

Review Article

Atypical Febrile Seizures, Mesial Temporal Lobe Epilepsy, and Dual Pathology

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Febrile seizures occurring in the neonatal period, especially when prolonged, are thought to be involved in the later development of mesial temporal lobe epilepsy (mTLE) in children. The presence of an often undetected, underlying cortical malformation has also been reported to be implicated in the epileptogenesis process following febrile seizures. This paper highlights some of the various animal models of febrile seizures and of cortical malformation and portrays a two-hit model that efficiently mimics these two insults and leads to spontaneous recurrent seizures in adult rats. Potential mechanisms are further proposed to explain how these two insults may each, or together, contribute to network hyperexcitability and epileptogenesis. Finally the clinical relevance of the two-hit model is briefly discussed in light of a therapeutic and preventive approach to mTLE.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common form of partial epilepsy in humans and is generally refractory to treatment [1]. It is characterized by seizures that originate in limbic structures, namely, the hippocampus, the parahippocampal gyrus and the amygdala. In approximately 65% of people suffering from this form of epilepsy, the underlying pathology is Ammon's horn sclerosis characterized by neuronal loss, gliosis and atrophy of the hippocampus. While mTLE classically begins in teenagers and sometimes even adulthood, the initial insult is thought to be neurodevelopmental and to happen in early life, namely, after prolonged febrile seizures (FSs) [2]. Two prevailing hypotheses exist to explain the possible relationship between prolonged FS, hippocampal sclerosis, and mTLE. The first hypothesis states that hippocampal sclerosis predisposes to prolonged FS and mTLE. The second, supported by a wide body of recent evidence, suggests that prolonged FS may in fact arise from an already predisposed brain due to anatomical and/or

genetic alterations, but it is the prolonged FS that leads to hippocampal sclerosis and mTLE later in life [3].

To study the pathophysiology of mTLE, several animal models have been developed in the past two decades. Experimental animal modeling stands on the important assumption that understanding fundamental mechanisms of action will help us in the elaboration of more effective treatments and therapeutic strategies for human diseases. The translational impact of experimental evidence from the study of FS and mTLE has been limited by the complexity of these clinical conditions, more specifically their uncertain causal relationship. However, recent clinical data appear to support the fact that prolonged FS, more specifically febrile status epilepticus, directly leads to hippocampal injury and mTLE [4]. Here, we will review several animal models that have been developed to study the putative biological substrate and risk factors behind the development of mTLE in humans. We will focus on two important developmental risk factors, namely, prolonged febrile seizures and cortical malformations as we propose a two-hit model of mTLE. To conclude

we will discuss the impact of these findings on future clinical management.

2. Animal Studies

2.1. Animal Models of Febrile Seizures. Febrile seizures (FSs) are a common neurological disorder that usually involves 2 to 5% of children between the age of 6 months and 6 years old with a peak incidence in toddlers of 12 to 18 months [5–7]. FSs can be separated into two categories: simple and atypical. Simple FSs are generalized and brief seizures (lasting <15 min) that do not recur within 24 hours. Atypical FSs are prolonged (>15 min), recurrent within 24 hours, or lateralized seizures or express more than one of these characteristics. In contrast to simple FSs that generally have no long-term consequences, prolonged FSs, more specifically febrile status epilepticus (lasting >30 min), have been associated with mTLE [3, 5, 8–10]. Based on retrospective clinical studies, it has been shown that up to 30 to 60% of patients with mTLE have a past history of prolonged FSs [2, 7, 11–13]. In one important yet controversial series, children with atypical febrile seizures showed an eightfold increased risk of developing epilepsy compared to those with simple FSs and controls [14]. Thus, one needs to understand what causes some individuals to experience prolonged FSs in order to try to prevent them. To study this, several animal models have been elaborated to mimic fever and FSs.

2.1.1. Hyperthermia as a Model of Febrile Seizures. Several experimental paradigms have been used to mimic the increase in core body temperature occurring during episodes of fever. Multiple studies have artificially evoked hyperthermia-induced seizures (HSs) to determine how FSs are generated. The most stable and most accepted model is hyperthermia-induced by hot dry air [11, 15–17]. HSs have been provoked in rats by many other methods such as exposure to an infrared lamp [18], infrared rays [19], microwaves [20, 21], a heated pad [22], or warm water [23]. However, the use of these apparatus was restricted because of high morbidity, mortality, and clinical variability. In contrast, models of HSs induced by exposure to heated dry air develop highly stereotypical generalized seizures that are reproducible and easy to characterize, with minimal or no mortality [2, 3, 7, 9, 11, 12, 15, 17, 24]. Like in humans, this model leads to the development of age-specific seizures that, when brief, do not lead to the development of spontaneous seizures later in life. However, when seizures are prolonged, up to 33% of naive rats develop electroclinical seizures in adulthood [11, 24]. The original studies have reported changes in hippocampal excitability, gene expression, and network effects but without the typical changes observed in mTLE such as neuronal loss, mossy fiber sprouting, or neurogenesis [25–27]. However, in these models, the duration of the seizure is determined by the duration of the exposure to high temperature rather than by individual vulnerability.

2.1.2. Lipopolysaccharide- (LPS-) Induced FSs. Many experimental models have used hyperthermia to induce convulsions as a model to study FSs [15, 18, 28, 29]. This is because

most of the developing animals experience seizures when they reach a high core temperature and because hyperthermia and fever share common mechanisms to elicit seizures such as the release of cytokines including interleukin-1 β (IL-1 β) [11, 27, 30]. This particular cytokine seems key to generate FSs in young rats based on the evidence that rats lacking the interleukin-1 receptor type I (IL-1R1) gene exhibit a much higher temperature threshold necessary to develop FSs [11, 27]. In the hippocampus, IL-1 receptors are expressed in high density [31] and their stimulation triggers a cascade of downstream effects through mitogen-activated protein (MAP) kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signalling. This could alter gene expression and transform normal neuronal circuitry into a proconvulsive epileptic network [5, 8, 32]. However, even if the IL-1 β pathway seems to be a crucial and shared mechanism of both hyperthermia and fever, its activation may not fully or appropriately imitate FSs as fever reflects a regulated increase of body temperature resulting from a broader immune challenge. The common precipitating event in both simple and prolonged FSs is an infection with a bacterial or viral agent. This induces a febrile response, which involves the elaboration of several inflammatory cytokines that include not only interleukin-1 β but also IL-6 and tumor necrosis factor (TNF) α . These cytokines, released by activated leukocytes, lead to the production of prostaglandins such as cyclooxygenase-2/3 and prostaglandin E2 in the preoptic nuclei of the hypothalamus. This then results in an upregulation in thermostatic set point for body temperature and then fever [33, 34]. However, apart from the fibrogenic properties of inflammatory cytokines, there is increasing evidence that they play a direct role in the generation of FSs. Clinical studies have shown that peripheral leukocytes obtained from children with FSs show an exaggerated IL-1 β release to a challenge with lipopolysaccharide (LPS) [35–37] or viral RNA [38]. Injection of bacterial lipopolysaccharide (LPS) *in vivo* in animals is another interesting experimental approach to study the role of proinflammatory cytokines in fever challenge at the systemic level. However, the rise in temperature is somewhat limited and is not sufficient to induce seizures in naive animals. Heida et al. were the first to demonstrate a causal relationship between IL-1 β and FSs in an experimental model of FSs using LPS [28, 30]. In this study immature rats were first injected with LPS, which produced a mild fever without a seizure but by giving a subconvulsive dose of kainite, seizures are induced in 50% of pups pretreated with LPS [28]. IL-1 β is thought to lead to the generation of FSs through its effects on inhibition, by reducing GABA_A receptor currents [39], or through promoting glutamatergic mediated excitatory effects, by increasing calcium conductance through N-methyl-d-aspartate (NMDA) receptors [40].

2.1.3. Viral Mediation of Febrile Seizures? Some clinical studies have pointed that the human herpes virus 6 (HHV-6) could be a putative link between FSs and mTLE. Some studies suggest that HHV-6 infection happens prior to the occurrence of FSs. Other studies found HHV-6 DNA in brain tissue removed during surgery for mTLE [41, 42]. However,

only a minority of primary HHV-6 infections may be associated with FSs [5, 43, 44]. Another virus of the herpes family, the Herpes simplex virus type 1 (HSV-1), causes the limbic seizures by reducing dynorphin expression in the dentate gyrus of hippocampus in rats, leading to seizures [45, 46]. Inherited dynorphin promoter polymorphisms are associated with temporal lobe epilepsy and febrile seizures in human. In animals, the dynorphin system in the hippocampus regulates excitability. These findings show a vulnerability of hippocampal dynorphin during herpes infection, and this may highlight a neurochemical basis for limbic seizures following viral infections.

Overall the evidence summarized here indicates that prolonged FSs contribute to epileptogenesis rather than being simply a marker of an epileptic tendency. In addition, the duration of the FSs seems to be an important factor of the development of subsequent epilepsy in the nonpredisposed brain. These findings suggest that preventing prolonged FSs could be a key therapeutic goal. However, it has recently been shown that prolonged FSs are often unrecognized in the emergency room [10]. Therefore, early identification of children at risk for prolonged FSs and epileptogenesis could be a better strategy to prevent mTLE.

2.2. Animal Models of Cortical Malformation. In order to understand how underlying cortical malformations may be implicated in epileptogenesis and developmental delay, various animal models were developed. A good animal model for malformation of cortical development should display (1) hyperexcitable brain regions and (2) macroscopic as well as microscopic structural abnormalities that are similar to the human pathology [47]. Many of these models have been yielding interesting results.

2.2.1. MAM Chemical Lesion Model. Methylazoxymethanol acetate or MAM is a teratogenic alkylating neurotoxin which specifically blocks mitosis of neuroepithelial cells actively dividing during development, without affecting the postmitotic cells. When administered to pregnant rats (intraperitoneal injection at embryonic day 15 (E15)) [48], MAM causes multifocal cerebral malformations in the rat pups including microcephaly, cortical thinning, loss of lamination, and cortical and hippocampal heterotopia [49, 50]. The heterotopic neurons displayed hyperexcitable properties, and these animals showed a diminished seizure threshold to various proconvulsant agents such as kainic acid [48, 51] or hippocampal electrical kindling [52]. Interestingly, no long-term spontaneous recurrent seizures (SRSs) were generally reported in this model, although Harrington et al. [54] described some electrographic seizures in 2 out of 11 MAM-treated animals. Some of the molecular and cell mechanisms of MAM-induced hyperexcitability include altered cell firing due to smaller calcium-activated potassium (K^+) currents affecting membrane potential after-hyperpolarization [53, 54], lack of fast A-type $Kv4.2K^+$ currents on heterotopic neurons [55], modification of N-methyl-D-aspartate receptor subtype 2A/B (NR2A/B) expression in heterotopic neurons [56], and diminution in inhibitory synaptic activity

in heterotopic neurons [57] suggesting profound changes of heterotopic neurons. The MAM model has the advantage of having a specific effect on neuroepithelial cells, not affecting astrocytic cells and not affecting cells from other organs which have a different ontogenic precursor [58]. However, in order for the MAM administration to be reliable, the first day of gestation must always accurately be identified. In any case, this model yields a more diffuse cortical dysplasia than what is observed clinically [59] and does not show spontaneous recurrent seizures alone [47]. Nonetheless, MAM-treated pups are more susceptible to the epileptogenic effects of prolonged FSs with all animals developing epilepsy [60].

2.2.2. In Utero Irradiation Model. The *in utero* irradiation model is obtained by exposing pregnant rats at E17 to radiation doses as low as 100 centigray (cGy) to as high as 225 cGy of external gamma radiation from a linear accelerator source [61, 62]. The irradiated cortex shows diffuse cortical dysplasia, similar to the MAM model, along with microcephaly characterized by a 50% diminution in cortical thickness [63], agenesis, hypoplasia, and the presence of heterotopic neurons, sign of a severe migrational abnormality [64]. Indeed, at E17 layer II/III cortical neurons are still migrating and are therefore most severely affected by the radiation [65]. Treated animals have been shown to display interictal epileptiform activity visible in the cortex as well as in the hippocampus; however, spontaneous recurrent seizures occurred only in a subset of irradiated animals, depending on the radiation dose. The manifestations of these clinical seizures was quite typical of limbic seizures including staring, facial twitches, wet dog shakes, and limb clonus [61, 64, 66]. Looking at the network and cellular levels, slices obtained from radiation-treated animals are more excitable as seen by spontaneous and evoked field potentials in slices of neocortex [62]. Furthermore, electrophysiological recordings have shown that the excitatory activity in slices coming from irradiated animals is greater relative to untreated controls and that the inhibitory activity is diminished [26], which may be explained by a diminution in activity of somatostatin and parvalbumin containing inhibitory interneurons in the irradiated group [67]. Therefore, an imbalance between excitation and inhibition is involved in the neocortical hyperactivity leading to the presence of epileptiform events in this model. The *in utero* irradiation model has the advantage of being noninvasive to the offspring, which induces less stress; however, it yields a diffuse type of cortical dysplasia distinct from the typical clinical situation [64]. In any case, studies looking at the vulnerability of irradiated pups to FSs have, to our knowledge, not yet been done.

2.2.3. Neonatal Freeze Lesion Model. The freeze-lesion-induced cortical malformation in rats was developed by Dvorak and Feit [68] and closely resembles the polymicrogyrus observed in humans, in that it yields the formation of a four-layer neocortex rather than the typical six. To achieve this model, one-day-old rat pups are anaesthetized with isoflurane, their scalp cut at the midline and opened, and a frozen 2 mm large probe is placed on the soft cranium overlying the

sensorimotor cortex for a period of ten seconds [9, 17]. It should be noted however that the probe width, the lesion duration, and the number of lesions may vary from one study to another. In all cases, contact with the frozen probe causes an immediate focal necrotic lesion, followed by neuronal migration to repair the damaged region, which explains why lesions should be done at a very young age when cells are still in a migratory state [69]. Indeed, glial fibrillary acidic protein (GFAP) as well as bromodeoxyuridine (BrdU) expressing cells were found in high levels within the dysplastic cortex suggesting the presence of still proliferating astrocytic cells [70]. The polymicrogyrus later obtained following the freeze lesion in rat is very similar to what would be observed in a focal human neuronal migration disorder [71, 72]. Fiber reorganization occurs within the cortical and subcortical layers of lesion rats as thalamocortical and corticothalamic projections are shown to be affected, possibly implicated in the process of epileptogenesis [73]. Disorganized projections were also seen by Brill and Huguenard who noted more inputs coming from infra- and supragranular cortical layers synapsing onto layer V pyramidal cells than in controls [74].

On top of the macroscopic modifications taking place in the dysplastic cortex, other changes at the molecular level occur and seem to unbalance the excitation/inhibition equilibrium favoring excitation. Looking at the expression of excitatory glutamate receptors, an autoradiography study showed that NMDA, AMPA, and KA receptor levels were elevated within the dysplastic cortex [75, 76], while they were unchanged when measures were taken in the surrounding normal cortex [77], suggesting the presence of a spatial gradient of ionotropic glutamate receptors with a greater concentration within the polymicrogyrus. Amongst the NMDA receptors, the NR2B subunit seems to be of great importance to the epileptogenicity of the lesion as the NR2B currents are functionally enhanced, and specific NR2B antagonists limit the spread of the epileptiform activity [71, 78], although it was shown that an AMPAR antagonist may block more widespread epileptiform activity measured extracellularly [79]. On the other hand, looking at inhibitory activity, the same autoradiography study showed lowered GABA_A and GABA_B binding within the dysplastic cortex [76] and a downregulation of GABA_A inhibition has been shown electrophysiologically in the freeze model [75]. However, no interneuron cell loss was reported near or far from the lesion [80, 81]. This widespread modification in various GABA_A subunits can be the cause of the decrease in inhibitory activity [82]. It is, however, also plausible that the GABA_A inhibition downregulation may not be directly involved in the hyperexcitability observed, as the somatostatin-positive interneuron loss occurred after the onset of epileptiform activity in their model [83]. The freeze lesion model of TLE is relatively easy to generate with reproducible results [69]. However, despite the hyperexcitability observed in brain slices from lesion animals, there are in this model no recurrent seizures occurring spontaneously *in vivo* [72] which is an important prerequisite to a good experimental model of human mTLE. We have therefore developed in our laboratory a two-hit model.

2.3. Two-Hit Rat Model of TLE. When the cortical polymicrogyrus model precedes another insult, this represents a two-hit model and mimics the human condition described in our clinical series [59]. A few models, having in common a cortical polymicrogyrus as a first hit followed by another insult [17, 60, 84–86], may lead to TLE development at a later age.

2.3.1. Freeze Lesion + Hyperthermia-Induced Seizure Model. In the case of the freeze lesion and HSs model, the FSs constitute the “second hit” occurring postnatally while the “first hit” is thought to occur at an early stage of brain development. Therefore, in this model, the freeze lesion is performed at P1, while the HSs are induced at P10 [17] (Figure 1).

At the time of HSs induction, the temperature necessary to induce a generalized convulsion during hyperthermia was diminished in rats with a cortical lesion compared to rats without lesion, and the latency to attain the generalized convulsion was also shorter [17]. More importantly, only the lesioned pups developed status epilepticus following a brief exposure to hyperthermia. This model therefore reproduces the selective vulnerability of some individuals to a common insult. Furthermore, a brain and ipsilateral hippocampal atrophy was already measurable ten days following HSs at P20 [12]. This suggests that the lesion alone seems to predispose the brain and the hippocampus to prolonged FSs and their consequences.

At P80, the hippocampal atrophy is more severe than at P20; however, it may be prevented by limiting seizure duration with diazepam at P10 [2]. Furthermore, using *in vitro* electrophysiological recordings, CA1 pyramidal cell hyperexcitability has been shown, yielding greater evoked excitatory postsynaptic potentials (EPSPs) and more frequent spontaneous excitatory postsynaptic currents (sEPSCs) specifically in the double-hit group onto pyramidal cells [87] and onto CA1 interneurons [88]. As the excitatory activity, the inhibitory activity is also altered with greater amplitude GABA_A and GABA_B inhibitory postsynaptic potentials (IPSPs) and evoked inhibitory postsynaptic currents (eIPSCs) on CA1 pyramidal cells in the double-hit group [87]. This would suggest an excitatory/inhibitory imbalance favoring excitation already at P20, prior to the occurrence of spontaneous recurrent seizures at P80.

In adulthood, we have found that the double hit results in the occurrence of spontaneous seizures occurring in 86–100% of male rats with the seizures arising ipsilateral to the lesion [2, 9, 12], numbers similar to the MAM model and more significant than the 33% observed in naive rats exposed to prolonged FSs [11]. Ipsilateral hippocampal atrophy persists in the double-hit group and is associated in adults with neuronal loss and memory deficits in performance of a hippocampus-dependent task [9].

2.3.2. Putative Mechanisms Implicated in TLE Generation in the Dual Pathology Model. Our data indicate that ionotropic glutamate receptor expression, especially the NMDA subtype, is upregulated in the double-hit animals: NR2B subtype being overexpressed at approximately P20 and NR2A at P80

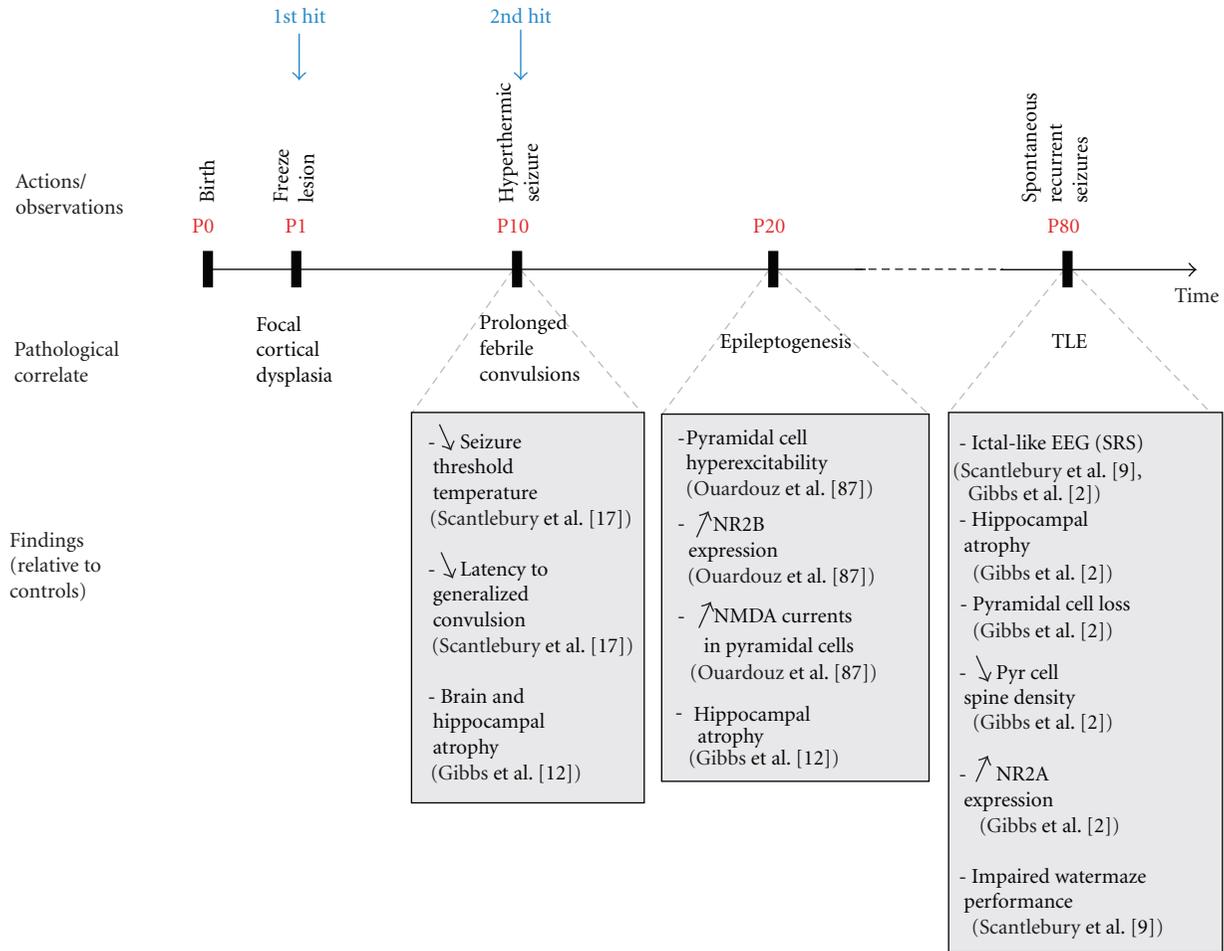


FIGURE 1: Lesion and hyperthermia model of TLE. Timeline and description of the different steps of the model, their pathological correlates, and the findings at various ages in the literature.

[87]. This is in accordance with findings from other two-hit models where high levels of NR2B expression are also found: such as in the MAM + pilocarpine model [84] or in the prenatal freeze lesion + electrical kindling [85]. The fact that lesion-only animals show higher NR2B levels and greater NMDA currents at P20 suggests that the lesion itself may underlie the hyperexcitability at P20 and may be a predisposing factor to prolonged HSs susceptibility at P10 [87], which is supported by a study in the freeze-lesion-only model [78]. Furthermore, it is possible that the IL-1 β expression during hyperthermia, as earlier stated, further exacerbates the effect of the lesion on NMDAR.

In parallel with the excitatory changes, the inhibitory activity is also altered in the model. In this case, HSs appear to be the key event in modifying inhibitory currents and potentials [87]. The findings of this study are similar to those in naive animals [89]. Whether the changes in inhibitory circuits reduce or increase the risk of recurrent seizures remains to be determined. In summary, the lesion alone and the hyperthermia alone appear to each leave the developing brain more vulnerable, but the presence of two hits strongly promotes epileptogenesis.

3. Clinical Relevance of the Two-Hit Models

In humans, development of mTLE is more and more thought to be a multistage process taking place in early life and including a history of childhood prolonged febrile seizures. A retrospective study from our group demonstrated that 66% of children affected with mTLE and a history of FSs had dual pathology with the coexistence of hippocampal sclerosis and of a cortical malformation on pathology [59]. More recently, the FEBSTAT study group was able to distinguish two sub-populations of FSs with those experiencing prolonged FSs being younger and with developmental delay [90]. In an earlier publication, they had demonstrated that these same children were more likely (OR = 4.3) to have imaging abnormalities on MRI including cortical malformations [91]. Although the models described here involve disorders of neuronal migration, other predisposing factors such as genetic susceptibility can represent the first hit. Indeed, it has been shown that, in familial mTLE, mesial temporal sclerosis develops in those who have experienced prolonged FSs in early life [92]. More so, prospective studies suggest that FS duration is a key factor in leading to hippocampal injury and that

developmental abnormalities are indeed also present in children with febrile status and mTLE [93]. Therefore, we believe that any child who presents with a febrile status epilepticus could benefit from a thorough imaging evaluation, including high-resolution MRI. Up to now, a true antiepileptogenic treatment is not available. However, experimental evidence suggests a potential role for NR2B antagonists as not only a good seizure medication but also a potential antiepileptogenic treatment in the developing brain.

The role of other potential first hits such as early-life stress in the development of mTLE remains to be properly studied. Only few animal models of mTLE models implying early-life stress paradigms exist in the present literature [94–98]. Both corticotropin releasing factor (CRF) and the glucocorticoid cortisol (or corticosterone in rodents) appear to exert potent proconvulsive or hyperexcitable effects on limbic structures in the developing brain [96, 99–107]. Although there is no clear evidence that isolated early-life stressors can induce epileptogenesis, the anatomical and physiological changes produced by these hormones could predispose the developing brain to a second hit.

In conclusion, a better understanding of the pathophysiology of mTLE in the developing brain will help us develop age-specific treatments not only to control the seizures but also to prevent their occurrence altogether, an important step toward our ultimate goal of no seizure, no side effect.

Disclosure

Dr. Nathalie T. Sanon and Dr. Sébastien Desgent shared the cofirst authorship.

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