Current Practice

Febrile seizures

Jithangi Wanigasinghe[1]

Sri Lanka Journal of child Health, 2009; **38**: 93-97

(Key words: Febrile seizures)

Febrile seizures (FS) are the most common seizure disorder in childhood. Studies from the developed world report 2-5% of all children between the ages of 6 months to 5 years being affected. Although 6 months is considered as the lower age limit by many paediatricians, the National Institute of Health (NIH) and International League Against Epilepsy (ILAE) definitions on febrile seizures use a lower age limit of 3 months and 1 month respectively[1,2]. It is defined as a seizure occurring in the context of a febrile illness, not secondary to a central nervous system (CNS) infection or an altered metabolic state in children who have not had neonatal or previous afebrile seizures. There are two main clinical forms: simple febrile seizures which are a single episode of generalised tonic clonic seizures lasting less than 10-15 minutes, occurring during the first 24 hours of a febrile illness. Majority (70-75 %) of FS are of this type. Those lasting longer or occurring after the first 24 hours or having multiple seizures during the same febrile illness or convulsions affecting one side of the body or occurrence of focal neurological deficits are called complex febrile seizures (9-35%). There is a third form which is febrile status epilepticus (FSE) and this constitutes 5% of all FS.

The phenotype of FS is not well defined; though in the NIH and ILAE definitions they are called an 'event', classically FS are generalised tonic clonic convulsions. Two conditions that may mimic FS in this age group are convulsions with gastroenteritis and febrile myoclonus. The first initially described amongst Asian children comprises convulsions that occur during gastroenteritis. These show similar presentation and characteristics to FS such as age of presentation, associated family history and recurrences[3]. However, they tend to cluster more often, are less associated with a family history and have a lower rate of recurrence compared to FS. Febrile myoclonus is myoclonic seizures occurring during a febrile illness in a neurologically normal child and which resolves when fever settles. This is a benign phenomenon and does not warrant unnecessary investigations and treatment[4]. Febrile syncope is a non epileptic phenomenon which often gets treated as a FS.

The aetiology of FS is considered to be a polygenic or multifactorial model; however, an autosomal dominant inheritance with reduced penetrance has been described in several families. Several chromosomal loci, particularly those on 19q and chromosome 2, have been identified. Gene mutations on voltage gated ion channels such as the alpha 1 subunit, the alpha 2 subunit and beta 1 subunit of sodium channel (SCN1A , SCN2A and SCN1B) and those affecting the gamma amino butyric acid (GABA) receptor have been shown to be strongly associated with the epilepsy syndrome of 'genetic epilepsy with febrile seizures plus' (GEFS+). Patients with GEFS+ may have different phenotypes comprising of FS, generalised tonic clonic convulsions, myoclonic or absence epilepsy.

Role of temperature

Although a change in body temperature is required for occurrence of FS, the convulsions are not specifically related to the rise in temperature or height of the temperature. They are considered to be due to increased neuronal excitability due to release of various pyrogens. This has raised a lot of interest over the role of the immunological system in the pathogenesis of FS. Animal studies have shown that the relative imbalance between the interleukin 1-beta and its natural antagonist interleukin 1 receptor antagonist (IL-1ra) during fever is responsible for causation of FS[5]. Several research groups have attempted to show a link between FS and release of pro-inflammatory cytokines. It has been shown that children with genetic defects associated with the interleukin system were more susceptible to FS. Interleukin 1-beta levels increase the neuronal excitability by activating both glutamate and GABA and have been shown to be elevated in children with FS than those presenting with other infections. Some

[1]*Senior Lecturer in Paediatrics & Honorary Consultant Paediatric Neurologist, Faculty of Medicine, University of Colombo*

of the other pro-inflammatory mediators considered include tumour necrosis factor alpha (TNFα), interleukin 1 alpha (IL-1α) and interleukin 6 (IL-6)[5-7].

Although hyperthermia is used in animal studies as a mechanism of seizure generation, in humans there is no definite evidence to support a link between the degree of temperature or the rate of rise of temperature and occurrence of FS. This is substantiated by occurrence of FS when there is no detectable temperature. In the preliminary findings of FEBSTAT study 21% of patients presenting with febrile status epilepticus (FSE) had no temperature at the time of admission with seizure[8].

The regular use of antipyretics (acetaminophen and ibuprofen) has not been shown to be effective in preventing recurrence of FS[9-11]. This indicates that blocking the action by COX-2 and thereby production of PGE2 will not prevent FS. Instead, the interleukin generation is considered to be responsible. Therefore, over enthusiastic control of temperature during a febrile illness in children susceptible to FS is no longer recommended unless to improve the general well being of the patient.

Natural history

Febrile seizures are the commonest type of seizures affecting humans. In the USA approximately one half million febrile seizure events occur per year[12]. The reported incidence in some parts of the world are much higher particularly 6-9 % in Japan [13]. It affects both boys and girls equally, mainly between 6 and 36 months with a peak at an age of 18 months. The majority are simple febrile seizures and therefore last a shorter duration and may abort spontaneously. The risk factors for developing febrile seizures are multiple and include both genetic factors such as positive family history of FS and environmental factors such as day care attendance, specific infections such as human herpes virus 6[14], influenza A virus[15] and metapneumovirus[16], prolonged stay in a neonatal unit, neuronal abnormality and iron deficiency anaemia[17].

FS are associated with a high rate of recurrence as seen in 30% of children with FS. The risk factors for recurrence are different and include family history of febrile seizures, low temperature of < 38º C noted at onset of FS, shorter duration of fever prior to onset of FS and younger age (less than 18 months)[18]. In children with all risk factors there is a 76% chance of recurrence compared to 4% in those without any. Interestingly, high temperature is not an identified risk factor. Stringent control of temperature therefore is unlikely to prevent recurrences.

The outcome of FS appears to be related to clinical phenotype. In simple febrile seizures, which form a majority, a benign outcome has been long established from both prospective and retrospective population studies[19]. They are not associated with any long-term intellectual or behavioural adverse outcomes[20,21]. Death after FS is not reported. A recent population based cohort study concluded that there is no extra risk of long-term morbidity following simple FS[22]. The outcome in those with complex FS and FSE may be more complicated. However, such complexities are only seen in a minority.

Association between FS and mesial temporal lobe epilepsy

An association between prolonged FS and development of mesial temporal sclerosis (MTS) and mesial temporal lobe epilepsy (MTLE) has long been reported. However, this association has been based on findings from retrospective studies and those originating from surgical series on patients with refractory MTLE. Prospective studies have failed to show such an association. It is not understood whether the occurrence of prolonged febrile seizures is due to an underlying dysplastic hippocampus or whether the hippocampal swelling seen immediately after FSE is caused by the effects of prolonged seizures[23,24]. Various animal models have been used to study this association of FSE and MTS. Prolonged experimental febrile seizures in these immature rodents have been shown to cause neuronal injury in the distribution of the cell loss and gliosis seen in humans with MTS. However, unlike in humans there was no neuronal cell loss, nor evidence of neurogenesis observed in these animals and mossy fibre sprouting was minimal in these regions.

These animal studies also detected several molecular functional changes after experimental prolonged seizures. These included altered expression of hyperpolarisation-activated cyclic nucleotide gated (HCN) channels that are responsible for the hyperpolarisation-triggered cationic current which contributes to the maintenance of neuronal membrane potential, sub-threshold oscillations and dendritic integration[25]. Alteration of endocannabinoid signalling due to increased inhibition of GABA release involved in promoting hyperexcitability has also been reported[26].

The FEBSTAT study, a multicentre prospective follow up study on children presenting with FSE, was

undertaken in an attempt to address this association between prolonged febrile convulsions and subsequent MTS and MTLE. Two hundred children presenting with FSE will be evaluated with initial MRI scanning during the first 72 hours. These children will then be followed up over time for development of epilepsy and for subsequent changes in their MRIs[8].

Evaluating a patient with FS and management

The initial evaluation includes exclusion of infection in the CNS. Children should be evaluated carefully bearing in mind the atypical nature of presentation of CNS infection in the very young children. A low threshold for lumbar puncture is recommended if it occurs below the age of 12 months, is a prolonged seizure, has abnormal focal neurological signs, or is a complex febrile seizure[27].

Immediate medical management includes treatment of the seizure if still continuing. Benzodiazepines administered rectally, buccally or nasally are useful for rapid control. However, in a majority they abort spontaneously. Therefore, observation for such over the first 5 minutes is recommended. Tepid sponging or pouring water over the child is not recommended as the lowered core temperature may trigger shivering which may be misinterpreted as continuation of seizure causing unnecessary panic. These same treatment principles can be utilized when managing a recurrence. If the parents are competent, they can be taught how to administer these medications at home for a seizure lasting more than 5 minutes. This will help to reduce the number presenting with prolonged seizures. These rescue medications are specifically indicated for those children who have had an initial prolonged seizure since they are more susceptible to develop recurrences which also may be prolonged.

The most important aspect needing emphasis in the management of FS is that the majority are simple FS and have an excellent outcome. They are not associated with an increased risk of death or associated with learning disabilities or a higher association with epilepsy later in life. This needs to be conveyed to the parents and their concerns should be addressed. The most frequent parental concerns upon seeing a FS in their child were fear of death (90%), future epilepsy (45%), and recurrence (19%)[28]. The long term effects include fear during every febrile illness (40%), concern over the other siblings on occurrence of epilepsy (22%) and FS (19%). In their study a large number of parents subsequently suffered from anorexia, insomnia and fever phobia (30-40%). The parents also consider their child to be “vulnerable” to a seizure and thereby risk of death etc. at any time. This perception is referred to as the "vulnerable child syndrome", and includes a compilation of behaviours such as those mentioned above that are thought to develop as a result of this excessive parental anxiety[29]. Therefore, management of FS should include initial stabilisation of the patient and also relieving parental anxieties. The attending doctors need to spend adequate time with the parents offering them explanations and addressing their primary concerns. The objective would be to relieve the fever phobia and empower the parents to face every future febrile illness with confidence knowing the minimal harm to their child during a brief FS. Demonstrating the rescue measures and teaching them how to use rectal, nasal or buccal anticonvulsant medications are likely to help parents in coping with recurrences. Providing parents with written instructions or information leaflets would also be helpful.

There is no place for antipyretics in preventing FS. Though it may seem that control of fever should help in preventing recurrences, the role of interleukins in the seizure generation highlighted above speaks against this. Several randomized clinical controlled trials have also proven the ineffectiveness of antipyretics (paracetamol and ibuprofen)[10,11]. Use of diclofenac sodium suppositories in children is not recommended for fever control in children less than 6 years[30]. Frequent tepid sponging at the time of seizure or during a febrile illness should be avoided if it causes distress to the child.

Long term anticonvulsant therapy

Since most FS are simple and abort spontaneously the use of intermittent or long term prophylaxis is not recommended. This is due to its benign outcome and the potential toxicities of these treatments outweighing the relatively minor risks associated with a recurrence of simple FS. Medications used for long term prophylaxis include phenobarbitone which causes significant cognitive and behavioural side effects when used long term in children. Sodium valproate is also effective in preventing FS but can be associated with life threatening hepatic and pancreatic complications when used in young children. In the review by Rantala one way of determining the efficacy of these medications was to look at the number of children that need to be treated to prevent recurrences[31]. To prevent one recurrence the number required to be treated was four children for phenobarbitone and eight children with sodium valproate indicating the number of children who

would unnecessarily be exposed to these adverse effects.

Diazepam over the first 24- 48 hours of each febrile illness has been in use since 1978 for intermittent prophylaxis; however its efficacy in the meta-analysis is controversial[31]. The effective dose of 0.33 mg/kg is associated with a higher frequency of adverse effects. Drowsiness would make it difficult for the clinician to exclude underlying CNS infection. This may lead to unwarranted treatment with antibiotics as well as performing CSF evaluations. The need to treat 26 children to prevent one recurrence highlights the large amount of cumulative side effects children may experience with this treatment. In the guidelines from the American Academy of Paediatrics (AAP), use of diazepam intermittently either orally or rectally is not recommended[32].

The complex FS may behave differently to the simple FS. If a child has prolonged febrile convulsions, he may be more likely to have another prolonged seizure. In children with very frequent atypical febrile seizures, particularly those with recurrent prolonged seizures, long term treatment with sodium valproate or topiramate may be beneficial.

Summary

Majority of FS are simple and have a benign outcome in spite of its tendency for recurrences. Most of the times they abort spontaneously and therefore do not require any specialized management. Therefore, it is important to convey this relatively good prognosis to parents and alleviate their concerns.

Overzealous temperature control and long term or intermittent prophylaxis are not recommended for those with simple febrile seizures. If one has developed a prolonged FS it is important to avoid further prolonged seizures. Use of per rectal diazepam or intranasal or buccal midazolam at home may help to prevent having such prolonged recurrences.

References

1. Freeman JM. Febrile seizures: a consensus of their significance, evaluation, and treatment. *Pediatrics* 1980; **66**(6): 1009.

2. ILAE: Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia* 1993; **34**(4): 592-6.

3. Hung JJ, et al. Rotavirus gastroenteritis associated with afebrile convulsion in children: clinical analysis of 40 cases. *Chang Gung Med J* 2003; **26**(9): 654-9.

4. Dooley JM, Hayden JD. Benign febrile myoclonus in childhood. *Can J Neurol Sci* 2004; **31**(4): 504-5.

5. Heida JG, Moshe SL, Pittman QJ. The role of interleukin-1beta in febrile seizures. *Brain Dev* 2009; **31**(5): 388-93.

6. Virta M, Hurme M, Helminen M. Increased plasma levels of pro- and anti-inflammatory cytokines in patients with febrile seizures. *Epilepsia,* 2002. **43**(8): 920-3.

7. Kira R, et al. Genetic susceptibility to simple febrile seizures: interleukin-1beta promoter polymorphisms are associated with sporadic cases. *Neurosci Lett* 2005; **384**(3): p. 239-44.

8. Shinnar S, et al. Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. *Neurology*, 2008. **71**(3): 170-6.

9. El-Radhi AS, Barry W. Do antipyretics prevent febrile convulsions? *Arch Dis Chil*d 2003; **88**(7): 641-2.

10. Uhari M, et al. Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; **126**(6): 991-5.

11. van Stuijvenberg M, et al. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. *Pediatrics* 1998; **102**(5): E51.

12. Applegate MS, Lo W. Febrile seizures: current concepts concerning prognosis and clinical management. *J Fam Pract* 1989; **29**(4): 422-8.

13. Nakayama J, Arinami T. Molecular genetics of febrile seizures. *Epilepsy Res* 2006; **70 (**Suppl 1): S190-8.

14. Barone SR, Kaplan MH, Krilov LR. Human herpesvirus-6 infection in children with first febrile seizures. *J Pediatr* 1995. **127**(1): 95-7.

15. Chiu SS, et al. Influenza A infection is an important cause of febrile seizures. *Pediatrics* 2001; **108**(4): E63.

16. Peiris JS, et al. Children with respiratory disease associated with metapneumovirus in Hong Kong. *Emerg Infect Dis* 2003; **9**(6): 628-33.

17. Naveedur R, Billoo AG. Association between iron deficiency anaemia and febrile seizures. *J Coll Physicians Surg Pak* 2005; **15**(6): 338-40.

18. Berg AT, et al. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med* 1997; **151**(4): 371-8.

19. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I--Prevalence and recurrence in the first five years of life. *Br Med J (Clin Res Ed)* 1985. **290**(6478): 1307-10.

20. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioural outcomes of children with febrile convulsions. *N Engl J Med* 1998; **338**(24): 1723-8.

21. Ellenberg JH, Nelson KB. Febrile seizures and later intellectual performance. *Arch Neurol* 1978; **35**(1): 17-21.

22. Vestergaard M, et al. Death in children with febrile seizures: a population-based cohort study. *Lancet* 2008. **372**(9637): 457-63.

23. Scott RC, et al. Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. *Brain* 2003. **126**(Pt 11): 2551-7.

24. Scott RC, et al. Prolonged febrile seizures are associated with hippocampal vasogenic oedema and developmental changes. *Epilepsia* 2006; **47**(9): 1493-8.

25. Chen K, et al. Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. *Nat Med* 2001; **7**(3): 331-7.

26. Chen K, Baram TZ, Soltesz I. Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. *Nat Med* 1999; **5**(8): 888-94.

27. Provisional Committee on Quality Improvement, S.O.F.S., Practice Parameter: The neurodiagnostic evaluation of the child with a first simple febrile seizure. *Pediatrics* 1996; **97**: 769-72.

28. Parmar RC, Sahu DR, Bavdekar SB. Knowledge, attitude and practices of parents of children with febrile convulsion. *J Postgrad Med* 2001; **47**(1): 19-23.

29. Perrin EC, West PD, Culley BS. Is my child normal yet? Correlates of vulnerability. *Pediatrics* 1989; **83**(3): 355-63.

30. British National Formulary for Children. 2008, Tavistock Square, London, UK: BMJ group and RPS publishing. 590.

31. Rantala HR, Tarkka, Uhari M. A meta-analytic review of the preventive treatment of recurrences of febrile seizures. *J Pediatr* 1997; **131**(6): 922-5.

32. Steering Committee on Quality Improvement and Management, S.O.F.S. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 2008. **121**(6): 1281-6.