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Review Article

Etiology and Risk Factors of Febrile Seizure – An Update

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Abstract:

Febrile seizures (FS) are the most common convulsive event in children. This condition has been described since the time of Hippocrates. The etiology of the febrile seizures are still unclear. In FS, there is a strong familial predisposition. This does not exclude infections as a causative factor because subtle genetic polymorphisms have been demonstrated to affect the course of infections. In an earlier review of the world literature (1924-1964), except for roseola infantum, viral infections as a cause of febrile seizures were rarely diagnosed. Reports of viral infections in the etiology of febrile seizures have increased in number in the past decade. In the first half of the twentieth century, infections identified with febrile seizures were mainly upper respiratory in type and the etiologic agent was unknown or bacterial. We review i) the role of infection – viral and bacterial; ii) the role of genetic and environmental factors; iii) the role of electrolyte and metabolic factors; and iv) the role of cytokines. With the help of new diagnostic tools such as PCR, the viral agents are detected in CSF far more often than previously thought, even in the absence of pleocytosis of the CSF. This makes it difficult to distinguish FS from acute encephalitis. FS may be caused by neuroinvasion or intracerebral activation of viruses. By reviewing etiology and risk factors of FS we can identify the points to be focused in therapeutic interventions and trials and also the fields of future studies will be explored.

Key word: *Febrile seizure**, Etiology and Risk factors.***

Introduction

The sociodemographic and epidemiological transition in developing countries has changed the morbidity and mortality pattern among communities. This has brought non-communicable diseases to the forefront of the health care delivery system. Within this group, neurological disorders constitute a significant proportion affecting morbidity, mortality, disability and quality of life [1].

Although childhood febrile seizures in most cases are benign and self-limiting, witnessing such seizures is a terrifying experience for most parents. Febrile seizures are one of the most common childhood neurological disorders. There has been a lot of confusion regarding the necessary evaluation of a patient with febrile seizures. The American Academy of Pediatrics (AAP) has recently published practice parameters for the evaluation and treatment of simple febrile seizures. International League Against Epilepsy and Italian League Against Epilepsy recently has published a recommendation addressing the instructions for management of the first febrile seizures, giving criteria for hospital admission, diagnosis, differential diagnosis, and treatment of a prolonged seizure [2].

An understanding of the febrile seizures will enable the physician to reassure the families and provide appropriate counseling and management while avoiding unnecessary diagnostic and therapeutic interventions.

Definition:

The National Institute of Health (NIH) consensus statement defines an FS as ''an event in infancy or childhood usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause for the seizure'' [3]. This definition excludes seizures with fever in children who have previously had afebrile seizures. This definition was revised by International League Against Epilepsy (ILAE) as "a seizure in association with a febrile illness in the absence of a central nervous system infection or acute electrolyte

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imbalance in children older than 1 month of age without prior afebrile seizures."(Commission on Epidemiology and Prognosis, International League Against Epilepsy: Guidelines for epidemiologic studies on epilepsy. International League Against Epilepsy, 1993). The temperature associated with the febrile illness must be greater than 38.4°C, although the temperature may not be evident until after the seizure. Prior epidemiologic studies have used either 1 month [4-9] or 3 months [10,11] as the youngest age of occurrence, whereas no specific upper age limit was employed. Febrile seizures have a peak incidence at about 18 months of age, are most common between 6 months and 5 years of age, and onset above age 7 years is rare, although it does occur. The child can be neurologically normal or abnormal [12].

Febrile Convulsion (FC)s are to be distinguished from epilepsy, which is characterized by recurrent non-FC [13]. Seizures with fever in children who have suffered a previous non-FC are excluded. This definition excludes seizures that accompany meningitis, electrolyte imbalance or toxic encephalopathy. Seizures in these instances may carry a more ominous prognosis than the benign course of FC owing to the effects of associated illness [14].

This condition has been described since the time of Hippocrates. It was initially thought to be due to teething. This may have been considered as the etiology because it happens most frequently in toddlers. In the Nineteenth century, febrile seizures were felt to be a form of epilepsy triggered by fever. We now understand that febrile seizures are an age dependent response of the immature brain to a febrile illness. Febrile seizures are considered to be benign and usually do not require any long term treatment. There has been a lot of confusion regarding the necessary evaluation of a patient with febrile seizures [15].

Cause and factors associated with febrile seizures

Table-I

Factors Associated With Febrile Seizures[16]

Infections	Other
Viruses:	Familial:
Respiratory	Genetics
Influenza virus A and B	Environmental
Parainfluenza 1, 2, and 3	Channelopathies:
Respiratory syncytial virus	Sodium, potassium, and calcium channels
Adenovirus	GABA-A
Enteric	Vaccination:
Entero viruses	Measles Mumps Rubella (MMR)
Enterovirus 71	Pertussis
Coxsackieviruses group A	Structural brain defects & perinatal events:
Rotavirus	Cerebral palsy (neurodevelopmental disabilities)
Herpesviruses	Cerebral dysgenesis
Human herpesvirus-6 and -7	Neonatal brain injury (low Apgar scores; prematurity)
Cytomegalovirus	Strokes
Herpes simplex virus-1	Vascular malformations
Bacteria	Tumors
Escherichia coli (urine)	pH:
Shigella dysenteriae (enteric)	Acidosis
Streptococcus pneumoniae (upper respiratory)	Alkalosis
Salmonella enteritidis (enteric)	Water, electrolyte imbalance:
	Sodium, potassium, chloride, magnesium, calcium
	Cytokines.

Infections Implicated in Febrile Seizures

Viral and bacterial infections are considered important causative factors of febrile seizures and have been comprehensively reviewed by Millichap and Millichap [17].

Influenza A and B:

Influenza A infection is an important cause of febrile seizures, especially in Asia. It is associated with a higher incidence of febrile seizures than any other respiratory virus, such as adenovirus or parainfluenza virus. Children, who developed febrile seizures with influenza A infection had a significantly higher maximum body temperature, a shorter duration of fever before seizure onset, and a more frequent occurrence of partial seizures than children who developed febrile seizures with negative viral studies. This apparent prevalence of influenza virus may simply reflect a higher geographic incidence of influenza and not a genuine neurotropic property causing febrile seizures. Effective vaccination may prevent development of febrile seizures, especially in those patients with a past history of febrile seizures. Rapid diagnostic testing for viral infections (eg, influenza A) seems cost-effective in the management of complex febrile seizures[17].

Respiratory Syncytial Virus

Neurologic complications, including encephalopathy with hypotonia and seizures or encephalopathy manifested as seizures, have been reported to be associated with respiratory syncytial virus [18]. Thus, by either direct or indirect inflammatory processes, respiratory syncytial virus may have a specific neurotoxic effect and cause an encephalopathy during acute respiratory tract infections.

Enterovirus

Enteroviruses have been reported in association with seizures. Central nervous system “cytokine storm” can occur in patients with enterovirus-71 infection. The causative agents of febrile illness associated with seizures in summer were primarily enteroviruses, especially coxsackieviruses group A. Febrile seizures also may be caused by several other enteroviral infections affecting the central nervous system [19].

Rotavirus

Rotavirus, the most common cause of dehydrating gastroenteritis in children, primarily affects children 3 to 24 months of age. A seizure occurring before the onset of gastroenteritis has been reported in 40% of cases. The loss of water and electrolytes in rotavirus diarrhea may also be involved in the pathogenesis of the accompanying seizure [17].

Herpesviruses

Several members of the herpes virus family possess neurotropism and cause neurologic disease in children: herpes simplex virus-1, herpes simplex virus-2, varicellazoster, Epstein-Barr, cytomegalovirus, human herpesvirus-6, and human herpesvirus-7. Of these, herpes simplex virus-1, cytomegalovirus, human herpesvirus-6, and human herpesvirus-7 have been associated with febrile seizures [17]. In a study of 63 children (ages 1 month to 5 years) presenting with febrile seizures lasting for 30 minutes or longer, 33% had serologic evidence of primary human herpesvirus-6 infection and 11% had evidence of primary human herpesvirus-7 infection [20].

Bacteria

Compared with rates of viral infections, bacteremia is an infrequent cause of febrile seizures.4 Studies to date have implicated childhood illnesses with Shigella dysenteriae(enteritis), Salmonella enteritidis (enteritis), Streptococcus pneumoniae (respiratory tract infection), and Escherichia coli (urinary tract infection) in relation to febrile seizures [17].

Familial: Genetics and Environmental

Genetic risk factors have long been known to contribute significantly to the etiology of febrile seizures. It tends to occur in families and one of the major risk factors is a first degree relative (parent or sibling) with febrile seizures. However, the exact mode of inheritance is not known. It is thought that approximately 10-20% of siblings of children with febrile seizures will develop febrile seizures. The likelihood for development of febrile seizures in children is higher if one of the parents also has a history of febrile seizures [21]. In a twin and family studies have shown that FS have a heritable component of about 70% [16]. Most studies support a polygenic or multifactorial mode of inheritance [16,22]. However, there are rare families with a monogenic inheritance model [37]. Although infantile FS are mostly benign, patients have an increased risk for developing epilepsy later in their life [6].

Table-II

Details the different mutation and their clinical correlations [24]

Mutation	Chromosome	Clinical syndromes	Comments
FEB1	8q13-q21	Febrile convulsion	
FEB2	19p13.3	Febrile convulsion	
FEB4	5q14-q15	Febrile convulsion	The most common linkage locus in febrile convulsion families
SCN1B	19p13.1	Generalized epilepsy with febrile convulsion plus (GEFS+)	Mutation in the voltage-gated sodium channel beta 1 subunit gene
SCN1A	2q24	Simple febrile convulsion	Mutation in alpha 1 subunit gene
AKAP18	6q22-q24	Simple febrile convulsion	
GABRG2 gene, encoding the GABA (A) receptor gamma 2 subunit		Febrile convulsion either with or without absence epilepsy	
1 beta (-511)		Increase frequency	Interleukin-1 beta polymorphism of febrile convulsion

Channelopathies

Related gene, mutations of the genes encoding various channels (SCN1B, SCN1A, and SCN2A for sodium channel; and GABRG2 for GABA-A receptor) have been described above.

Vaccination

Fever is a common side effect of immunizations. Both febrile and afebrile seizures have been associated with immunizations [25]. They are more likely after the administration of certain vaccines, particularly live attenuated vaccines such as the measles, mumps, rubella (MMR) vaccine, and toxin-containing or whole cell preparations, such as whole cell pertussis vaccines [25]. The replacement of whole cell pertussis vaccines with acellular vaccines occurred in the late 1990s in many areas of the developed world and has decreased the incidence of adverse effects following pertussis vaccination to approximately one third of whole cell preparations [40]. However, the whole cell vaccines continue to be administered in developing countries due to cost.

Structural Brain Defects and Perinatal Events

Cerebral palsies, cerebral dysgenesis, neonatal brain injuries, low Apgar scores at 5 minutes of life, strokes, vascular malformations, and tumors have been reported to be associated with febrile seizures. Premature birth, delayed discharge from the neonatal intensive care unit, and developmental delay are potential markers for suboptimal brain function, but currently there is conflicting evidence definitively linking these factors to febrile seizures [25]. Neonatal discharge at 28 days or later, and parental impression of slow development have also been reported as risk factors for first febrile seizures [26].

pH (Acidosis and Alkalosis)

A rise in brain pH enhances neuronal excitability. In experiments with rats, hyperthermia induces respiratory alkalosis in the immature brain and febrile seizures are experimentally precipitated [27]. Both the duration of the alkaline cortical pH shift after injection of bicarbonate and the associated behavioral seizure activity were more brief (less than 5 minutes) than those observed with hyperthermia but were otherwise similar [27].

Water and Electrolyte Imbalance

In 1953, Lennox suggested the possible importance of hydration and increased permeability of cell membranes as a mechanism of febrile seizures [28]. An elevation of the “threshold” to febrile seizures which occurs with increasing age is associated with developmental changes in the balance of water and electrolytes, especially hyponatremia [17]. On the other hand, during acute infections not involving the nervous system directly, an expansion of the plasma volume has been observed as a result of fever per se [29].

Cytokines

Pyrogenic cytokines such as interleukin-1beta have been reported to be involved in the pathogenesis of febrile seizures. A common viral component that induces host cell immune responses is double-stranded RNA. Significantly greater levels of interleukin-1beta production from double stranded RNA-stimulated leukocytes in febrile seizure patients in the absence of infection has been reported and suggests that the response of leukocytes to viral infection might be enhanced in patients who experienced febrile seizures. Research during the past 2 decades has indicated that both astrocytes and microglia secrete numerous cytokines, such as interleukin-1beta, tumor necrosis factor-alpha, and interleukin-6, and that astrocytes and microglia actively participate in inflammation and infection. Elevated concentrations of cerebrospinal fluid proinflammatory cytokines (such as tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6) have been found in children with acute encephalitis or encephalopathy [30].

Serum and CSF zinc levels are decreased in children with FS, and zinc deprivation may play a role in the pathogenesis of FS [31].

Iron deficiency anemia has been found to be commoner in children with FS than controls and may also be related to FS [24].

Çaksen et al. [32] have reported an immunoglobulin deficiency in FS, which may be of significance in causing of FS or the fever. Others have reported a possible immunological derangement in the cytokines and interferon axis in FS that may correlate with the pathogenesis of FS or at the fever [32].

Risk Factors for the First Febrile Seizure

Two studies have examined risk factors associated with experiencing a febrile seizure (Table 3) [6,33]. In a 1993 case control population-based study, four factors were associated with an increased risk of febrile seizures: (1) a first- or second- degree relative with a history of febrile seizures, (2) a neonatal nursery stay of >30 days, (3) developmental delay, or (4) attendance at day care. There was a 28% chance of experiencing at least one febrile seizure for children with two of these factors[33]. A second case-control study examined the issue of which children with a febrile illness were most likely to experience a febrile seizure using febrile controls matched for age, site of routine pediatric care, and date of visit [6]. Significant independent risk factors, on a multivariable analysis, were the height of the temperature and a history of febrile seizures in a first- or higher-degree relative. Gastroenteritis as the underlying illness appeared to have a significant inverse (i.e., protective) association with febrile seizures.

Table-III

Risk Factors for First Febrile Seizure

In population [33]
• First- or second-degree relative with history of FS
• Neonatal nursery stay of >30 days
• Developmental delay
• Attendance at day care
• Two of these factors 28% chance of at least 1 FS
In children with a febrile illness [6]
• First- or second-degree relative with history of FS
• Height of temperature

Risk Factors for Recurrent Febrile Seizures

Overall, approximately one third of children with a first febrile seizure will experience a recurrence; 10% will have three or more febrile seizures. An assessment of various factors potentially associated with the recurrence of febrile seizures is shown in Table 4. The most consistent risk factors reported are a family history of febrile seizures and onset of first febrile seizure at <18 months of age [12]. This relationship is not attributable to a greater tendency to experience seizures with each specific illness but rather the longer period during which a child with a younger age of onset will be in the age group at risk for febrile seizures[17,34]. Two other definite risk factors for recurrence of febrile seizures are peak temperature and the duration of the fever prior to the seizure [6,-8,34]. In general, the higher the peak temperature, the lower the chance of recurrence. In one study, those with peak temperature of 101°F had a 42% recurrence risk at 1 year, compared with 29% for those with a peak temperature of 103°F, and only 12% for those with a peak temperature of 105°F [6,7,34]. Second, the shorter the duration of recognized fever, the higher the chance of recurrence. The recurrence risk at 1 year was 46% for those with a febrile seizure within an hour of recognized onset of fever, compared with 25% for those with prior fever lasting 1 to 24 hours, and 15% for those having more than 24 hours of recognized fever prior to the febrile seizure. Children with multiple risk

factors have the highest risk of recurrence. A child with two or more risk factors has a greater than 30% recurrence risk at 2 years; a child with three or more risk factors has a greater than 60% recurrence risk.5 In contrast, the 2-year recurrence risk is less than 15% for a child with no risk factors (eg, older than 18 months with no family history of febrile seizures, who experiences a first febrile seizure associated with a peak temperature >40°C after a recognized fever of more than 1 hour). A recurrent febrile seizure is also more likely to be prolonged if the initial febrile seizure was prolonged. The relationship between a family history of unprovoked seizures or epilepsy and the overall risk of febrile seizure recurrence appears to be doubtful. Some studies report a modest increase in the risk of febrile seizure recurrence in children with a family history of unprovoked seizures, but a large study in Rochester, Minnesota, found no difference in recurrence risk between children with a family history of epilepsy (25%) and those with no such family history (23%)[8]. Other studies have found equivocal results [6,17,34]. The presence of a neurodevelopmental abnormality in the child or a history of complex febrile seizures has not been shown to be significantly associated with an increased risk of subsequent febrile seizures. Ethnicity and sex have also not been associated with a clear increased risk of recurrent febrile seizures [12].

Table-III

Risk Factors for Recurrent Febrile Seizures[12]

Definite risk factor
• Family history of FS
• Age <18 months
• Height of temperature
• Duration of fever
Possible risk factor
• Family history of epilepsy
Not a risk factor
• Neurodevelopmental abnormality
• Complex FS
• >1 complex feature
• Sex
• Ethnicity

Risk for subsequent development of epilepsy

The major concern for physicians and parents faced with a child with febrile seizures is the question of increased risk of epilepsy. Even though there is a slight increase in the risk of epilepsy in children with prolonged febrile seizures, the risk is very small. It has been estimated that the risk of epilepsy in the general population is approximately 0.5%. The risk of epilepsy in children who have prolonged febrile seizures is approximately 1.5%; still with 98.5% chance that the child will not develop epilepsy. At the same time, one can look at this same information and state that children with febrile seizures have a three fold increase in risk of developing epilepsy [21].

Risk factors for development of epilepsy in children with febrile seizures presented in the table 5.

Table-V

Risk Factors for Subsequent Epilepsy[12]

Definite risk factor
• Neurodevelopmental abnormality
• Complex FS
• Family history of epilepsy
• Duration of fever
Possible risk factor
• >1 complex feature
Not a risk factor
• Family history of FS
• Age at first FS
• Height of temperature
• Sex
• Ethnicity

Data from five large cohorts of children with febrile seizures indicate that 2 to 10% of children who have febrile seizures will subsequently develop epilepsy [11,17,35]. In each of these five large studies, the occurrence of a family history of epilepsy and the occurrence of a complex febrile seizure were associated with an increased risk of subsequent epilepsy [11,17,25,35]. The occurrence of multiple febrile seizures was associated with a slight but statistically significant increased risk of subsequent epilepsy in two studies [25,35]. One study found that children with a febrile seizure that occurred within 1 hour of a recognized fever (i.e., at onset) had a higher risk for subsequent epilepsy than those children with a febrile seizure associated with longer fever duration [25]. Two

studies have found that very prolonged febrile seizures (i.e., febrile status epilepticus) were associated with an increased risk of subsequent epilepsy above that of a complex febrile seizure that was less prolonged [25,35]. The number of complex features in a febrile seizure may possibly affect the risk of recurrence. Although one study found that patients with two complex features (eg, prolonged and focal) had further increased risk of subsequent epilepsy [35], another study did not detect this association [25]. A family history of febrile seizures, age at first febrile seizure, and the height of fever at first seizure are not associated with a differential risk of developing epilepsy [11,17,25,35]. The only common risk factor for both recurrent febrile seizures and subsequent epilepsy was duration of fever prior to the febrile seizure; this may be a marker for overall seizure susceptibility.

The types of epilepsy that develop are variable [29, 35]. In general, the types of epilepsy that occur in children with prior febrile seizures are varied and are not very different from those that occur in children without such a history [36]. Febrile seizures can also be the initial manifestation of specific epilepsy syndromes, such as severe myoclonic epilepsy of infancy. It is controversial whether febrile seizures are simply an age-specific marker of future seizure susceptibility or have a causal relationship with the subsequent epilepsy [12]. Two factors support the former, and not the latter, interpretation. There is no increased incidence of epilepsy in populations with a high cumulative incidence of febrile seizures (eg, 10% in Tokyo, Japan) [16]. Second, no evidence exists that treatment of febrile seizures alters the risk of subsequent epilepsy [7,9,12].

Febrile Seizure and Temporal Lobe Epilepsy(TLE)

This remains one of the most controversial issues in epilepsy. Studies have approached the question from different perspectives and not unexpectedly, the results remain unclear and often contradictory. Retrospective studies from tertiary centres report that as many as 40% of adults with intractable temporal lobe epilepsy give a history of complex (specifically prolonged) FS in childhood [37].

A recent study by Trinka and colleagues found a strong association between prolonged and focal FS and the development of TLE [38]. These findings are supported by magnetic resonance imaging (MRI) studies showing hippocampal sclerosis and atrophy in patients who experienced prolonged FS in childhood [39]. The selection of children and the timing of neuroimaging have varied between studies, making evaluation of any potential evolving process difficult. A specific study employing MRI as a research tool, that was undertaken within 48 hours of a prolonged FS (including febrile status epilepticus), showed evidence of temporal lobe (hippocampal) oedema [40]. Subsequent follow up imaging within 12 months in this population showed resolution of the oedema and did not show any hippocampal atrophy or mesial temporal sclerosis (MTS) in the previously swollen temporal lobes [40]. The identification of hippocampal atrophy in patients with a previous history of prolonged FS does not necessarily prove a causal relation, and in the study by Kuks and colleagues [39], 64% of 107 patients with hippocampal atrophy and MTS had no history of FS.

Early histological reports suggested a possible causal relation between prolonged childhood FS and MTS[41]. However, more recent neuropathological data from 33 children with refractory TLE, with and without a history of preceding risk factors for TLE, showed cortical dysplasia in 21 patients (66%), including 73% of patients (11/15) with a history of FS. Cortical dysplasia (which typically has an onset in early fetal life), rather than FS, could arguably explain the development of late and intractable epilepsy. Finally, animal data support the hypothesis that, over time, prolonged FS may enhance hippocampal excitability[42].

In summary, most retrospective analyses from tertiary (often epilepsy surgery) centres have suggested a definite, though inconstant, association between TLE and early, prolonged FS, with, generally, an excellent response to surgical treatment [51]. However, it is clearly possible that these centres may have overestimated the frequency and therefore the impact of an uncommon or rare association.

In contrast, prospective and controlled, population based studies have failed to confirm this apparent association [35,38]. It has been argued that prospective studies would have to be much larger and conducted over a longer period, to identify the small group that develop complex partial (focal) seizures of temporal lobe origin. This is because hippocampal atrophy or MTS may not be demonstrable until late childhood, adolescence, or early adulthood—although MTS has occasionally been shown in children as young as 4 years of age. It is possible that this was already present (and responsible for the initial, prolonged FS), as MRI

would not normally be undertaken at the time of the initial FS. A recent, prospective MRI study of 329 unselected patients with FS failed to show any hippocampal injury and reasonably concluded that there may be no causal relation between FS and MTS. Although there is some evidence that the severity or extent of hippocampal atrophy may be directly related to either frequent secondarily generalized tonic-clonic seizures or the duration of epilepsy, this may simply reflect the effect of frequent afebrile (that is, epileptic) seizures in and throughout childhood, rather than a prolonged FS in infancy.

Current opinion supports an association between prolonged FS and pre-existing lesions within the temporal lobe—and that this may subsequently facilitate the development of hippocampal atrophy. In addition, the contradictory findings obtained from epidemiological, neuroimaging, and pathological studies would also suggest that the association of complex FS with hippocampal atrophy and TLE reflects complex interactions with genetic or environmental factors (or both), which may subsequently facilitate the development of TLE. This increased susceptibility is likely to be multifactorial but may involve cytokines, and specifically interleukin-1 [43].

Conclusion:

Febrile seizure is associated with wide spectrum of etiological and risk factors, it is the appropriate time to reconsider the everyday use of the term febrile seizure. Particular attention should be focused on a practical strategy based on the underlying causes and circumstances that will assist in the clinical management of this frequent childhood event. There is increasing recognition of the value of having a more specific infectious diagnosis. Future studies could determine whether morbidity is decreased with rapid and specific diagnostic testing for viral and bacterial infections, the appropriate use of neuroimaging studies, the timely administration of antiviral and antibacterial drugs, and the acute, subacute, and chronic administration of anticonvulsants in simple and complex febrile seizures.

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