Febrile Seizures: Current Views and Investigations

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ABSTRACT: Febrile seizures (FSs) are seizures that occur during fever, usually at the time of a cold or flu, and represent the most common cause of seizures in the pediatric population. Up to 5% of children between the ages of six months and five years-of-age will experience a FS. Clinically these seizures are categorized as benign events with little impact on the growth and development of the child. However, studies have linked the occurrence of FSs to an increased risk of developing adult epileptic disorders. There are many unanswered questions about FSs, such as the mechanism of their generation, the long-term effects of these seizures, and their role in epileptogenesis. Answers are beginning to emerge based on results from animal studies. This review summarizes the current literature on animal models of FSs, mechanisms underlying the seizures, and functional, structural, and molecular changes that may result from them.

RÉSUMÉ: Connaissances actuelles et recherche sur les convulsions fébriles. Les convulsions fébriles (CF) sont des crises convulsives qui surviennent au cours d'un épisode fébrile, habituellement au moment d'un rhume ou d'une grippe. Il s'agit de la cause la plus fréquente de crises convulsives dans la population d'âge pédiatrique. Environ 5% des enfants âgés de 6 mois à 5 ans présenteront un épisode de CF. Au point de vue clinique, ces crises convulsives sont classifiées comme étant des événements bénins et ont peu d'impact sur la croissance et le développement de l'enfant. Cependant, des études ont établi un lien entre les CF et un risque accru de développer de l'épilepsie à l'âge adulte. Plusieurs questions demeurent sans réponse : quel est le mécanisme sous-jacent; quels sont les effets à long terme de ces crises et quel est leur rôle dans l'épileptogenèse? Des réponses commencent à émerger des résultats d'études animales. Cette revue résume sommairement la littérature actuelle sur les modèles animaux de CF, les mécanismes sous-jacents et les changements fonctionnels, structuraux et moléculaires qui peuvent en résulter.

Febrile seizures (FSs) are acute symptomatic seizures that occur in response to a fever in an age-specific manner[1,2]. In the pediatric population, FSs are the most common neurological events, affecting between 2 and 14% of children worldwide[3]. Retrospective studies have shown that up to 70% of patients undergoing surgery for treatment-resistant temporal lobe epilepsy (TLE) have a history of FSs in childhood[4,5]. However, prospective analyses have failed to support such a profound relationship, and maintain that FSs are relatively benign events[2,6]. These conflicting reports have created some controversy over the long-term effects of FS. In this context, it is important to identify the types of FSs and recognize that each type may differentially contribute to an increased risk for TLE. Epidemiologic studies indicate that simple FSs, which are generalized seizures with a duration of less than 10-15 minutes, normally do not lead to adverse long-term sequelae[7]. However, complex FSs, defined as focal, prolonged (>30 minutes) or repetitive seizures, appear to be associated with negative long-term consequences[8]. Therefore many experimental investigations have aimed to model complex FS to increase our knowledge of the underlying propensity for, and mechanisms of FSs in order to systemically evaluate the risk for subsequent epileptic disorders.

Animal Models

Age-Appropriate Models

Febrile seizures usually occur in children between the ages of six months and five years-of-age, with a peak incidence around

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1.5 years of age[1,2]. Therefore, one of the first requisites of an animal model of FSs must be that the seizures are induced in an animal at a similar developmental stage. Unfortunately, it is difficult to correlate the timing of brain development in humans and rodents, as different aspects of the nervous system do not develop at the same rate in both species. Since the hippocampus is a particular area of interest in FS research, most animal models are induced at an age mimicking the time when important milestones in hippocampal development take place. The second postnatal week in rat development is thought to correspond to the first year of human life, while the third postnatal week might correlate with the toddler years[9]. In most animal models, FSs are induced as early as postnatal day (P)7 to as late as P16. There is evidence that a FS which occurs in the first year of human life has different outcomes than one occurring later[10,11], so interpretation of experimental FS studies must take into account the animal's age at time of FS.

Hyperthermic Seizures

For many decades the study of FSs has focused largely on the role of body temperature[12-14], which has resulted in the development of several animal models where exogenous heat is used to raise core body temperature (hyperthermia) and produce convulsions[15]. Some models of hyperthermic seizures (HSs) use heat from a hair dryer[12], a microwave[16], hot water[17], or an infrared heat lamp[13] to increase body temperature to around 41°C to generate seizures. While these are relatively simple and effective ways to induce a convulsion, it is not reflective of the natural course of physiological (febrile) responses to a pathogen[18,19]. Hyperthermia is an increase in body temperature that results from excessive exogenous heat application that exceeds the body's capacity for thermoneutrality. Conversely, fever is an endogenous process that comprises a regulated rise in body temperature in response to an immune challenge[20-22]. The pathways activated to evoke fever and hyperthermia are different in each case[23]. Fever is also an inflammatory response that involves both central and peripheral cytokine and prostaglandin signalling that is somewhat different from that produced by hyperthermia[18,19]. While this may bring into question the validity of such HS models in the study of "febrile" seizures, these studies cannot be ignored as they have provided significant advances in our knowledge about the mechanisms and sequelae of FSs[24].

"Febrile" Seizures

The Pittman laboratory has developed a novel and more ethologically relevant model of FSs using an inflammatory dose of the bacterial endotoxin lipopolysaccharide (LPS) which evokes an immune reaction and a bona fide fever response (about 1-1.5°C), coupled with what is normally a subconvulsant dose of kainic acid (KA) in immature rats (P14)[25-27]. This model mimics the most essential features of a FS: the immune response and fever; nonetheless, just as the 'hyperthermia' model has drawbacks as indicated above, this model requires augmentation of excitation with KA. The reason that all models employed to date rely on more than just a true fever is that, at least at the ages tested, even in immature common laboratory rat strains FSs are difficult to evoke. Why humans develop true febrile convulsions,

whereas immature rodents generally do not is still unknown. Our laboratory has also demonstrated long-term changes in the seizure susceptibility of animals that experienced FSs during development[26]. Currently, the mechanism by which such change takes place is not completely understood; however, considerable data is available indicating that other models of FSs (such as HSs) can modify the brain in such a manner to induce increased susceptibility to seizures in adulthood[28-30].

Mechanisms of Febrile Seizures

Temperature

One of the fundamental questions about FSs that remains unanswered is why they develop in some children with a febrile illness but not others. It does not appear to be the magnitude of fever which plays a role. Children with a lower fever at the time of FS have an increased risk for subsequent convulsion with another febrile illness, perhaps because they have a lower threshold for FSs in the first place[1,31,32]. However, as a group, children with a FS present to the emergency department with fever of higher magnitude than febrile controls, suggesting children susceptible to FSs may regulate temperature differently[33], or that their infections are more severe. Clinically it is very difficult to determine the exact temperature at seizure onset, and sometimes FSs can occur as the presenting sign of febrile illness[1]. While fever is defined as a temperature of at least 38.4°C, some clinical studies of FSs have accepted temperature values as low as 38°C[34,35], a temperature below that thought to create central nervous system (CNS) dysfunction[36].

Why should a rise in temperature cause a seizure in the first place? Hyperthermia (>38.3°C) can decrease gamma-aminobutyric acid A (GABA$_{(A)}$) receptor-mediated inhibition to a greater extent than it decreases excitation, which may shift the balance towards excitation and contribute to seizure generation[37]. This appears to be mediated by reducing GABA release from pre-synaptic terminals, but hyperthermia may also decrease post-synaptic GABA$_{(A)}$ receptor function[38]. While this phenomenon has only been studied in hyperthermic models, it also likely occurs when temperature is increased from physiologic fever.

Typically children will only have a single FS in the course of a febrile illness. Is the first seizure protective against subsequent seizures? In experimental HSs the temperature threshold for the second or third seizure is significantly and progressively higher than for the first, although this pattern is abolished by a neuropeptide Y antagonist[39]. It is possible that the typical clinical picture of a single FS in children may involve inhibitory actions of neuropeptide Y, but further work has yet to be done. Likewise, with respect to true FSs, it is important to remember that a number of transmitters and modulators are involved in the febrile process within the brain. Some of these, for example, arginine vasopressin, have been implicated in experimental FS[40], but their actions have not been investigated in sufficient detail to comment further.

Inflammatory Mediators

Cytokines have been shown to play a significant role in a number of neurological disorders[41,42] including seizures[43-46]. Pro-inflammatory cytokines include tumour necrosis factor

(TNF)α, interleukin (IL)-1α, IL-1β, and IL-6[47], while IL-1 receptor antagonist (IL-1ra), IL-10, and IL-18 are considered anti-inflammatory[48]. Interleukin-1β can influence seizures by changes to N-methyl-D-aspartate receptor phosphorylation[49], inhibiting astrocytic reuptake of glutamate[50], and by increasing the release of glutamate from glia[51] and neurons[52], leading to increased excitability. Interleukin-1β also decreases $GABA_{(A)}$ receptor mediated currents, decreasing inhibition[53].

Helminen and Vesikari[54] suggested that an enhanced IL-1β response in children with FS could play a role in the production of seizures. They showed that peripheral mononuclear cells extracted from children with FSs showed a significantly exaggerated IL-1β response to LPS application when compared with samples from children with bacterial infections that did not have seizures[54]. Leukocytes from children with a previous FS also have an exaggerated IL-1β response in a viral infection model[55]. Specific IL-1β promoter polymorphisms increase IL-1β production[56], and may contribute to genetic susceptibility for FSs[57-60], as may IL-1ra polymorphisms[60]. However, some studies have shown plasma levels of IL-1β are comparable in children with FSs and those with a febrile illness without seizure, suggesting increased production of the cytokine is not involved in the pathogenesis of FSs[61,62], and there is no difference in the distribution of IL-1β, IL-1α, or IL-1ra genotypes and alleles in children with FS versus healthy controls[63]. While plasma levels may not accurately reflect activity in the brain, these findings are also supported by unchanged levels of IL-1β[47,61], TNF-α[47] and IL-6[47] in the cerebrospinal fluid of children after a FS. However, there is ample evidence from animal experiments that peripheral inflammation, and associated cytokine changes, are reflected by the appearance of a 'mirror' inflammation in the brain, reflected by increases in inflammatory cytokines in the brain[64-66]. Thus, it is quite possible that cerebrospinal fluid levels of cytokines may not accurately reflect parenchymal levels in children with FS.

In addition to a possible role in FSs, CNS inflammation and cytokines also play a role in other age-dependant seizures. The prototypic inflammatory epilepsy is Rasmussen's encephalitis, or chronic focal encephalitis, comprising intractable focal seizures with onset in childhood, progressive hemiparesis, and cognitive impairment. This is accompanied by progressive unilateral cerebral atrophy and inflammatory changes. Approximately half of children with Rasmussen's encephalitis have a preceding infection or inflammatory episode in the six months prior to presentation[67], although the actual etiology of this disorder is still unknown[68-71]. Interestingly, while inflammation is present, FSs do not occur in the context of this disorder.

Other situations where there is brain inflammation, such as the inflammatory viral encephalitides caused by herpes simplex, Epstein-Barr, and varicella zoster viruses, are characterised by epileptogenic seizures, but not necessarily FSs[72]. Other age-dependant epilepsies, such as benign childhood focal epilepsies (rolandic epilepsy, Panayiotolpoulos syndrome, and idiopathic childhood occipital epilepsy of Gastaut) and generalized epilepsy with febrile seizures plus, are not characterized by an inflammatory state. However, FSs can be highly prevalent in these conditions[73-75]. Therefore, the role of CNS inflammation in seizures and epilepsy in general, and in FSs in particular, is still controversial as the association is not absolute.

While human data appear to be conflicting, animal data reveal a great potential for new immunological treatments and interventions for patients with seizures and epilepsy. Exogenous IL-1β administration to immature mice reduces their threshold for HSs, while mice deficient for the IL-1β receptor are resistant to HSs even in the presence of exogenous IL-1β[76]. In the LPS/KA FS model, rats with a FS showed increased IL-1β levels in the hippocampus and hypothalamus compared with febrile controls, with an increased rate of seizures after intracerebro-ventricular IL-1β administration, and a decreased seizure rate after IL-1ra administration[27]. While increased excitability in the presence of IL-1β is likely one mechanism promoting FS generation, there is currently a large amount of ongoing work which will hopefully add to our knowledge about the role of cytokines in seizures and epilepsy.

Alkalosis

Evidence suggests that there is an increased respiratory rate in children with fever[77,78], although it is unclear whether this actually leads to a respiratory alkalosis. This possible link may be important, as alkalosis increases neuronal excitability[79-81]. Animal HS models cause respiratory alkalosis[82,83], and suppressing the alkalosis with CO_2 administration quickly abolishes HSs and prevents some of the long-term effects found with these models[82]. It is unclear whether this mechanism plays any role in seizure generation in the child with a FS.

The "Double-Hit" Hypothesis

Apart from FSs, developmental malformations such as focal cortical dysplasias and microdysgenesis have also been implicated in the development of TLE[84]. Rats with experimental neuronal migration disorders have a lower threshold for HSs, which cause increased neuronal damage compared to HS alone[85]. In an animal model of focal cortical lesion plus HSs there is a lowered threshold for the HSs and prolonged ictal manifestations[86], with animals displaying impaired performance on the Morris water maze and 80% developing spontaneous seizures[87]. This model also results in decreased volumes of the whole brain, of the hemisphere ipsilateral to the cortical lesion, and of the hippocampus compared with HSs in non-lesioned animals, resulting in impairment of normal brain development[88]. These results suggest that FSs may have more severe consequences when occurring in a susceptible brain which has already seen some form of injury.

Consequences of Febrile Seizures

Functional Changes

There has always been great interest in the risk of developing epilepsy after a FS. In a large population cohort of children from Denmark, those with a history of FS had a greater than five-fold increase in the risk of developing epilepsy later in life, although less than 7% developed epilepsy within 23 years of follow-up[89]. Camfield and colleagues have found that FSs most often precede the development of generalized tonic-clonic afebrile seizures and rarely idiopathic intractable complex partial seizures[90]. However, others have found a link with epilepsies with complex partial seizures, notably TLE. Retrospective studies have shown that up to 70% of patients undergoing surgery for treatment-

resistant TLE have a history of FSs in childhood[7,8]. On the contrary, prospective follow-up studies have found the occurrence of mesial temporal sclerosis is uncommon after FSs[91] and that while a higher proportion of children with complex FS than simple FS develop subsequent epilepsy, the overall risk is still low[2].

While the association between FSs and the development of epilepsy is still controversial, there do appear to be differences in patients with TLE who have a history of a FS and those who do not. Adults with TLE and a prior history of FS have poorer seizure control and more resistance to drug therapy[92-94]. On the other hand, these patients have better surgical outcome[93,95,96].

Just as in human studies, animal studies are conflicted as to whether early-life HSs or FSs lead to the development of epilepsy and spontaneous seizures. Most studies have focused on the development of limbic seizures, to further knowledge about the role of development of TLE after FS in humans. With the HS model spontaneous limbic seizures have been demonstrated in 35% of animals three months after HS, with interictal epileptiform discharges in 88%[29]. Animals with spontaneous seizures have increased levels of immunoreactivity of a glutamate transporter in the dentate gyrus, and immunoreactivity for markers of interneurons in the hilus[97]. Studies looking at other forms of epilepsy and seizure susceptibility have found repetitive HSs facilitate seizures induced by the chemical convulsant pentylenetetrazol at six months-of-age, but do not affect absence seizures in the genetic WAG/Rij rat model[98]. Electrical kindling studies have revealed lower afterdischarge thresholds and longer afterdischarge durations in adults with previous FS compared with febrile controls, but the amygdala kindling rate was the same[26]. This model appears to alter seizure susceptibility but not epileptogenesis.

Epilepsy is not the sole functional consequence of importance after a FS. Complex FSs may have an effect on global brain development, as patients with epilepsy and a history of complex FS have smaller total cerebral volumes than epileptic patients without complex FS[99]. However, in school-age children, a history of FS did not have adverse effects on behaviour, scholastic performance, or neurocognitive attention[10,100,101]. In fact, those with previous FS performed significantly and consistently better on tasks of working memory[11], suggesting intact function of the hippocampi. However, if the FS occurred in the first year of life then the children had deficits in learning, consolidation, and delayed recognition[11] and required special schooling more often than those with later FSs[10]. As mentioned earlier, these findings make it very important to take the age of FS into account when interpreting data from animal studies. It is possible that an experimental FS induced at P10, which correlates with a time point within the first year of human life[9], may lead to very different long-term consequences than a seizure induced at P14, correlating with toddlerhood[9].

While a single HS at P10 has also been correlated with a hyperanxious phenotype in adulthood[102], many studies have found no memory deficits in adulthood[102-105]. One study provoking single HSs found significantly more Morris water maze errors in adult rats with previous HS at P5, and to a lesser extent those with HS at P15[106]. While there is controversy about the long-term sequelae of a single seizure, it seems that repetitive HSs beginning on P10 cause long-term memory deficits, and

impaired intermediate and long-term memory in a model whereas a single HS had no effects[107]. These discrepancies may be in part due to age of seizure onset, supported by the findings in humans, but also may be model specific.

Structural Changes

The most obvious avenue to pursue when looking for mechanisms of epileptogenesis after a FS, particularly in association with TLE, would be structural changes in the limbic system. While magnetic resonance imaging (MRI) is not usually required in the diagnostic work-up of FSs, MRI studies have revealed a great deal about hippocampal changes associated with FSs. In 11 children with MRI studies after febrile status epilepticus, seven had abnormal hippocampal signal intensity within 72 hours post seizure, and five of these children met criteria for mesial temporal sclerosis at follow-up imaging (mean follow-up was nine months), while these changes were not seen in any of the children without initial MRI changes[108]. Children with both focal and prolonged FSs are more likely to have MRI abnormality than those with simple FS, suggesting underlying abnormality may predispose to lowered seizure threshold[109]. Duration of FS has also been linked to hippocampal changes, as more prolonged FS results in larger hippocampal volumes and higher signal intensity within five days[110]. These MRI changes may correlate with edema, but may also be due to structural changes leading to increased predisposition to the later development of epilepsy. Hippocampal asymmetry seen after the resolution of edema may represent a pre-existing hippocampal abnormality predisposing to FSs[111]. Long-term studies reveal history of a simple FS is associated with decreased hippocampal volume and increased T2 relaxation time in an MRI study greater than 15 years after the FS[112].

Febrile seizures are for the most part thought not to cause cell death and are still considered benign in children. However, evidence from animal studies indicates structural changes may in fact be occurring, which could lead to long-term consequences. Again, evidence is conflicting and may be model specific. Within HS models in rats, T2 signal enhancement on MRI within the dorsal hippocampus, piriform cortex, or amygdala was seen in 72% of animals at 24 hours post-HS, and in 87% of animals at eight days, but there was no evidence of neuronal injury or death[113]. This is consistent with other studies finding no hippocampal cell loss after prolonged HS[29,107,114,115] or FS[25]. However, one study has reported death of up to 60% of neurons in the CA1 and CA3 regions of the hippocampus[116].

While cell death does not occur in all models of HSs or FSs, there appear to be other pathological cellular processes occurring which may promote epileptogenesis. Mossy fibre sprouting has been found in some HS models[17,114], which may be disrupting the normal circuitry of the limbic system, though again this is not a consistent finding across models[107]. There is also the possibility that limbic system circuitry may also be disrupted by altered neurogenesis after a FS. There is an increase in the number of newly developed granule cells and synaptogenesis in the dentate gyrus six to nine weeks after a HS[97], although this may be unique to the male sex[117]. There was no effect on the GABAergic population, but there was less expression of neuronal excitatory amino acid transporter 3, which functions to remove glutamate from the synaptic cleft[118]. This change may also alter the balance

of excitation within the limbic system, promoting increased seizure susceptibility in later life. However, not all studies have found altered neurogenesis after prolonged HSs[114].

Molecular Changes

Structural changes are not the only changes responsible for altered levels of excitability, and given the lack of evidence for substantial structural changes focus has shifted to changes at the molecular level which may alter epileptogenesis after a FS. Hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels present in neuronal tissue are activated by hyperpolarisation, generating a depolarizing current called $I_{(h)}$[119,120]. After a prolonged HS there is a long-lasting enhancement of $I_{(h)}$ which converts potentiated synaptic inhibition to hyperexcitability in an activity-dependant manner[121]. The gene expression of various isoforms of HCN channels is altered in a cell-specific manner within the hippocampus[122], with developmental seizures causing a formation of heteromeric channels[123] and a reduction in the amount of spike broadening in the hippocampus[124], provoking persistent hippocampal hyperexcitability. These changes in HCN channels appear to be due to the presence of GluR2 subunit-lacking AMPA receptors, allowing increased calcium permeability with downstream effects on gene expression[125].

While alterations to HCN channels lead to increased excitability, other changes can lead to decreased inhibition. The endocannabinoid system is another important mediator of altered excitability. Hyperthermic seizures cause a selective increase in pre-synaptic inhibitory transmission in GABAergic synapses into adulthood[126]. This is mediated by an increased number of pre-synaptic CB1 receptors, which causes persistent enhancement of activity dependant, retrograde inhibition of GABA release by endogenous cannabinoids in the hippocampus[127]. Hyperthermic seizure models have also been shown to modify binding of GABA and benzodiazepines to the $GABA_{(A)}$ receptor[128], and down-regulate $GABA_{(B)}$ receptor expression[129], decreasing $GABA_{(B)}$ receptor-mediated inhibition in the hippocampus[130]. These alterations in inhibition, together with the mechanisms for increased excitability mentioned above, are likely contributing to epileptogenesis seen after HSs.

Conclusions

While animal models have significantly added to our knowledge of FSs, we must be cautious in our interpretations of these studies. Hyperthermic seizures are not necessarily the best model of FSs, and mechanisms involved in the generation of these types of seizures, such as respiratory alkalosis, may not be applicable to the human condition. Experimental FSs resulting from the administration of LPS and KA do rely on the generation of a true fever, but are still using a chemical convulsant to induce the seizures, which again may make results from this model inapplicable to children with FSs. However, these models have allowed us to make important discoveries about the mechanisms and consequences of FSs. The mechanisms by which FSs are generated appear to involve genetic factors and inflammatory mediators, and may be related to pre-existing abnormalities in the brain. Febrile seizures lead to epilepsy in some models, likely through molecular changes which alter the balance of excitation and inhibition in the limbic system. Cell death does not appear to be required in this form of epileptogenesis. Future studies in both children and animals will hopefully lead to a better understanding of these seizures, so that we can then shift focus towards strategies aimed at preventing epileptogenesis and other undesired consequences of FSs.

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