevent epileptic activity from worsening developmental outcomes.

Introduction

Epilepsy is defined by the International League Against Epilepsy as "an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition."[1] As the definition recognizes, the neurophysiological dysfunction that leads to unprovoked seizures in persons with epilepsy (PWE) often occurs not in isolation but alongside other functional impairments. Indeed, these comorbidities can be the main drivers of quality of life for PWE. In this review, we focus on comorbid "encephalopathy," i.e., pronounced brain dysfunction affecting mental status and cognitive processes, as the epitome of the potential for epilepsy to affect the developing central nervous system. In children, encephalopathy is commonly comorbid with epilepsy and leads to altered developmental trajectories and outcomes.[2-4]

The relationship between epilepsy and brain dysfunction is complex. Epilepsy and encephalopathy may have a shared origin (e.g., acquired brain injury, genetic disorder), but another, nonmutually exclusive alternative, is for epileptic activity itself to be causative of encephalopathy. Because epilepsy involves recurrent abnormal paroxysmal electrical activity in the brain, normal neurophysiological processes that underlie brain function (e.g., plasticity important for learning and memory) can be compromised by epileptic activity both between (interictal) and during (ictal) seizures. There are indications that epileptic activity has the potential to progressively erode the function of established brain circuits.[5] Moreover, young children have networks that are still being established, and disruption can cause their development, which relies on functional activity patterns, to slow, plateau, or regress. The incidence of epilepsy is highest during these consequential first years of life.[6-8]

In this review, we will discuss clinical evidence that epileptic activity may worsen developmental outcomes and review experimental evidence that provides mechanistic insight into how epileptic activity has the potential to impact normal brain processes and the development of neural networks. We will then discuss opportunities to improve developmental outcomes in epilepsy.

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Part I: Epileptic encephalopathy

Clinical management of epilepsy regardless of age focuses on controlling seizures to improve daily quality of life for PWE and reduce the risk of complications such as sudden unexpected death in epilepsy patients (SUDEP). In pediatric epilepsy, optimizing developmental outcome is an additional major goal. The importance of this fact is reflected by the International League Against Epilepsy's focus on a conceptual framework for encephalopathy in the setting of epilepsy. Epileptic encephalopathy (EE) is the concept that epileptic activity can be a cause of encephalopathy, i.e., when "the epileptiform activity itself contributes to severe cognitive and behavioral impairments beyond that expected from the underlying pathology alone."[9] As alluded to in the definition, some impairments may be anticipated from the underlying etiology, and this baseline component is termed *developmental encephalopathy* (DE) (Fig 1).[10] In the context of the developing brain, the implication of EE is slowing, plateauing, or frank regression due to ictal and interictal epileptic activity, either superimposed upon normal development or upon pre-existing developmental delay (Fig 2). The combination of both DE and EE is termed *developmental and epileptic encephalopathy* (DEE).[10]

In practice, it can be challenging to distinguish the respective contributions from EE and DE when both are present. For some epilepsies there are no sufficiently effective antiseizure treatments that could address the EE, limiting the ability to dissect the two processes. At an individual level, especially because development is a moving target, it may be challenging to quantify improvements in the trajectory that are potentially attributable to effective management of epileptic activity, especially in the short term.[11] In addition, antiseizure medications, which are typically used in combination for patients with refractory epilepsy, have potential adverse cognitive and behavioral effects that can further complicate the clinical picture.[12] Indeed, even when developmental plateauing/regression is temporally correlated with deterioration of ictal and interictal activity patterns, it can be difficult to establish whether epilepsy is driving encephalopathy, whether an underlying cause is driving both epilepsy and encephalopathy to worsen concurrently, or whether both situations are present. In what follows, we will review four epilepsy syndromes to highlight EE in different pediatric epilepsy contexts.

West syndrome

A prime example of EE is West syndrome, characterized by the triad of epileptic spasms, developmental regression, and hypsarrhythmia on electroencephalography (EEG). West syndrome is now considered under the broader term infantile epileptic spasms syndrome (IESS) that encompasses infants presenting with epileptic spasms, with or without fulfilling all the criteria for West syndrome.[13] The condition presents during infancy with recurrent seizures that last only seconds each and consist of sudden muscular contraction and subsequent tonic stiffening. Infants usually regress with the onset of epileptic spasms, and the EEG shows high-amplitude disorganization with multifocal epileptic activity. The causes of West syndrome are markedly heterogeneous when they can be determined. For a subset of patients, an etiology cannot be identified. Known etiology (e.g., tuberous sclerosis complex) or the presence of developmental delay preceding onset is the most important prognostic factor,[14] in part because this aspect may distinguish cases with DEE from cases with EE. Regardless, however, IESS has the potential to negatively impact developmental trajectory as demonstrated by studies showing that early treatment and successful resolution leads to improved outcomes.[15-18] For additional details, see the excellent review on outcomes in infantile spasms by Riikonen, 2020.[14]

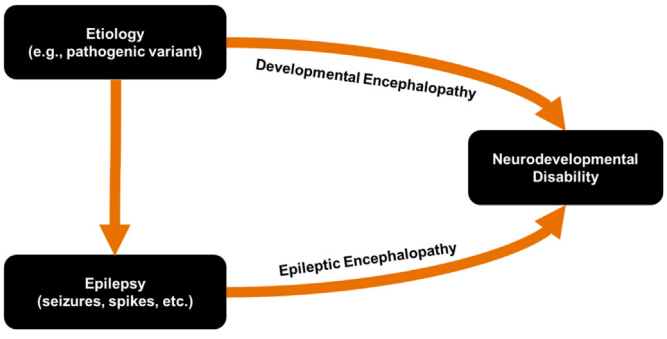

FIGURE 1. Epilepsy and encephalopathy. Diagram showing conceptual framework for the relationships between epilepsy and encephalopathy. An underlying etiology drives developmental outcomes directly (developmental encephalopathy) and also results in epilepsy. The abnormal epileptic activity itself may contribute to developmental outcomes (epileptic encephalopathy). The color version of this figure is available in the online edition.

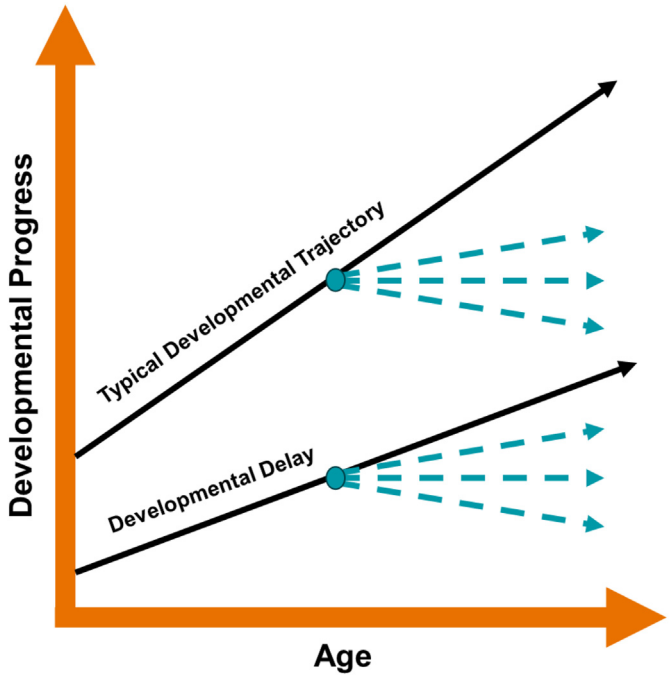

FIGURE 2. Developmental trajectories. Schematic demonstrating potential deleterious effect of epileptic activity (dashed arrows) on developmental trajectories superimposed on normal development or pre-existing developmental delay (solid arrows). Epileptic encephalopathy (e.g., infantile epileptic spasms syndrome) may lead to slowing of developmental progress, developmental stagnation, or frank regression (top, middle, and bottom dashed arrows, respectively). The color version of this figure is available in the online edition.

Dravet syndrome

Dravet syndrome (DS) is a drug-resistant epilepsy, caused in over 85% of cases by pathogenic loss-of-function *SCN1A* variants, that presents in infancy with prolonged febrile and afebrile, focal (usually hemiclonic), and generalized tonic-clonic seizures.[13] Development and EEG is normal at onset, but developmental plateauing and regression occurs between one and three years with the emergence of other seizure types (e.g., myoclonic seizures). DS was considered a prime example of EE because the initial early development is normal with regression occurring after seizure

onset. However, on closer examination, epileptic activity is not necessarily predictive of outcomes in DS,[19] and DS is now conceptualized as a prime example of *DEE*, as opposed to EE alone.

For most DEEs with a defined genetic etiology, the relative contributions of EE and DE to outcomes remains to be established, but there is a strong sense that etiology is the primary determinant. Indeed, for many of these conditions there are pleiotropic effects on cerebral networks beyond those responsible for seizures that can be shown to be separable experimentally, for instance, using conditional mouse models to dissect disease phenotypes based on the neuronal subtype or brain region affected.[20] On the other hand, such studies have also provided support for a role of epileptic activity in driving outcomes in the context of a pathogenic variant, including for DS.[21,22] Ultimately, the presence of EE is important to recognize in DEEs because it provides an opportunity to impact developmental outcome[23]; this stands in contrast to the DE aspect, for which at the current time there is rarely a specific effective intervention even when the etiology is known.

Rasmussen encephalitis

Rasmussen encephalitis (RE) presents an illustrative example of how the independent effects of epileptic activity can drive progression of encephalopathy. RE is a rare, devastating, progressive pediatric condition caused by an immune attack restricted to one cerebral hemisphere. Children develop unilateral focal epilepsy that becomes refractory in association with progressive hemiparesis and cognitive decline. Although the underlying pathology is unihemispheric, studies have repeatedly demonstrated the spread of epileptic spikes to the side contralateral to the pathology, as well as cognitive deficits referable to the unaffected hemisphere.[24] Longaretti et al. noted the association of epileptic discharges on the contralateral side with greater neuropsychologic deterioration (loss of 30 points versus loss of less than 15 points from full-scale intelligence quotient) and made an explicit and compelling argument for EE in RE.[25] RE is thus a case study of how epileptic activity may drive outcomes independent of the underlying pathology.

Developmental and/or epileptic encephalopathy with spike-wave activation in sleep

Developmental and/or epileptic encephalopathy with spike-wave activation in sleep (D/EE-SWAS), previously referred to as *encephalopathy related to electrographic status epilepticus during slow sleep* (ESES), or continuous spike-and-wave in sleep, is a spectrum of disorders characterized by abundant 1.5- to 2-Hz spike and wave discharges activated during non-rapid eye movement sleep in association with regression in any number of domains, including behavior, language, cognition, attention, social interaction, and motor skills.[26,27] The Landau-Kleffner syndrome is a subtype in which the ability to understand language (receptive aphasia) and even the salience of sounds is progressively impaired (auditory agnosia). D/EE-SWAS affects children with a peak at age four to five years and resolves with adolescence, but the associated deficits may persist. Electroclinical seizures occur in some, but not all, affected children. Etiology is heterogeneous and includes perinatal brain injury (especially with thalamic involvement),[28] polymicrogyria, and genetic disorders (e.g., pathogenic variants in *GRIN2A*).[29] There is an accumulated body of retrospective clinical literature reporting patients with regression in association with SWAS and correction with successful treatment.[30-33] Although in some ways the paradigmatic EE, there are a number of challenges. There is no consensus on the electrographic criteria for SWAS (what abundance of spikes are necessary for the diagnosis)—a spike-wave index of 85% (spikes present for over 85% of the non-rapid eye movement sleep recording) was the original description,[34] but rates over 25% to 50% have been associated with clinical symptoms. The field is further challenged by lack of consensus on how to quantify spikes on EEG (e.g., how to calculate a spike-wave index), by inconsistent assessment of cognitive and behavioral symptoms, and by clinical heterogeneity across affected individuals.

In this section, we have sought to survey the concept of EE across a diverse selection of pediatric epilepsy syndromes to illustrate its broad applicability and highlight how the potential for EE is a ubiquitous concern in pediatric epilepsy. The concept implies that treatment of ictal and interictal epileptic activity may have benefits that extend beyond symptom management (e.g., preventing seizures), improving the ultimate developmental trajectory in a way that is essentially disease modifying. In the next section, we turn to mechanistic considerations for how uncontrolled epileptic activity may negatively impact the developing brain.

Part II: Experimental evidence for the disruptive effects of epileptic activity on the brain

Mechanisms by which epileptic activity can disrupt brain function

Clinical studies of children with epilepsy have established the prevalence of associated cognitive and behavioral comorbidities (Table). However, determining causal relationships between epileptic activity and these functional impairments is challenging within the clinical sphere due to the inhomogeneity of patient populations, the existence of multiple confounders, and impracticality of many experimental designs within these populations. Animal models offer the opportunity to control many epilepsy-related variables, broadly survey electrophysiologic activity, and concurrently assess aspects of cognitive and psychiatric function.

Such studies have demonstrated that severe seizure activity in rodents can result in persistent alterations in neural firing within brain regions critical for memory, such as the hippocampus, and concomitant poor performance on memory tasks.[35,36] These effects also occur in neocortical regions, such as the medial prefrontal cortex, where seizure-related alterations of short-term plasticity have been observed.[37] Early seizures in rodents are similarly associated with long-term abnormalities in social behavior and tendency toward anxiety.[38,39] The mechanisms mediating emergence of these symptoms remain somewhat speculative but could involve derangement of the hypothalamic-pituitary-adrenal axis or serotonergic transmission between the raphe nucleus and hippocampus.[40,41] Thus, seizure activity, particularly in the developing brain, may set into motion a cascade of electrophysiologic and neuromodulatory changes that chronically shape the function of neural networks.

Similarly, studies have shown that artificial induction of epileptic activity results in long-term neural network dysfunction. In the kindling paradigm, seizures are repeatedly evoked in rodents, leading to establishment of interictal epileptic activity, progressively lowered seizure threshold, predisposition to longer and more severe seizures, and rendering of projection areas more susceptible to recruitment into epileptic activity, consistent with structural and functional network alterations.[42-44] *In vitro*, propagation of hippocampal seizures is capable of establishing a mirror seizure focus in the contralateral hippocampus, dramatically demonstrating the potential for epileptic activity to pathologically sculpt network behavior.[45]

In addition to a pathologic role for ictal epileptic activity on brain network function, interictal epileptic activity has also been implicated in affecting both local and large-scale network function. Hippocampal interictal spikes that occur during consolidation or retrieval disrupt performance on hippocampal-dependent memory

TABLE
Mechanisms of Epileptic Encephalopathy

Epileptic Activity	Potential Mechanisms	Consequences
Seizures Interictal spikes/sharp waves Pathologic high frequency oscillations	Disrupted synaptic homeostasis Altered network connectivity Disrupted physiologic activity patterns Altered network maturation Kindling Excitotoxicity/cell death	Impairments in learning & memory, cognition, language, behavior, motor skills, etc. Lowered seizure threshold, increased seizure severity, enhanced susceptibility of projection areas to recruitment into epileptic activity, establishment of novel epileptic foci

tasks.[46,47] Induction of interictal spikes during development is linked to longstanding cognitive deficits,[48] suggesting that whereas some effects are transient, others may chronically alter network properties necessary for cognition. In this case, there was impairment of new cell formation locally within the hippocampus,[48] but anatomically connected brain regions can be affected through induction of temporally linked oscillations.[47] The repetitive pathologic activation of cortex by interictal activity may shape the ability of this cortex to generate physiologic oscillations involved in local computation.[49] For example, one mechanism of EE in D/EE-SWAS is thought to be interference by interictal epileptic activity with synaptic homeostasis during sleep, leading to disruption of plasticity essential for cognitive development during childhood. Normally, the slope of slow waves during sleep decreases over the course of sleep, reflecting normal homeostatic downscaling of synaptic strength. In children with D/EE-SWAS, sleep slow wave slope does not change over the course of the night, consistent with a failure of sleep homeostatic processes.[50] This abnormality in slow wave slope dynamics is linked with neuropsychologic outcomes in D/EE-SWAS and normalizes when neuropsychologic improvement is observed.[51-53] Such data suggest the possibility that novel approaches that target pathologic properties of the interictal network could play a role in addressing long-term outcomes of EEs.[54]

However, execution of complex brain functions requires synergy of numerous physiologic constituents, and its dysfunction is similarly multifactorial. The underlying etiology of the EE and various treatments employed (such as antiseizure medications) likely contribute to the cognitive dysfunction of patients with these conditions as well. The interplay of all these factors within a developing brain further complicates the picture.

The developing brain has unique sensitivities and resistances to epileptic activity

Although neurons are active from the earliest stages of brain development, their ability to encode and process information is progressively acquired over time. Across brain regions, there exist precise trajectories that guide expression of neural network dynamics. Early activity patterns are generally geared toward promoting large-scale synchrony, aided by the long kinetic properties of channels in immature neurons. The capacity for faster, temporally precise activity patterns emerges later and parallels development of more advanced behaviors.[55,56] Developmental trajectories are also influenced by spontaneous activity within the network. For instance, the relationship between neural patterns and muscle twitches induces activity-dependent synaptic plasticity that refines synaptic connections and is associated with proper expression of nociceptive withdrawal reflexes.[57,58] A unique developmental oscillatory pattern, the spindle burst, synchronizes neurons into functional cortical columns that are necessary for the generation of functional sensory maps.[59,60] Therefore, introduction of pathologic activity patterns into these developing networks has the potential to disrupt the trajectory and delay or prevent acquisition of features critical for brain function.[61] Indeed, altered connectivity has been reported in children with IESS,[62,63] reflecting the potential consequences of pathologic activity patterns on the developing brain.

Epileptic activity characteristically involves coordinated neural firing that leads to the appearance of sharply contoured waveforms (sharp waves and spikes) or pathologic high-frequency oscillations (HFOs). These epileptic patterns are difficult to distinguish from physiologic HFOs, which are implicated in mediating cognitive processes, on the basis of waveform properties alone.[64] Despite the coexistence of physiologic and pathologic HFOs in patients with epilepsy, their occurrence rate and relationship with ongoing brain oscillations aid with differentiation and motivate consideration of pathologic HFOs as key biomarkers of epileptogenic tissue.[65] In some animal models, increasing occurrence of pathologic activity is associated with decreased observation of physiologic HFOs.[47] Interestingly, physiologic-high frequency activity is absent early on in developing neural networks. For instance, hippocampal sharp wave ripples (100 to 250 Hz), which play a causal role in memory, are not reliably observed in rodents until the second postnatal week[66,67] and manipulations that induce HFOs in the adult brain fail to do so during the first postnatal week.[68,69] In contrast, under epileptic conditions such as repeated application of kainate, oscillations in the range of 40 to 120 Hz can be generated during epileptiform bursts even at early time points.[70] These pathologic HFOs are associated with establishment of secondary epileptogenic foci, suggesting their importance in promoting long-term adverse changes in network function.[45,70] Because physiologic HFOs and their coordination across brain regions are linked with various learning and memory processes,[71,72] derangements in this frequency band during critical periods of development have particular potential to impair the machinery required for intact cognitive functioning.

Finally, preclinical and clinical data support direct neuronal damage and loss as a result of seizure activity. Although some preclinical studies have suggested resilience of the developing brain to seizure-related injury, newer experimental models show that seizures can lead to neuronal injury in the immature brain.[73,74] These findings have been paralleled by detailed clinical studies of febrile status epilepticus that demonstrated subsequent hippocampal atrophy and sclerosis in a significant proportion of patients.[75,76] Neuronal loss related to uncontrolled seizure activity may alter the cellular composition of brain networks, such as those involving the mesial temporal lobe, compromising circuit formation during critical developmental epochs.

Part III: Opportunities to modify epileptic activity to affect cognitive/behavioral outcomes

Future opportunities

Targeting the etiology

Interventions targeted at improving cognitive and behavioral outcomes in EEs are hampered by the potentially numerous and

adversely synergistic contributing mechanisms. When the specific etiology of an EE or DEE is known, targeted pharmacologic or genetic treatments become a possibility. The idea is that directly targeting the underlying disease mechanism would address both EE and DE (Fig 1). For example, RNA interference-based therapy approaches can address seizures and neurological deficits in mouse models of gain-of-function disease[77] and conditional mutations have provided proof of principle for gene therapy strategies.[78] The efficacy of such targeted approaches has been variable, especially when translated to clinical use. For instance, administration of everolimus (a potent mammalian target of rapamycin inhibitor) in patients with tuberous sclerosis complex (TSC), a disorder characterized by dysregulation of the mammalian target of rapamycin pathway, can decrease (but not eliminate) seizures for some (but not all) patients.[79] The developmental outcomes associated with everolimus in this population remain under investigation, but have not yet shown definitive improvement. In general, it is unclear how successful such disease-modifying approaches will be over the course of development, but the suspicions are (1) that the earlier treatment is given, the more likely it is to be successful and, relatedly, (2) that they will be more effective in preventing pathology than reversing it.

There is also evidence to suggest that the pathologic activity patterns associated with the underlying disorder can subsequently further derange the network such that targeting the underlying etiology alone is no longer sufficient. Channelopathies associated with EE can lead to abnormal neural firing and developmental synaptic rewiring in mouse models,[80] suggesting a potential basis for the variable response of patients with such genetic channelopathies to pharmacologic agents that should theoretically normalize their channel currents.[81] In an animal model of TSC, everolimus led to an improvement in social behavior only for mice that had not undergone status epilepticus in the developmental time frame, indicating that severe epileptic activity may lead to network changes that are less responsive to treatment of the underlying disorder.[82]

The identification of thousands of variants in hundreds of genes responsible for neurodevelopmental disability and/or epilepsy has spurred the development of such targeted genetic approaches, although it remains unclear how the vision of personalized medicine (e.g., n-of-1 antisense therapies) can be realized at scale. At the same time, EE for which the specific etiology is unknown remains untreatable via such approaches. Modulating pathologic network activity directly presents an alternative approach.

Modulating pathologic network activity

To directly test the hypothesis that epileptic activity can initiate or worsen cognitive and behavioral symptoms in EEs, an effective and specific intervention is required. Such an intervention could be modeled upon network-level manipulations demonstrated to enhance cognition in physiologic circumstances. Responsive electrical stimulation protocols that extend memory-related physiologic oscillations or increase their ability to couple with downstream brain regions can improve performance on behavioral memory tasks in rodents.[83,84] Open-loop deep brain stimulation has similarly shown efficacy in ameliorating cognitive deficits in models of Rett syndrome.[85,86] Electrical stimulation protocols have been developed that prevent interictal epileptic activity from coupling with downstream brain regions,[87] presenting the opportunity to evaluate the cognitive impact of modulating network effects of epileptic activity. Another promising approach is to leverage gene therapy that drives the expression of a hyperpolarizing potassium channel only in hyperactive neurons, providing a cell-autonomous block to epileptic activity.[88] Importantly, such circuit-level manipulations have been implemented in developing rodents, providing feasibility for the pediatric population.[89] Further investigation is required to determine the efficacy of this type of approach in EEs.

Current opportunities

Epilepsy surgery

Although many promising avenues for precision medicine and neuromodulatory protocols are opening for children with epilepsy, it is critical to determine how to improve developmental outcomes for the child neurologist treating patients now with the tools currently available. Chief among these approaches must be early consideration of resective surgery in appropriate cases of medically refractory epilepsy. A key example is the subset of epilepsy diagnoses, including RE, that are frequently managed with hemispheric resection or disconnection surgery: Despite the presence of pre-existing DE and acute loss of remaining cerebral functions residing in the disconnected hemisphere, surgery often leads to stabilization of decline or *even improvements* in certain domains, presumably due at least in part to alleviation of the impact of abnormal epileptic activity on the rest of the developing brain (i.e., effective treatment of the EE component). Consistent with this notion, outcomes are generally better with earlier surgery (i.e., shorter duration of epilepsy).[90-93] Similar effects are seen in more limited resective surgical treatments (such as lesionectomy) that effectively address targeted pathology.[11]

Optimizing medical management

Improved pharmacologic management of epilepsy represents an opportunity for enhancing outcomes and quality of life. Genetic diagnosis can lead to preferential treatment with the most effective antiseizure medications and/or avoidance of potentially detrimental medications to improve pharmacologic management for some children.[94] Principal examples include avoidance of sodium channel blockers in *SCN1A* loss-of-function variants-associated DS[23] and first-line treatment with sodium channel blockers for *KCNQ2* and *KCNQ3* loss-of-function self-limited neonatal epilepsies and KCNQ2 encephalopathy.[94-96] A recent evidence-based practice guideline by the National Society of Genetic Counselors recommends genetic testing for all patients with unexplained epilepsy,[97] and such testing has been demonstrated to lead to changes in clinical management.[98]

Despite all that has been said about the pathologic effects of epileptic activity on developing brain networks, it is also the case that medications, especially multiple medications in combination, have the potential to functionally impact children. For example, antiseizure medication withdrawal in children following epilepsy surgery is independently associated with improvements in neuropsychologic outcomes.[99] Adverse effects are often rated by PWE to be more important as drivers of quality of life than seizures themselves.[100] Such effects may be particularly problematic in children with DEE.[101] Being attuned to adverse effects of medications and striking the right balance between the cumulative impact of medications and the risks associated with epileptic activity is part of the art of providing individualized care to PWE. Educational programs targeting clinicians focusing on patient perspectives and providing strategies for avoiding “overtreatment in epilepsy” may be a useful approach.[102]

Improving treatment of (and preventing?) infantile epileptic spasms syndrome

Optimizing management for IESS represents a critical opportunity to improve developmental outcomes. Despite consensus on first-line therapies (corticosteroid hormonal therapy and vigabatrin), treatment is not uniform across patients, and a recent report

in the United States highlighted inequalities in use of first-line treatment in non-Hispanic black children and in children with public, as opposed to private, insurance.[103] Resolving such disparities in management across socioeconomic strata for IESS and other EEs must be made a priority.

Even when first-line treatments are appropriately given, there is room for improvement with respect to timing. Evidence supports that the earlier first-line treatments are given, the more likely they are to be effective. In addition to educational efforts to minimize the delay to diagnosis among providers, even after diagnosis there is room for improved efficiency. In a prospective study of patients who failed the first treatment, the second treatment was more effective in the group receiving the first treatment within four weeks of onset, arguing for expeditious treatment trials.[104] As it is possible to identify most responders within the first week of treatment,[105] rapid sequential use of a second first-line therapy is feasible and could be facilitated through implementation of a treatment pathway. Alternatively, there has been recent focus on the idea of giving concurrent rather than sequential treatment. A randomized open-label multicenter study comparing hormonal therapy with or without concurrent vigabatrin suggested the superiority of combination therapy.[106] Although this isolated study, which has substantial limitations, does not provide a definitive answer to the question of concurrent versus sequential treatment, the goal of shortening time to trial of a second first-line agent is of clear importance.

Preventing IESS from developing in the first place may be within reach for certain high-risk groups. For TSC, EPISTOP investigators conducted a prospective nonrandomized study of preventative vigabatrin when spikes were detected on surveillance EEGs compared with standard of care, following patients to age five years. It was observed that 50% of preventatively treated patients did not develop seizures, whereas only 5% were without seizures in the standard group.[107] If borne out in future studies, the power to prevent epilepsy (including infantile spasms) from developing in TSC would have an immediate impact on outcomes through elimination of this EE from the clinical course of these children.

Treatment of interictal spikes in D/EE-SWAS and beyond

Treatment in epilepsy is usually geared toward seizure prevention, whereas the goal of spike suppression, e.g., in D/EE-SWAS, presents challenges. Some of these challenges relate to the rarity of the condition and lack of large randomized controlled studies to determine what treatments (spike suppressing antiseizure medications, immunomodulation, ketogenic diet) are most effective. A meta-analysis suggested, among medications, the superiority of corticosteroid treatment followed by benzodiazepine therapy.[108] A randomized, controlled, multicenter trial (RESCUE ESES, Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep) (ISRCTN42686094) is in progress and may provide further guidance on the best treatment.

In the setting of frank regression, considerations of adverse effects associated with treatments may be more easily set aside in the interest of attempting to improve developmental outcomes, analogous to IESS. The matter is less straightforward if the impact of interictal epileptic activity is more insidious. For example, self-limited epilepsy with centrotemporal spikes (SeLECTS), formerly referred to as benign rolandic epilepsy, is one of the most common epilepsies of childhood and shares with D/EE-SWAS sleep activation of interictal spikes. SeLECTS shows persistent increased network connectivity during sleep,[109] and an accumulating body of evidence supports the likely accrual of neuropsychologic impairments over the course of the epilepsy syndrome, particularly related to language function.[110] For additional details, see the excellent review by Baumer et al. 2018.[111] Given that D/EE-SWAS and SeLECTS persist for about a decade, with treatments that are often only partially and/or temporarily successful in suppressing spikes and can be associated with nontrivial adverse effects, it will be paramount to understand (as with IESS) whether the timing of intervention matters and how much interictal spike reduction over what period of time is necessary to be clinically meaningful or sufficient to rescue development. Such information will more clearly open the doors to opportunities to improve developmental outcomes by targeting both ictal and interictal epileptic activities.

Conclusion

One of the paramount clinical considerations in the treatment of pediatric epilepsy is optimization of developmental outcomes. Epileptic activity in the brain poses a threat to normal physiology and brain development. Although often dwarfed by the effects of the underlying etiology, uncontrolled epileptic activity, nevertheless, has the potential to impact developmental outcome, in some cases to a great extent. Until we have treatments that reliably target and effectively treat the etiology of epilepsy and associated DE, a major goal of management is to prevent epileptic activity from worsening developmental outcomes.

Declaration of competing interest

Tristan Sands is a paid consultant for BioMarin Pharmaceuticals. Jennifer Gelinas has none.

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