

Susceptibility to Febrile Seizures: More Than Just a Faulty Thermostat!

Asuri N. Prasad, Shashi S. Seshia

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A febrile seizure is generally defined for epidemiological purposes as 'an event' (i.e. a seizure) in infancy or childhood usually occurring between three months and five years of age associated with a fever, but without evidence of intracranial infection or defined cause.¹ With an incidence of about 5%,² possibly higher in some countries like Japan, febrile seizures are common in pediatric practice.

COMMENTS ON THE PAPER OF GORDON ET AL³

In the March 2009 issue of the Journal, in a paper titled 'Is temperature regulation different in children susceptible to febrile seizures?', Gordon et al explored the relationship between "the presence and magnitude of fever and susceptibility to febrile seizures, defined as a known family history of febrile seizures."³ They did not explain why they elected to re-analyze information collected between 1989 and 1991,⁴ instead of performing a more current study designed to address their objectives. They concluded their data supported the speculation of Rantala et al⁵ that "regulation of temperature is different in children susceptible to febrile seizures"; 'regulation of temperature' was not defined in either paper. We suggest evidence has not been provided to support their conclusion. We also have reservations with the assumption that a family history of febrile seizures is an unqualified marker for susceptibility to febrile seizures.

Gordon et al³ drew attention to the biases in their study. These will not be discussed with the exception of one: the measurement of temperature, the key variable in reports such as theirs. A variety of factors, especially inter- and intra-observer variability in measurement and the method used for recording, influence temperature data. These were not addressed.

Their paper is a stimulus to briefly review the factors that may contribute to febrile seizure susceptibility.

FEVER, DEVELOPMENTAL MATURATION AND FEBRILE SEIZURES

The clinically observed association between fever and the age-dependent vulnerability to febrile seizures is implicit in the definition. The peak body temperature is an important variable.⁶ Millichap opined that "seizures occurred when the degree of fever reached or surpassed the threshold convulsive temperature for each individual patient" (emphasis ours). He suggested that the factors determining this threshold were likely inherited. Experimentally too, there is an age-dependent vulnerability,⁷⁻¹¹ although the responsible factors have to be explicitly identified.

IS THE CAUSATIVE AGENT OF FEVER IMPORTANT?

Millichap postulated that the source of fever could contribute independently to febrile seizures.⁶ Until recently, the infective

agent has not generally been considered relevant for susceptibility. Now, information suggests that some viruses such as human herpesvirus-6 may have a more than chance association with febrile seizures, especially recurrent.⁷ Therefore, Millichap's suggestion⁶ needs to be investigated with renewed vigor, factoring in possible geographic differences.

NEUROBIOLOGICAL CHANGES ASSOCIATED WITH FEVER

The neurobiological changes that occur during experimentally induced hyperthermia are different from those that occur during illness related fever.¹⁰ The pyrogenic response to an inflammatory stimulus is the result of a complex series of interactions between neural, endocrine and immune systems.¹² Prostaglandins and endogenous cytokines involved in central and peripheral mechanisms responsible for the febrile reaction may have a role in causing febrile seizures.¹³⁻¹⁵ Genes coding for proteins and signaling molecules involved in thermoregulation may influence the degree and height of fever, the individual threshold for and susceptibility to febrile seizures. Evidence to support such speculation is needed.

Schuchmann et al have suggested that hyperthermia causes tachypnea which results in respiratory alkalosis in the immature brain.¹⁶ The resultant rise in brain pH enhances neuronal excitability and produces febrile seizures. The authors suggested that alterations in the pH sensitivity of mutated channels associated with well characterized epilepsy syndromes (see below) provide a potential mechanism for susceptibility in these conditions; in addition, genes coding for proteins involved in the control of respiration, could provide other candidate modifier or susceptibility genes.¹⁶

Potentially, there could be many 'needles' in the 'thermoregulatory haystack', contributing to susceptibility.

OTHER SYSTEMIC FACTORS

The issue of iron deficiency (a common early childhood problem) and susceptibility to febrile seizures¹⁷ needs further

From Pediatrics & Clinical Neurosciences, Dept. of Pediatrics (ANP), Schulich Medicine & Dentistry, Children's Hospital at London Health Sciences Centre, London, Ontario; Department of Pediatrics (SSS), Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

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Correspondence to: Shashi S. Seshia, 10 Stockton Place, Winnipeg, Manitoba, R3P 1X2, Canada.

study clinically and experimentally. Other under-explored areas include biochemical and metabolic abnormalities in patients with febrile seizures, particularly recurrent.

GENETIC INFLUENCES

The incidence of febrile seizures in 1st degree relatives of children presenting with Febrile seizures (FSs) ranges from at least 9%-22%.^{4,18-20} There is a higher concordance rate in monozygotic than dizygotic twins.^{18,21,22} Males are more susceptible than females, surely another area for further investigation.

At least six susceptibility loci have been mapped, although the causative genes have not been identified in most patients: FEB1 (8q13-q21), FEB2 (19p13), FEB3 (2q23-q24), FEB4 (5q14-q15), FEB5 (6q22-q24), and FEB6 (18p11).²³ The FEB4 locus may account for 70% of commonly encountered febrile seizure susceptibility.

Over the past decade, families with Mendelian inheritance patterns and single gene defects have been described with distinct genotype phenotype correlations. Febrile seizures, often recurring, are key features in these cases. These syndromes include: (i) generalized epilepsy febrile seizures plus (GEFS+)²⁴⁻²⁸ and (ii) Dravet syndrome.^{29,30} Ceulemans et al suggest that the clinical spectrum of SCN1A gene mutations ranges from simple febrile seizures to Dravet syndrome.³⁰ Currently, such syndromes are considered to explain only a minority of those with febrile seizures; the majority are genetically heterogeneous and of complex inheritance. Advances in population genetics studies, pooling of genetic data and the availability of haplotype mapping, should lead to identification of other susceptibility loci and modifier genes associated with febrile seizures. The study of the relative contributions of genetic variants in the coding and non coding regions of the human genome (known and unknown mutations, polymorphisms of pathogenic significance) and epigenetic factors in individuals and families with febrile seizures may provide additional clues.

Kang et al showed temperature dependent trafficking and/or accelerated endocytosis of heterozygous mutant $\alpha 1\beta 2\gamma 2$ receptors containing $\gamma 2$ subunit mutations associated with febrile seizures.³¹ They suggest that febrile seizures may be produced by a temperature-induced dynamic reduction in the expression and recycling of mutant surface GABA_A receptors in response to fever. Thus, molecular genetics is helping to not only define the clinical spectrum of febrile seizures and febrile seizure+ syndromes but is also providing insights into possible mechanisms determining susceptibility.

The report of sudden unexpected death in two members of a family who had GEFS+ with an SCN1A mutation suggests a possible association between channelopathies affecting brain and heart in families with comparable mutations.³² We speculate that gene defects could underlie the increased risk of death in (some of) those with complex febrile seizures.³³ Yet another aspect for investigation.

NEURONAL MIGRATION DISORDERS AND EARLY ACQUIRED LESIONS

In 1976, Wallace suggested that preexisting developmental defects could predispose to febrile seizures,³⁴ an opinion now

supported experimentally and neuroradiologically.³⁵⁻³⁷ Strictly, these experimental models and cases would not meet the clinical criterion for febrile seizures, as there is an underlying symptomatic cause. Nevertheless, these studies have clinical relevance, especially for complex and recurrent febrile seizures, as dysgenesis may need to be looked for diligently and microdysgenesis may only be detected by pathological examination. These issues exemplify the challenges of differentiating between idiopathic, symptomatic and cryptogenic causes for seizures, one of the areas currently being tackled by the Commission on Classification and Terminology of the International League against Epilepsy (ILAE).³⁸

SUMMARY

Febrile seizures, always a hot topic, continue to fire up the interest of a wide spectrum of clinical and basic neuroscientists. Several clinical investigators, amongst them the Halifax group (spearheaded by the Camfields to whom we owe a great debt of gratitude for their contributions in this field), have provided us with a sound foundation for clinical management. We now need to explore febrile seizures in new ways to clarify factors and identify mechanisms that contribute to the intriguing age-dependent susceptibility. The complex processes involved in thermoregulation and the febrile response are important pieces of the puzzle. The contributory factors are likely different for isolated simple febrile, recurrent febrile and complex febrile seizures. A 'systems biology approach' is needed to investigate the intricate genome-proteome-metabolome interaction in determining susceptibility. Population studies that incorporate current clinical, experimental, infectious and molecular genetic knowledge in their concept and design will help to 'conquer' the final frontiers of febrile seizures. In 2006, Engel suggested that febrile seizures could 'encompass many different entities',³⁹ an increasingly plausible opinion. A higher profile for febrile seizures and related syndromes in the ILAE classification scheme will further catalyze progress in the field. The resultant knowledge can only improve management.

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