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Origins of Temporal Lobe Epilepsy: Febrile Seizures and Febrile Status Epilepticus

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Abstract Temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) commonly arise following early-life long seizures, and especially febrile status epilepticus (FSE). However, there are major gaps in our knowledge regarding the causal relationships of FSE, TLE, HS and cognitive disturbances that hamper diagnosis, biomarker development and prevention. The critical questions include: What is the true probability of developing TLE after FSE? Are there predictive markers for those at risk? A fundamental question is whether FSE is simply a marker of individuals who are destined to develop TLE, or if FSE contributes to the risk of developing TLE. If FSE does contribute to epileptogenesis, then does this happen only in the

setting of a predisposed brain? These questions are addressed within this review, using information gleaned over the past two decades from clinical studies as well as animal models.

Keywords Febrile Seizures · Febrile Status Epilepticus · Temporal Lobe Epilepsy · Hippocampal · Sclerosis · Epileptogenesis

Introduction

Temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) commonly arise following early-life long seizures, and especially febrile status epilepticus (FSE). However, our knowledge is incomplete regarding the causal relationships of FSE, TLE, HS and cognitive disturbances. These gaps hamper the diagnosis, biomarker development and prevention of epilepsy and the associated cognitive impairments.

A fundamental question is the causal relationship between FSE and TLE. There is a broad spectrum of views regarding this question. For example, some believe that FSE arises primarily in individuals with a predisposed or compromised brain. This predisposition might derive from genetic factors, a developmental dysplasia, or a pre- or postnatal ‘acquired’ problem such as stroke or trauma. In this scenario, FSE might simply be a marker of individuals who are destined to develop TLE. Alternatively, FSE might occur in children with a ‘normal’ or uncompromised brain, but lead to TLE only in a compromised, predisposed child. Finally, some authorities consider that FSE in and of itself might lead to TLE in individuals, compromised or not, who otherwise might not develop epilepsy.

Uncovering the contribution of FSE to TLE is important for FSE management and potential preventive interventions. If FSE does not contribute to TLE, then its management should be conservative. Alternatively, if FSE contributes to TLE (either in the setting of a predisposed brain or in all individuals) two types of interventions should be considered: (a)

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aggressive management of the FSE itself or (b) an opportunity to intervene subsequent to the FSE and prevent TLE. This possibility requires understanding of the mechanisms by which FSE promotes TLE. Also needed are suitable biomarkers that will distinguish children who will develop TLE from those who will not.

A similar set of questions pertain to cognitive impairments found in individuals with epilepsy that follows FSE as well as in animal studies. Do the same mechanisms that govern post-FSE epileptogenesis also mediate memory and other cognitive deficits? Are the cognitive problems a result of the original insult or of the ensuing epilepsy? This review addresses these major questions in the field and presents our current knowledge of these issues.

Epidemiology of Febrile Seizures (FS)

FS are defined as seizures associated with a febrile illness without a CNS infection or electrolyte imbalance in children 1 month and older without prior afebrile seizures [1, 2]. While most FS are brief and benign, a proportion are prolonged and 5 % to 9 % last >30 minutes [3–5] meeting criteria for status epilepticus (SE) [1, 6, 7]. FS are common, occurring in 2–5 % of all children [3, 8–10]. FS are so frequent that although FSE represents a minority of FS cases, they account for 25 % of childhood SE [6, 7, 11, 12] and over 70 % of SE that takes place in the second year of life [11]. It is estimated that there are 25,000 to 35,000 cases of FSE annually in the US.

Genetics

The occurrence of FS is both sporadic and familial, suggesting a contribution of both environmental and genetic components to their onset [13]. Increased susceptibility to the development of FS is now known to result from mutations of several genes, including sodium channels [14–16], GABA_A receptors [17–20], and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [21–23]. Other single gene mutations, such as in the interleukin (IL-1) gene promoter, have also been implicated in a vulnerability to FS or TLE [24, 25] and interaction among several genes might increase the probability of developing FS in a given individual [26, 27].

In immature rodents, fever is very difficult to generate [28]. FS-like seizures can be induced by hyperthermia [29–38] or hyperthermia coupled with lipopolysaccharide (LPS) and kainic acid (KA) [39, 40]. Seizures typically arise in all hyperthermia-sustaining animals [41] suggesting that genetic susceptibility is not necessarily required for their generation. However, seizure-temperature thresholds (a measure of excitability) vary among mouse strains with differing genetic make-up [26, 42]. In addition, single gene mutations,

including those found to be associated with FS and FS related epilepsy syndromes, modulate the threshold to the onset of FS-like hyperthermia-induced seizures [16, 22, 42, 43]. These findings support the involvement of genetic factors in these seizures. Thus, in rodents, the contribution of genetic factors to FS and to their consequences is complex.

The contribution of genetic factors to FS in children is vastly more complex than in rodent models, where many variables can be controlled. FS in general and FSE in particular can clearly occur without any predisposing factors. In fact, more than half the cases of FS in a population occur in children with no risk factors and no family history of FS or epilepsy [13]. However, FS are one of the classic examples of interplay between underlying susceptibility and an environmental insult.

Thus, the children that do have a predisposition based on either genetic or structural reasons are more likely to experience a FS when a febrile illness occurs during the susceptible age window. For example, approximately 20 % of children with childhood onset epilepsy of all types, including those thought to be genetic in origin such as childhood absence and Rolandic Epilepsy, will experience an episode of FS during early childhood [44, 45]. These are clearly not causally related. In addition, if one looks at children with FSE, there is an over-representation of children with pre-existing neurological abnormalities [7, 11, 46]. These complexities make it more difficult to tease out the role of pre-existing genetic factors versus the actual FS/FSE in causing subsequent TLE and HS.

How are FS Generated?

Fever involves an elevation of brain temperature, and temperature influences both pyramidal cells [47] and interneurons [48] through several mechanisms. These include modulation of the function of specific ion channels. For example, the transient-receptor-potential vanilloid (TRPV) 1 and 4 channels are regulated by brain temperature in the physiological and fever ranges, and have been implicated in febrile seizures in animal models [49] where elevated brain temperature leads to augmented neuronal firing, facilitating seizures. Similarly, HCN channels [22, 50] and Cav1.2 calcium channels [51] seem to contribute to the hyperexcitability that results in febrile seizures. In children, increased temperature per se, resulting from hot baths or anticholinergics overdose, may lead to seizures [52], but the mechanisms are likely multifactorial [53] and remain obscure.

In addition to raising brain temperature, fever involves inflammatory mediators including cytokines such as TNF- α and interleukin-1 β (IL-1 β) that promote neuronal hyperexcitability. IL-1 β augments calcium permeability of glutamate receptors [54] and the function of kinases (ceramide-induced Src-family of tyrosine kinases) enhancing seizures of many

kinds [55]. Endogenous IL-1 β contributes to the generation of experimental FS, and a mutation in the IL-1 β gene promoter that results in higher levels of this cytokine has been reported in some individuals with FS and TLE [24, 25]. Whereas some infections (especially human herpes virus 6) seem to be a strong provoker of FS [56], it is unknown if this augments levels of cytokines in a child's brain. Clearly, a number of additional factors, including dehydration or alkalosis [57, 58], might interact with the genetic background of a given child to contribute to the mechanisms by which a febrile seizure arises [52].

TLE and FSE: Clinical Data

There is little evidence for an enduring adverse impact of short FS on the developing brain in either animal models or epidemiological data [52, 59, 60]. However, prolonged FS and especially FSE have been associated with a higher risk of epilepsy in general and TLE in particular but until recently it has been difficult to distinguish association from causal relationship. Retrospective studies from tertiary epilepsy centers report that many adults with intractable TLE give a history of prior prolonged FS in childhood [61–65]. Children with prolonged FS are at increased risk for developing epilepsy and those with FSE are at highest risk [3, 66–69]. Despite this, cohort studies of FS have minimized the role of prolonged FS in causing HS and TLE, attributing both the FS and ensuing epilepsy to pre-existing pathology [3, 66]. Consistent with this hypothesis, recent studies of FSE have reported low morbidity and a high proportion of pre-existing neurological abnormalities [5]. However, because MRIs were not performed in these studies, and the latency to the development of TLE is 8–11 years [63–65], which is longer than the follow-up period in many of these prospective studies, acute hippocampal injury and subsequent TLE may have been missed. More recently, imaging studies utilizing MRI show that hippocampal injury can occur after FSE but the small numbers, inability to exclude pre-existing hippocampal abnormalities, and lack of long-term follow-up make definitive conclusions difficult [70–75]. FEBSTAT, a prospective study of children with FSE was specifically designed to address the occurrence of hippocampal injury, atrophy and HS following FSE, the evolution of epilepsy syndromes (including TLE), and the relationship between HS and subsequent epilepsy [76]. Early findings are now available. They demonstrate that there are subtle pre-existing hippocampal abnormalities in a subgroup of children with FSE. However, the majority appears to have normal hippocampi, with neuroradiological evidence of hippocampal injury in approximately 12 % [60, 77]. While the neurobiological basis for the relationship between FSE and subsequent HS and TLE is not fully understood, the preponderance of data are now in favor of a causal relationship

between FSE and TLE though not with other forms of epilepsy.

One should note that a predisposition and causality are not mutually exclusive. For example, in a series of children with familial hippocampal malformation and febrile seizures, Fernandez et al. [71] demonstrated that those with prolonged FS go on to have HS and TLE whereas those with brief FS do not, though they do have abnormal hippocampi. These data suggest that FSE is required for TLE even in the presence of predisposing factors. Because it is practically impossible to eliminate the predisposition, understanding how FSE contributes to TLE is crucial to prevent the epileptogenic effects of this insult on the brain. This question is discussed below.

The Mechanistic Relationship of TLE and FSE

The examination of questions surrounding the mechanism or mechanisms linking FSE to TLE has been greatly facilitated by the employment of animal models. These models allow for causal and mechanistic studies to be carried out and the time frame of prospective studies investigating the evolution of FSE to TLE is shortened [52, 78]. However, creating such a model is hampered by the fact that immature rodents do not readily develop fever [28, 52]. There have been several animal models used to approximate FSE [29–40, 79]. Some strive to generate febrile convulsions (FC) in rats by injecting the bacterial endotoxin LPS accompanied by a usually subconvulsive dose of the pro-convulsant drug KA while maintaining animals in a warm room (30 °C) [80]. LPS raises the rat's temperature by 1–1.5 °C which mimics fever and enhances the convulsant actions of KA. This method creates FC in approximately 50 % of experimental animals [80, 81]. While this model imitates important features of FSE (an inflammatory response and fever), a drawback is that these animals do not have seizures with LPS alone and need KA, which draws concerns about which mechanisms are specific to the febrile (LPS and/or the warm room) or convulsive (KA) events. While these animals have a prolonged reduction in seizure threshold (as shown with amygdala kindling 8 to 10 weeks after LPS/KA injections), they do not develop spontaneous seizures later in life [81].

Several groups have employed a hyperthermic model of FSE in immature rodents at ages where the development of the hippocampus is analogous to that of human infants (P10–11 in rats) [82]. This model relies on a stream of warm air, which raises core and brain temperature and leads to seizures. Endogenous inflammatory mediators including IL-1 β are involved in the generation of these experimental febrile seizures, because mice deficient in the IL-1 β receptor were resistant to hyperthermic seizures [83]. The durations of hyperthermia and the seizures are regulated to generate “experimental FSE” [34, 35, 84]. Whereas control rats never become

epileptic, hyperthermic seizures generate a susceptibility to KA [85], and a subset of experimental FSE rats (~45 %) becomes epileptic later in life [35]. This demonstrates that experimental FSE alone can create epilepsy in a brain that would have been normal without this insult, suggesting that epileptogenic processes are initiated by the FSE itself [35, 52]. To date these models have led to the discovery of many of the consequences of FSE, in terms of both epilepsy and cognitive problems. These include HCN channelopathies, deficits in synaptic plasticity and decreased inhibition by the endocannabinoid system amongst others [86–88]. The hyperthermia model also allows for the study of epileptogenic mechanisms that could ultimately lead to post FSE interventions to prevent TLE [89, 90].

What are these mechanisms and how might they be addressed? Inflammatory mediators and mechanisms are an attractive possibility for two reasons. First, a large body of work (see Vezzani, et al. 2011 for review), has demonstrated that many insults that provoke epileptogenesis also lead to activation of inflammatory mechanisms. Second, evidence for inflammation is found in human epileptic hippocampi [91]. In the instance of FSE-related epilepsy, the case for inflammation is even stronger, and derives from the interplay between inflammation and fever. Generation of fever requires the action of inflammatory mediators (prostaglandins and cytokines) [92].

Conversely, our collaborative group and others, found that increased brain temperature (hyperthermia) per se leads to activation of inflammatory pathways, and specifically cytokine release [83, 93]. Indeed, IL-1 β release seems to be required for the generation of FS in the experimental model of hyperthermia induced seizures. In the context of FS related epileptogenesis, inflammation occurs both during and as a result of FSE [55, 83]. Therefore, inflammation (cytokine expression, morphological changes of glia, infiltration of pro-inflammatory cells into the CNS) has been a focus of intense study. Refuting or validating a role for inflammation in FSE related epilepsy is important, because it will enable translating the results to the clinic.

Dubé et al. [83] demonstrated the importance of the pro-inflammatory cytokine IL-1 β in a hyperthermic model of FSE. An upregulation of IL-1 β occurs 24 hours post FSE in the hippocampus of all FSE rodents. Interestingly, only rats that go on to experience TLE have maintained IL-1 β upregulation in hippocampus. Whether or not this upregulation is a cause or consequence of spontaneous seizures is unknown. In the HC model using LPS and KA, a similar role of IL-1 β has been found, in that there was an increase in hippocampal IL-1 β 2 and 4 hours post seizures [80, 94]. These studies suggest that because inflammation is induced by seizures, and has been shown to be involved in epilepsy in other contexts, inflammation may aid in the development of post-FSE epilepsy. How might inflammation influence brain excitability?

IL-1 β has been shown to increase excitability by increasing the amount of glutamate in synapses and by enhancing NMDA receptor-mediated intracellular calcium [95, 96]. While compelling, blocking IL-1 β production and signaling in other models of epileptogenesis (electrical SE and pilocarpine) did not change spontaneous seizure onset, intensity or duration [97]. While these results would need to be replicated in the more naturalistic FSE model to enable inferences about translation to FSE related TLE, they suggest that pan-inflammatory interventions rather than targeting individual cytokines might be tried [78].

Any intervention given post FSE would preferably be administered as soon as possible post insult. Looking upstream of IL-1 β production and release to find a “master regulator” of FSE induced inflammation might be beneficial in preventing complex and intricate inflammatory cascades that potentially lead to TLE [97, 98]. Additionally, preventing global or specific inflammatory cascades post FSE and monitoring the development of TLE will shed light onto the therapeutic potential of anti-inflammatory agents and either confirm or refute inflammation as a cause (rather than a concurrent event) of epileptogenesis. These studies should take place in animal models (preclinical studies) as a preamble to their potential use in the clinic.

Cognitive Consequences of FSE

In the hyperthermia model of FSE a subset of rats developed spatial memory deficits when tested months later [99]. Remarkably, whereas MRIs obtained one month after the seizures identified rats with cognitive problems, the MRI at this late time-point did not predict development of epilepsy, consistent with the idea that cognitive disturbances were separate from and likely independent from epileptogenesis. The spatial memory deficits were accompanied by, and likely a result of, significant disturbances in the function of hippocampal place cells that encode and sustain information about spatial orientation, a fundamental prerequisite for spatial cognition. Similar reorganization of cognitive networks has also been described in the HC model of FSE [40]. These findings are important because they suggest that impairments in memory are a result of the inciting FSE rather than of ensuing epilepsy.

In several large, well-designed studies utilizing either sibling controls or population based controls, the cognitive and behavioral outcomes of children with FS including FSE are similar to those of children without FS [3, 67, 100–104]. However, these studies did not look specifically at FSE, and often included a very small number of cases of FSE. In addition, they did not specifically address the issue of memory. Memory is of particular concern as animal models have demonstrated that FS appear to be of limbic origin [32, 52]

and both clinical studies and experimental models suggest that when injury occurs following FSE, it is observed in the hippocampus [33, 70, 73, 77, 99, 105].

In addition, memory is well known to be impaired in patients with chronic TLE [106, 107]. The FEBSTAT study is designed to address whether or not FSE causes memory deficits in those who have evidence of injury but that portion of the study is still in progress. Obviously, these facts and the deficits found in animal models indicate that it is important to examine if prolonged FS/FSE generate cognitive defects in a subgroup of individuals, to uncover the underlying mechanisms, and to define biomarkers that will identify those at risk and enable intervention. The working hypothesis of the FEBSTAT study, in line with the separation of cognitive problems and epileptogenesis in the animal model [99], is that some children will have memory deficits that will precede the development of TLE and may be present even in children who do not develop TLE [76].

Identifying Biomarkers for FSE-Related TLE/HS

The previous paragraphs indicate that FSE is a significant and likely causal risk factor for developing TLE. However, a major barrier to developing preventive therapies to FSE-related TLE stems from the current inability to identify those who develop TLE after FSE until clinical seizures emerge. Because the mean time to TLE onset following FSE is 8–12 years, a predictive marker should facilitate identification of candidates for future targeted interventions.

The optimal surrogate or bio-marker should be non-invasive, quantifiable and amenable to repeating to enable monitoring of disease progression. MRI has most of these characteristics. Indeed several small studies have demonstrated that imaging abnormalities, more specifically increased T2 signal in the hippocampus can occur following FSE [70, 72–75, 108, 109]. The larger prospective FEBSTAT study has shown that this occurs in approximately 12 % of cases [110]. The T2 signal was maximal in CA1 and the Apparent Diffusion Coefficient (ADC) indicates that the T2 signal reflects acute injury rather than gliosis [77]. When imaged one year later, almost all the children whose acute post-ictal MRI showed evidence of increased T2 now had a shrunken hippocampus and usually had evidence of persistent T2 signal and met the radiologic criteria for HS [77]. The ADC was now consistent with gliosis. Very few of these children had developed epilepsy at this time. In summary, FSE can directly lead to a radiologic picture of HS in a small subset of children. These children are now being followed to see if they develop TLE and if they have memory deficits. While clinical TLE may take years to develop, the MRI provides radiologic evidence of HS providing a potential marker for injury that can serve as

a target for therapeutic interventions to prevent the development of TLE following FSE.

MRI has also been used in rodent models of FS and FSE [35, 84, 105]. MRI signal changes in hippocampal CA1, similar to those found in children were noted one month after the seizures. However, the increased T2 at one month following the FS was not predictive of the development of TLE-like limbic epilepsy. More recently, acute MRI studies, within hours of FSE were investigated as a predictive marker for TLE, employing an established rat model of FSE, where 30–40 % of animals develop TLE [35]. These have yielded signal changes in limbic structures that were informative in predicting TLE [111]. These exciting data are now being validated.

EEG as a Potential Predictive Marker for TLE That Follows FSE

An EEG is not felt to be useful in the diagnostic evaluation of the child with a simple febrile seizure [10]. However, it is part of the diagnostic evaluation of children with status epilepticus of all causes including FSE [112]. In cases of complex febrile seizures, EEG abnormalities are more common but their significance remains unclear [113–116]. A limitation of the prior studies is that they lacked imaging data to correlate with the EEG findings. In the FEBSTAT study, both EEG and MRI were performed in the postictal state [76, 117]. Overt epileptiform abnormalities were uncommon, however focal slowing or attenuation or both (usually maximal over the temporal area) were present in over 30 % of the cases. These were highly correlated with the presence of hippocampal T2 abnormality on imaging. The EEG findings were more sensitive but less specific than the MRI results. In thinking about EEG, one realizes that the absence of epileptiform activity and the presence of focal slowing or attenuation is what we should have expected. In the vast majority of these cases, we are not dealing with a case of epilepsy but with an acute neurological insult (FSE) that may lead to subsequent epilepsy. Therefore, focal slowing and attenuation is precisely what one would expect in the acute phase with the development of epileptiform activity years later. While not as precise as an MRI, the EEG may prove to be an attractive biomarker to help select patients at risk for developing TLE for an interventional trial. If the drug needs to be initiated within a narrow time window, it is far easier to obtain a bedside EEG, than it is to get a MRI for an acutely sick child. The evolution of the EEG findings and their correlation with MRI and the development of TLE and other forms of epilepsy are currently being studied.

In rodent models, a number of groups obtained EEGs during experimental FS/FSE [31, 32, 58] and some have characterized its features [118]. However, the role of immediate postictal EEG as a predictor of epileptogenesis and

subsequent development of spontaneous seizures has not been systematically analyzed.

Summary and Conclusions

- FSE is common, occurring in over 25,000 children yearly in the U.S.
- The role of genetic factors in the generation of FSE and FSE-related TLE is progressively being clarified and defined.
- New data from prospective human studies and rodent models highly support a causal role for FSE in the development of subsequent TLE.
- An understanding of the mechanisms generating FSE and those involved in FSE related HS and TLE is emerging from the confluence of human and animal studies
- The focus of efforts in the coming years is to identify predictive markers, and mechanism-based agents for therapeutic interventions.

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