Long-term Neuroplasticity Effects of Febrile Seizures in the Developing Brain

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Febrile seizures (FS) are the most common seizure disorder in childhood, occurring in 2%-5% of children. Regarding the large number of children with FS, it is important to delineate whether early-life FS alters long-term neuroplasticity, especially the neurocognitive function and subsequent temporal lobe epilepsy (TLE). Recent epidemiological studies reassure that most FS do not adversely affect global intelligence and hippocampal function, such as memory. However, there are concerns regarding those children who experience FS during the first postnatal year, having prior developmental delay and pre- or peri-natal events. The epidemiological data do not support a causal relationship between FS and TLE. However, magnetic resonance imaging studies confirmed that prolonged and focal FS can occasionally produce acute hippocampal injury that evolves into atrophy. Moreover, the common coexistence of hippocampal sclerosis and asymmetric cortical dysgenesis in TLE patients argues for a ‘double-hit’ theory for TLE. Animal studies have revealed that the exposure of hippocampal neurons to FS early in life, particularly prolonged or frequently repetitive FS, or together with brain malformation, may lead to sustained dysfunction of these cells including long-term memory impairment or epileptogenesis, in spite of the absence of neuronal damage. Recent clinical and molecular genetic studies suggest that the relationship between FS and later epilepsy is frequently genetic, and there are a number of syndrome-specific genes for FS. However, these channelopathies account for a small proportion of FS cases. The clinical management, therefore, is based mainly on the phenotypic features of FS and the subsequent seizures. (Chang Gung Med J 2008;31:125-35)

Key words: febrile seizures, temporal lobe epilepsy, mesial temporal sclerosis, hippocampus, neuroplasticity

Febrile seizures (FS) are the most common seizure disorder in childhood, occurring in 2%-5% of children.1,2 The definition of FS is a seizure event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined causes. Typically, remission occurs spontaneously before the age of 5 years. As FS are by definition
always provoked by fever, they are not considered to be an epileptic condition. Based on the seizure type, FS are divided into simple and complex. The features of complex FS include a prolonged duration (> 15 minutes), focal seizure onset or recurrent seizures within 24 hours of a fever episode. These features are absent in simple FS, which make up 75% of attacks. The two types of FS may form biologically distinct conditions with different risks for future seizures and neurological sequelae.

Although epidemiological studies have made substantial contributions to our understanding of the frequency, natural history and seizure recurrence of FS, there are critical issues that remain unanswered. The impact of early-life FS on the developing brain has not been fully resolved. The controversy as to whether FS initiate pathophysiological cascades that ultimately lead to mesial temporal sclerosis (MTS), which is characterized by overt cell loss in the cornu ammonis, CA3 and hilar subregions of the hippocampus, and hence temporal lobe epilepsy (TLE), has been an area of intense debate. Since FS are the most common seizures in children, it is important to delineate whether early-life FS alter long-term neuroplasticity, especially the neurocognitive function and subsequent epilepsy. We will review the recent progress of FS, based on epidemiological, neuroimaging, and animal and genetic studies, on two important issues: (1) Do FS cause neuronal damage and neurocognitive dysfunction? (2) Do FS provoke TLE?

FS recurrence and subsequent epilepsy

One-third of children with FS will have recurrent FS, whereas 2%-10% will later develop epilepsy. The major predictors of recurrent FS are onset of FS before the age of one year, a family history of FS and FS associated with a low grade fever. The risk factors for epilepsy in children with FS are complex FS, a family history of epilepsy and neurological impairment prior to the onset of FS. Prevention of recurrent FS does not alter the risk of developing epilepsy.

Subsequent epilepsy following FS is roughly divided into: (1) those with focal epilepsy, where the seizures arise from a particular part of the brain (often but not always the medial temporal region); and (2) those who have generalized epilepsies, such as absence epilepsy and myoclonic-astatic epilepsy, particularly the syndrome of generalized epilepsy with FS plus (GEFS+). GEFS+ patients have classic FS, FS that persist beyond the age of 5 years (FS plus, FS+) and subsequent afebrile seizures, including absences. Some epileptic syndromes with poor prognosis, such as severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome), may occur in association with fever or even be mistakenly diagnosed as FS. SMEI has recently been recognized in childhood epilepsy populations, triggered by the discovery of mutations in the neuronal sodium channel α1 subunit (SCN1A) gene. Patients with SMEI typically present with recurrent febrile hemiclonic or generalized status epilepticus at around 6 months of age. Between 1 and 4 years of age, other seizure types appear, including myoclonic and partial seizures. Neurodevelopment may be normal in the first year and then slow. The epilepsy is often intractable, developmental outcome is poor and death in childhood is not rare (Fig. 1).

Risk factors for FS

Preexisting disorder and environment factors

FS occur when a susceptible child of a critical age has a fever. Susceptibility factors have been assessed by population-based studies from Finland, Canada, Sweden, the United Kingdom, the United States and Taiwan. These studies imply that environmental and genetic factors are both important for FS. Concomitant brain disorders (pre- or peri-natal factors, prior neurological and developmental abnormalities and increased exposure to infectious illness (day-care attendance, increased number of febrile illnesses) increase the risk of FS.

Genetic factors

About 20%-30% of children with FS have a family history of FS. Genetic factors indeed contribute significantly to the etiology of FS. A family history of FS is the most important risk factor; the more relatives affected, the greater the risk for FS. Linkage studies have identified several chromosome loci that are associated with FS. Segregation patterns in families with FS suggest different modes of inheritance. Most studies have supported a polygenic or multifactorial model, with an estimated heritability of 75%. However, in families of probands with multiple FS, the inheritance pattern is consistent with a single-major-locus model that
Recent molecular advances are beginning to explain the pathogenesis of FS. Mutations in the Na+ channel subunit SCN1A and SCN1B genes, and the gamma-aminobutyric acid A (GABA_A) receptor subunit GABRG2 and GABRD genes have been identified in certain families with GEFS+, (14) and at least in one example in a family with simple FS. (15) However, mutations in these genes seem to account for only a minority of children with FS. It has been recently demonstrated that no mutations were found in four members of the GABA_A receptor subunit gene family in 74 unrelated patients with focal epilepsy subsequent to FS. (16)

**Do FS cause neuronal damage and neurocognitive dysfunction?**

1. Epidemiological evidence

The neurocognitive prognosis of FS in early literature from hospital-based studies was fairly pessimistic (8%-22% mental retardation and 30% behavioral disturbance) due to the inclusion of symptomatic causes of seizures other than fever. (17) Furthermore, the hospital-based studies may be skewed toward disproportionately severe cases. (18) In contrast, six long-term population-based cohort studies showed children with FS have comparable global neurocognitive developmental and academic performance compared to controls. (11,19-26) Behavioral sequelae appear to be minimal. The results were not affected by whether the seizures were simple or complex, or single or recurrent in most of these studies. Only one study reported that children with prolonged FS had a significantly lower nonverbal intelligence compared with those with simple FS and controls. In addition, the study found that children with multiple FS recurrences performed more poorly in all neurological and neuropsychological tests compared to those with single FS or controls. (26) Therefore, the current viewpoint is that the vast majority of children with FS are doing well in terms of global measures of cognition and behavior.

However, prior epidemiologic studies on the
outcome of children with FS did not specifically examine memory. Why we concerned specifically about memory and hippocampal function in children with FS? The association of hippocampal sclerosis after FS, as demonstrated by neuropathological and neuroimaging studies, raised the possibility of subtle sequelae of late emergency.\(^\text{(27,28)}\) Using well-defined, sophisticated measures of hippocampal-dependent memory function may allow relatively subtle deficits to be detected. In a population-based case-control study, we performed computerized neurocognitive tasks to dissociate the mnemonic and executive aspects of working memory, including learning, memory retrieval and memory consolidation, in school-aged children with a history of FS.\(^\text{(29)}\) The interesting findings were that the majority of children with prior FS had significantly better mnemonic capacity, more flexible mental processing and higher impulsivity than their age-matched control subjects, except those with the onset of FS before the age of one year, prior developmental delay and pre- or perinatal events. Interestingly, FS onset before the age of one year was also a risk factor for poor outcome in a British study.\(^\text{(20)}\) These studies reassure that most FS do not adversely affect global measures of intelligence and nor do FS harm specific hippocampal function such as memory. However, there is concern regarding those children who experienced FS during the first postnatal year.\(^\text{(29)}\)

2. Neuroimaging studies

Magnetic resonance imaging (MRI) studies performed on 21 children within 48 hours of prolonged (> 30 minutes) FS revealed large hippocampal volume and prolongation of T2 relaxation time.\(^\text{(30)}\) When these children had follow-up investigation 4-8 months later, there was a significant reduction in hippocampal volume and T2 relaxation time between the first and second investigation but there was no difference in the hippocampal volume or T2 relaxation time in patients compared with controls.\(^\text{(31)}\) These results suggest that patients with prolonged FS develop acute hippocampal edema that resolves within several months of acute events.

In another study,\(^\text{(27)}\) MRI performed within 6 days after complex FS in 27 infants found imaging abnormalities in 6 of the 15 infants with focal FS but in none of the 12 who had generalized FS. MRI showed preexisting bilateral hippocampal atrophy consistent with a history of peri-natal insult in 2 of the 6 infants with lateralized FS. The remaining 4 infants had MRI changes suggesting acute edema in the hippocampus of the cerebral hemisphere where seizures originated. Follow-up MRI on all 4 patients revealed hippocampal sclerosis. The 4 subjects all had significantly long seizure duration, with an average duration of 99 minutes. When the clinical parameters were analyzed for correlation with MRI abnormalities, hippocampal injury was most likely associated with prolonged focal FS. These findings confirm that prolonged and focal FS can occasionally produce acute hippocampal injury that evolves into atrophy.\(^\text{(27)}\) It remains unclear what the necessary substrates are for it to occur.

An additional potential mechanism of complex FS and hippocampal injury is limbic encephalitis. Studies of infants presenting with FS indicate that a significant percentage of them suffer from initial infections with human herpesvirus-6 (HHV6) and many have HHV6 DNA in their cerebrospinal fluid.\(^\text{(32)}\) Human herpesvirus-7 (HHV7) has also been associated with FS, exanthem subitum and neurological dysfunction.\(^\text{(33)}\) It is reasonable to hypothesize that if viral invasion of the nervous system is common in FS then, in rare instances, focal limbic encephalitis could occur and account for an unknown fraction of patients with prolonged complex FS and hippocampal injury.

3. Animal studies

Prolonged FS. Animal models can permit induction of FS of controlled length and frequency, rapid prospective studies, and interventions addressed at dissecting out their mechanisms and consequences. Experimental FS can be evoked in infant rats at the age when hippocampal development is equivalent to that of human infants. These seizures are limbic in semiology and involve hippocampal formation.\(^\text{(34)}\) In an infant rat model of prolonged (~20 minutes) FS, cytoskeleton changes in neurons were evident within 24 hours and persisted for weeks but did not lead to hippocampal cell loss.\(^\text{(35)}\) Using serial MRIs, 75% and 87.5% of these immature rats had abnormal T2 signal enhancement at 24 hours and 8 days, respectively, after prolonged FS. The altered T2 values involved the dorsal hippocampus, piriform cortex and amygdala but the changes were not accompanied by neuronal death or injury in these regions.\(^\text{(36)}\) Thus,
the frequent T2 signal increase found in the hippocampus after experimental prolonged FS likely represents reversible changes.

Repetitive FS. Most children with FS experience brief and recurrent seizures. Therefore, we examined the impact of recurrent and brief experimental FS in infant rats. There was no acute neuronal damage, chronic neuronal loss or long-term aberrant mossy fibers sprouting in the hippocampus of infant rats exposed to frequent FS. However, persistently altered functional properties of the hippocampus were evident. Compared with control and single FS groups, the frequent FS group had impaired hippocampus-dependent long-term memory as measured by Morris water maze and inhibitory avoidance tests. The memory impairment was correlated with decreased activation of a transcription factor, cAMP response element-binding protein (CREB). It was related to a selective alteration in N-methyl-D-aspartate (NMDA) receptor-mediated signaling defects, which resulted in CREB activation deficits in the hippocampus of the frequent FS group. These findings were not observed in rats who had experienced single FS or hyperthermia only. These data demonstrate that frequent early-life FS can cause long-term functional impairment rather than significant morphological changes in the hippocampus of adult rats.

Pre-existing cortical lesion. In contrast to the studies examining effects of experimental FS on normal rat pups, rat pups with induced cortical dysgenesis or prior lesions were more susceptible to experimental FS than controls. The recent study also demonstrated that combined subtle brain malformation and FS resulted in mild memory deficits without histological evidence of hippocampal cell loss. Thus, it is conceivable that the exposure of hippocampal neurons to FS early in life, particularly prolonged or repetitive FS, or together with brain malformation, may lead to sustained dysfunction of these cells in spite of the absence of neuronal damage.

4. Genetic studies

There is evidence for an underlying genetic predisposition to prolonged FS or status epilepticus based on both epidemiological and twin studies. However, studies using monozygotic twins with identical genetic makeup have shown that these twins may be discordant for FS, as well as for seizure-induced structural and functional changes. Although there is strong evidence that genetic susceptibility is an important contributor to risk for the occurrence, duration, recurrence and sequelae of FS, little is known about the precise genes involved or the mechanism by which their influence might be exerted. Although several foci that are associated with an increased risk of FS have been identified thus far, it is clear that these account for only a small fraction of patients.

Do FS provoke TLE?

1. Epidemiological evidence

Retrospective studies from tertiary epilepsy centers report that many adults with intractable TLE have a history of prolonged or atypical FS in childhood. In contrast, FS followed by intractable TLE is rarely seen from a population perspective. In general, the types of epilepsy that occur in children with prior FS are varied and not very different from those that occur in children without such a history. Also of note is that a population with a cumulative incidence of FS up to 10%, such as in Japan, do not have an increased incidence of epilepsy. Furthermore, there was no evidence from prospective randomized trials suggesting that treating FS prevents subsequent epilepsy.

It should be noted that there are several limitations to these prospective and population-based studies. First, FS followed by TLE may be rare and, therefore, difficult to detect by epidemiological studies, whereas within a sample of patients with intractable TLE this event may be much more common. Second, hippocampal sclerosis will not be detected in epidemiological studies that cannot employ MRI because hippocampal sclerosis typically remains subclinical for between 8 and 11 years before TLE emerges. Third, there may be other mitigating factors that interact with complex FS to place the child at higher risk for later TLE, such as preexisting pathology of subtle focal cortical dysgenesis.

Although the epidemiological data do not support a causal relationship between FS and TLE, neither do they rule out the possibility that a causal relationship exists in a small proportion of cases. It should be noted that there is a much higher risk of epilepsy following febrile status epilepticus in these...
Complex FS are clearly associated with increased risk of subsequent epilepsy. In addition, there is a much higher rate of prior FS in studies of epilepsy of all types, including both generalized and partial epilepsy. The epidemiological data are much more consistent with FS being a marker of increased seizure susceptibility than being causally related to epilepsy in general and TLE in particular. Those with generalized FS are more likely to develop a generalized epilepsy whereas those with focal FS are more likely to develop a partial epilepsy.

2. Neuroimaging studies

Several retrospective neuroimaging studies that specialized in hippocampal MRIs of adult patients with MTS revealed greater atrophy of the hippocampus in those who had a history of complex FS compared to patients with hippocampal sclerosis but no such history. A systemic MRI study of 55 children diagnosed with TLE revealed that the incidence of MTS was 57%, comparable to the adult incidence of 65%. Hippocampal sclerosis was noted in 76% of those children who had preceding neurological insults and in only 21% of those without preceding insults. Of 22 children with histories of complex FS, 17 had hippocampal sclerosis on MRI. On the other hand, age at onset of TLE and duration of TLE did not correlate with the presence of MTS, giving no support to the hypothesis that hippocampal sclerosis develops as a result of recurrent temporal lobe seizures across a number of years.

The common coexistence of hippocampal sclerosis and asymmetric cortical dysgenesis in TLE argues for a casual connection between cortical dysgenesis and hippocampal injury. More recently, dysgenesis of the hippocampus has been suggested as a possible etiology for FS. MRI studies of two families with genetically determined unilateral hippocampal dysgenesis demonstrated that only family members with the malformation had FS. The concept of two insults leading to hippocampal sclerosis, one preceding a severe seizure and serving as a nidus of hyperexcitability accounting for the localization of the seizure and the second insult due to and occurring during the severe seizure, is becoming more popular.

3. Animal studies

Experimental brief FS, even when very frequent, in infant rats did not cause long-term specific neuronal loss and chronic mossy fiber sprouting, neither did they alter the seizure threshold. Experimental prolonged (~20 minutes) FS in infant rats, however, did possess a persistently decreased seizure threshold. Recent studies have demonstrated that prolonged experimental FS can induce recurrent, spontaneous, behavioral and electrographic seizures later in life in 35% of rats. In addition, interictal epileptiform discharges were recorded in 88% of the prolonged FS group but in none of the controls. These findings suggest that experimental prolonged FS modified limbic (temporal lobe) circuits in adulthood.

The hippocampal slices of rats experiencing prolonged FS also demonstrated increased hippocampal excitability and decreased seizure threshold, in spite of an up-regulated pre-synaptic inhibitory GABAergic neurotransmission. The mechanisms for these profound pro-epileptogenic changes did not require cell death and were associated with long-term slowed kinetics of hyperpolarization-activated mixed-cation channels (HCNs). Further analysis of the HCNs mRNA expression demonstrated that prolonged FS can induce isoform- and region-specific transcriptional regulation of the HCNs. These changes result in long-lasting alteration of the HCN phenotypes of specific hippocampal neuronal populations and have profound consequences on hippocampal network excitability.

Experimental FS also predispose to subsequent spontaneous recurrent seizures in rat pups with a prior brain lesion. Eighty-six percent of rat pups with a focal microgyrus plus FS experienced development of spontaneous recurrent seizures recorded from the amygdala ipsilateral to the lesion, although no hippocampal cell loss was found. The ‘two-hit’ hypothesis for TLE may have relevance to clinical findings: the hippocampus of patients with intractable epilepsy who had an initial precipitating injury early in life had more severe sclerosis than did those without a precipitating injury.

4. Genetic studies

In view of recent clinical and molecular genetic studies, it appears that the relationship between FS and later epilepsy is frequently genetic, and there are a number of syndrome-specific genes for FS. To specifically focus on familial TLE, 41% of epileptic
patients had refractory seizures and 61% had MRI findings of MTS. There were antecedents of complex and simple FS in only 14% and 8% of patients, respectively. In another study of 98 affected individuals from 22 families in whom more than 2 patients had mesial TLE, 57% of patients had MRIs suggestive of MTS. There were heterogeneous clinical presentations: about half had good seizure control with medication and the other half had refractory TLE. Hippocampal atrophy was also found in patients who did not fulfill the criteria for mesial TLE: 60% with recurrent generalized tonic-clonic seizures, 25% with a single partial seizure and 30% with only simple FS in childhood. It should be noted that, despite the frequent hippocampal abnormalities, a history of FS was uncommon among these patients with familial mesial TLE. The recent study has demonstrated that families with SCN1B mutation have GEFS+ spectrum but also TLE. It is known that a proportion of individuals with FS that lead to TLE can have mutations in Na+ channels but these probably account for a small proportion of cases. These findings from familial cases suggest that the association of FS with TLE results from complex interactions with genetic or environmental modifiers, or both.

**Future investigations**

The recent studies suggest that IL-1β contributes to the generation of FS, and potentially contributes to long-lasting hyperexcitability and excitotoxicity associated with hippocampal epilepsy. IL-1β receptor-deficient mice were resistant to experimental FS. Polymorphisms in the IL-1β gene have been associated with FS. Specifically, increased frequency of the IL-1β-511*2 allele, a variant that promotes enhanced expression of the cytokines, has been found in children with FS when compared with the appropriate ethnic cohort. Increased IL-1β levels have been reported in the cerebrospinal fluid of children with FS. Interestingly, homozygosity for the same gene variant was overexpressed in TLE patients with hippocampal sclerosis compared with both control subjects and TLE patients without hippocampal sclerosis. It is of note that IL-1β type 1 receptor and NMDA receptors are colocalized on the dendrite of hippocampal neurons, promoting cross talks between proinflammatory and excitatory pathways. Better understanding of this relationship should lead to therapeutic strategies targeting the IL-1β signaling cascade.

There is also some progress in unraveling the pathogenesis of FS. Mutations in the genes that encode the GABAa receptor subunits’ GABRG2 gene, which account for some familial FS cases, have been recently shown to cause a temperature-dependent intracellular trafficking defect. It is known that GABRG2 is important in receptor trafficking, clustering and synaptic maintenance of GABA receptors. It is possible that the ‘real-time’ reduction in the inhibitory GABA receptor expression caused by the elevated temperature in the brain may trigger FS. Whether this proposed mechanism can be generalized to most cases of FS where GABA receptor mutations are not implicated remains to be determined. It is of note that temperature-dependent reduction in cell surface expression of membrane proteins is a well-known consequence of mutations that cause human diseases. It is intriguing to delineate the roles of these membrane proteins in FS.

The cause of febrile illness may influence not only whether FS occur but also their duration and whether they result in hippocampal injury. The potential role of HHV6 and HHV7 in causing very prolonged FS and hippocampal injury is of particular interest. One report showed that HHV6 and HHV7 combined account for 53% of first FS presenting to the emergency department in children below the age of 3 years. It has been reported that children with primary HHV6 infection are more likely to have prolonged focal FS and to have postictal paralysis than those with FS not associated with HHV6 infection. It remains unclear whether these viruses are associated with prolonged FS due to the high fever during the infection or whether they are also involved in the pathogenesis of seizure-induced injury.

**Conclusion**

There is now a broad consensus that simple FS are benign and rarely require treatment. There is less agreement regarding complex FS, although many authorities feel that the optimal treatment is abortive therapy (Fig. 1), which will prevent the occurrence of status epilepticus. MRI studies have confirmed that prolonged and focal FS can occasionally produce acute hippocampal injury that evolves into atrophy. Animal studies have revealed that the exposure of hippocampal neurons to FS early in life, particu-
larly prolonged or frequently repetitive FS, or together with brain malformation, may lead to sustained dysfunction of these cells, including long-term memory impairment or epileptogenesis. Recent clinical and molecular genetic studies suggest that the relationship between FS and later epilepsy is frequently genetic, and there are a number of syndrome-specific genes for FS. Therefore, there is a small group of children in whom FS-induced injury does occur. Once we can identify the target population and the suitable surrogate for epileptogenesis, prevention of epileptogenesis after FS will be the ultimate goal of therapy.

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熱性痙攣對幼兒腦部神經可塑性的長期影響

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熱性痙攣是幼兒最常見的抽筋，發生於2%~5%之孩童，由於許多孩童曾有熱性痙攣，對於熱性痙攣是否會造成長期神經可塑性的改變，尤其是神經認知功能及誘發顳葉癇癇的反應異常值得進一步釐清。近年人口學調查發現熱性痙攣不致造成長短期智力及海馬回功能如記憶力之不良影響，但對於熱性痙攣發作年齡小於一歲，或之前有發展遲緩，或產前、產後期問題者，則可能有影響。同時人口學研究亦發現熱性痙攣不致造成之後的顳葉癇癇。但是磁振造影發現持續太久的局部性熱性痙攣，可以造成海馬回水腫及繼發性的萎縮，近年亦發現許多顳葉癇癇患者除了海馬回硬化外，亦合併單側之大腦皮質發育不全。故目前仍為“雙重打擊”很可能是熱性痙攣繼發為顳葉癇癇之一重要原因。動物實驗也發現鼠自經過太快或太頻繁的熱性痙攣，或幼鼠本身之前已有腦傷或腦皮質不正常發育者經歷熱性痙攣，即使海馬回的細胞沒有死亡，亦會造成海馬回功能的改變，如記憶力缺失或抽筋閾值下降。最近的分子生物學研究，亦可解釋一些熱性痙攣及其繼發性之癇癇之家庭之致病機轉與離子通道的基因有關，然而這只侷限於少數的一些家庭。臨床上的處理，主要仍依賴熱性痙攣的表現型態及其續發抽筋的情形來決定。(長庚醫刊 2008;31:125-35)

關鍵詞：熱性痙攣，顳葉癇癇，顳葉內側硬化，海馬回，神經可塑性