INTRODUCTION

Febrile seizure is defined as a seizure attack associated with a febrile illness unrelated to brain infection or acute electrolyte imbalance in children older than six months without any previous history of afebrile seizure ***(Shinar, 2006; Buchbalter, 2009)***.

Febrile seizures are one of the most common neurologic problems during infancy and childhood periods, occurring in 3-4% of the children, with an excellent prognosis. They occur rarely before 6 months and after 5 years of age, with a peak incidence between 14 -18 months of age ***(Arzimanoglou, 2004).***

Febrile seizures are classified to simple (typical) and complex (atypical) types. A single seizure of <15 min duration in the presence of fever without focal features was defined as a simple FS, whereas seizures were defined as complex if they lasted >15 min, had focal features, or occurred more than once in 24 h. On the other hand, the etiology of febrile seizures is not clear. Different factors have been considered including familial (genetic) factors, prenatal factors, present acute illness, the highest degree of fever and finally, anemia ***(Shinar, 2006).***

The risk of recurrence after the first febrile seizure is about 33%, and about 9% will have three or more recurrences. The risks for recurrence are: occurrence of the first febrile seizure at a young age; family history of febrile seizures; short

duration of fever before the seizure; relatively low fever at the time of the initial seizure; and possibly a family history of an afebrile seizure. It has been observed that the time of recurrence is usually within the first year of onset. Although complex febrile seizures are not usually associated with recurrent febrile seizures, they may be a risk factor for epilepsy later in life. Febrile seizures seem to run in families, but their mode of inheritance is unknown. The risk for other siblings developing febrile seizures is about 10-20%, but may be higher if the parents also have a history of febrile seizures themselves ***(Hirtz, 2006).***

Febrile seizures usually occur in the first 24 hours of the onset of fever. It has been suggested that it is the rapid rise in the child's temperature, which causes a febrile seizure rather than the actual height of the fever itself; however, there is no substantial proof to support this suggestion. The seizures are usually generalized and tonic-clonic, but other types may be present as well. Parents may describe stiffening, jerking, apnea, cyanosis and incontinence, usually followed by drowsiness (commonly called post-ictal for short). There may be variations to this such as staring without stiffness, jerking movements without prior stiffening, and localized stiffness or jerking. Simple, benign febrile seizures should be short, usually 1 to 2 minutes, but some may be longer (up to 15 minutes). Because of the short duration, medical attention usually occurs after the seizure has ended ***(Hirtz, 2006).***

Although the diagnosis of febrile seizure is likely in a 6 month to 5 year old with fever and a convulsion, one should consider other causes such as meningitis, encephalitis, Shigella gastroenteritis, medications/toxins (such as diphenhydramine, tricyclic antidepressants, amphetamines, and cocaine), hypoglycemia, electrolyte abnormalities (that could be due to dehydration), shaken baby syndrome, accidental head trauma, and epilepsy ***(Hirtz, 2006).***

Iron deficiency is the most common cause of anemia in childhood ***(Blackwell, 2001).*** Prevalence of iron deficiency ranges from 5% to 29% of the population, with higher numbers seen in inner city and socioeconomically deprived populations ***(Boothy, 1997; Segel, 1988***). It is most common in toddlers and in the adolescent age groups (periods of rapid growth and higher potential for inadequate dietary iron) ***(Wharton, 1999)***. In infants, early introduction (at age 6 or 8 months) of whole cow's milk into the diet is clearly associated with iron deficiency anemia, and patients consuming larger amounts of milk are at higher risk of anemia ***(Boothy, 1997).*** This is due to three factors: 1) Cow's milk exerts a direct toxic effect on the intestinal mucosa of infants, leading to prolonged microscopic blood loss in the stools. 2) The caloric value of whole cow's milk is high due to fat content, decreasing the appetite and leading to less intake of potential iron-rich foods. 3) The bioavailability of iron in cow's milk is low.

Presenting signs and symptoms may be mild because of the gradual onset and the body's ability to compensate for low hemoglobin concentration. Pallor, fatigue, exercise intolerance, headache, or dizziness may be present. Physical exam may reveal pale mucus membranes and skin, especially of the palms, tachycardia with or without heart murmur, and orthostatic hypotension. Laboratory evaluation reveals a low MCV, low hemoglobin and hematocrit, low reticulocyte count, and often an elevated platelet count. The red cell distribution width (RDW), a measure of the difference in size between the smallest and largest RBCs in circulation, may be elevated, denoting a dual population of cells: small (microcytic) iron deficient cells and some normocytic cells with adequate iron. Evaluation of the blood smear reveals microcytosis and hypochromia. Serum iron is low, and total iron binding capacity (TIBC) is elevated with low % saturation. Erythrocyte protoporphyrin is increased. Low serum ferritin is diagnostic of iron deficiency, but normal levels can be misleading because ferritin is an acute phase reactant and can be falsely elevated in inflammation ***(Wharton, 1999).*** Low-normal ferritin values must be interpreted in light of clues from the history, physical, and other laboratory studies.

Iron deficiency anemia, the most common type of anemia during infancy and childhood, occurs usually between 9- 24 months of age and this period coincides with the peak incidence of febrile seizures ***(Glader, 2007).*** Iron has an important role in

multiple physiological functions of neurotransmitters. Many of the nervous system enzymes are iron-dependent for their proper activities. It has been determined that iron depletion has negative effects on neurocognitive functions of children and supplemental iron can reduce breath-holding spells. On the other hand, fever can exaggerate the negative effects of anemia on brain ***(Andrews, 2003).***

From the foregoing, the importance of febrile seizures and iron deficiency anemia cannot be ignored specially in our population. There are controversies regarding the positive and negative effects of iron on the occurrence of febrile seizures and so we decided to study the relationship between febrile seizures and iron deficiency anemia in 6-month to 5-year old children, the common age of febrile seizures.

Aim of the Work

The aim of this study to determine if iron deficiency is a possible risk factor for febrile seizures in children aging between 6 months to 5 years and to determine if it's related to the frequency of seizures or not.

FEBRILE CONVULSIONS

Definition

A febrile seizure refers to an event in infancy or childhood, usually occurring between six months and five years of age, associated with fever but without evidence of intracranial infection or defined cause ***(Millichap, 1986)***. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded from this definition. Febrile seizures are not considered a form of epilepsy, which is characterized by recurrent nonfebrile seizures ***(Millichap, 1986 and Berg et al., 2010)***.

Generally accepted criteria for febrile seizures include:

- A convulsion associated with an elevated temperature greater than 38°.5C.
- A child older than six months and younger than five years of age.
- Absence of central nervous system infection or inflammation.
- Absence of acute systemic metabolic abnormality that may produce convulsions.
- No history of previous afebrile seizures.

Febrile seizures are further divided into two categories, simple or complex, based on clinical features ***(Nelson, 1976).***

- Simple febrile seizures, the most common type, are characterized by seizures that are generalized, last less than 15 minutes, and do not recur in a 24-hour period. Since most simple febrile seizures last less than five minutes, a cutoff of 10 minutes has been proposed as a more appropriate threshold for distinguishing between simple and complex ***(Hesdorffer et al., 2010).***
- Complex febrile seizures are characterized by episodes that have a focal onset (eg, shaking limited to one limb or one side of the body), last longer than 15 minutes, or occur more than once in 24 hours ***(Berg et al., 1996).***

Note that these definitions cannot be accurately applied with regards to seizure duration if treatment (eg, rectal diazepam) is given after five minutes.

The distinction between simple and complex has prognostic implications, with most studies indicating that patients with complex features have a higher risk of recurrent febrile seizures and a slightly higher risk of future non febrile seizures.

Epidemiology

Febrile seizures are the most common neurologic disorder of infants and young children. They occur in approximately 2 to 4 percent of children younger than five years of age, with a peak incidence between 12 and 18 months. A higher prevalence has been reported in certain populations, including the Japanese (7 percent) and the Pacific Mariana

Islands (14 percent). There is a slight male predominance, with an estimated male to female ratio of 1.6:1 ***(Millichap, 1968).***

Risk factors

Febrile seizures are an age-dependent phenomenon, likely related to a vulnerability of the developing nervous system to the effects of fever in combination with an underlying genetic susceptibility. Aside from age, the most commonly identified risk factors include high fever, viral infection, recent immunization, and a family history of febrile seizures.

- ***High fever***

The maximum height of a fever, rather than the rate of rise, is the main determinant of risk in febrile seizures. This has been demonstrated in animals and confirmed in clinical studies ***(Millichap, 1956; Berg et al., 1996).*** In a study of 110 children with febrile seizures, the mean of 110 recordings with seizures was significantly higher than the mean of the 51 highest fevers unassociated with seizures (104.0°F versus 103.3°F, $p<0.001$) ***(Millichap, 1956).***

A key variable that modulates the impact of fever is seizure threshold, which varies by individual and with age and maturation. Seizure threshold is lower in infants and is modified by certain medications and water and electrolyte imbalances, especially hyponatremia ***(Millichap, 1968).***

- ***Infection***

Viral infections are commonly identified in association with febrile seizures, whereas bacterial infections are infrequent. Febrile seizures are not thought to be viral specific, but rather dependent upon the degree of temperature elevation. Viral infections associated with high fever, such as human herpesvirus 6 (HHV-6) and influenza, appear to pose the highest risk ***(Shah et al., 2002)***.

HHV-6 is the virus most frequently associated with febrile seizures in the US and has been identified in one-third of all first-time febrile seizures in US children up to two years of age ***(Hall et al., 1994).*** In a European study, HHV-6 was isolated in 35 percent of children with febrile seizures, adenovirus in 14 percent, respiratory syncytial virus in 11 percent, herpes simplex virus in 9 percent, cytomegalovirus in 3 percent, and HHV-7 in 2 percent ***(Bertolani et al., 1996).***

The preponderance of HHV-6-associated febrile seizures is linked to the unusually high fevers associated with HHV-6 infection ***[Millichap, 2008].*** The mean maximum fever in infants with primary HHV-6 infection is generally 39.5°C (103°F) or higher, and the incidence of febrile seizures associated with primary infection has been estimated to be as high as 36 percent in the 12 to 15 month age group ***(Hall et al., 1994).*** This may be an overestimate of the actual risk, however, since children with milder infections were likely underrepresented in the sampled emergency department

population. In one community-based cohort study in which children's saliva was tested weekly for HHV-6 DNA for the first 24 months of life, only one-third of children with a well-defined acquisition were seen by a clinician ***(Zerr et al., 2005).*** Febrile seizures associated with HHV-6 have been associated with an increased rate of complex features, recurrence, and febrile status epilepticus ***(Hall et al., 1994; Suga, 2000).***

In Asia, influenza A virus is most commonly isolated in children with febrile seizures, accounting for 20 percent of cases in a Hong Kong study ***(Epstein et al., 2012).*** Parainfluenza (12 percent) and adenovirus (9 percent) were also common. In a separate hospital-based case-control study, the incidence of febrile seizures in children requiring admission for a viral illness was similar with influenza, adenovirus, and parainfluenza infections (6 to 18 percent), and somewhat less common with respiratory syncytial virus and rotavirus (4 to 5 percent). These viral infections were the cause of fever in children with febrile seizures, and they occurred with the same frequency in a control group of patients with fever but without seizures ***(Chiu et al., 2001).***

Except for the common association of HHV-6 or influenza A virus, the type of viral infection is not important in predicting future recurrence of a febrile seizure or a complex febrile seizure. A specific neurotropism or central nervous system (CNS)-invasive property of HHV-6 and influenza A

viruses and bacterial neurotoxin (*Shigella dysenteriae*) are implicated but unproven ***(Millichap, 2006).***

Seizure recurrence may be caused by a reactivation of the HHV-6 virus and a mild and transitory encephalitis, a theory that is an exception to the accepted definition of a febrile seizure. Multiple factors may be involved, including a proinflammatory cytokine and immune response to infection ***(Chiu et al., 2001).***

- ***Immunization***

The risk of febrile seizures is increased after administration of certain vaccines, including diphtheria, tetanus toxoid, and whole-cell pertussis (DTP), measles, mumps, and rubella (MMR), although the absolute risk is small. The risk varies according to vaccine preparation and age when the vaccine is administered ***(Barlow et al., 2001).***

For DTP immunization, the risk of febrile seizure is highest on the day the vaccine is administered (when fever tends to occur) and varies by preparation. DTP has been associated with an increased risk on the day of vaccination (adjusted relative risk [RR] 5.7) only, with an absolute risk estimated at 6 to 9 per 100,000 children ***(Barlow et al., 2001).*** Combination diphtheria, tetanus toxoid, and acellular pertussis (DTaP)-inactivated polio (IPV)-*haemophilus influenzae* b (Hib) vaccine has also been associated with a three- to six fold increased risk of febrile seizure on the day of the first and second doses, although the absolute risk is small (<4 per

100,000 vaccinations) ***(Sun, 2012).*** In contrast, in a cohort of more than 430,000 children who received DTaP alone, there was no increase in risk of seizures within zero to three days after vaccination ***(Huang, 2010).***

The occurrence of a febrile seizure within three days of DPT vaccination is considered a precaution to administration of subsequent doses of the vaccine, but the risk of recurrence is not well studied. Decisions about repeat vaccination should be individualized and take into account the presence of certain factors (eg, a pertussis outbreak) where the benefits of immunization outweigh the risks.

In comparison with DPT, the risk of febrile seizures related to MMR vaccination is slightly higher and peaks later, 8 to 14 days after vaccination. The absolute risk associated with MMR vaccination was estimated at 25 to 34 per 100,000 children in one large study ***(Barlow et al., 2001).*** Among children age 12 to 23 months, MMR-varicella (MMRV) combination vaccine is associated with an approximately twofold higher risk of febrile seizures than MMR and varicella vaccines given separately. Nonetheless, the absolute risk of febrile seizures with MMRV in this age group is still quite low (approximately 40 per 100,000 children) ***(Klein et al., 2010; Marin et al., 2010)***.

Age at time of vaccine administration is also important. The risk of fever and seizure following a measles-containing vaccine is significantly lower when administered at age 12 to

15 months than at 16 to 23 months ***(Rowhani, 2013; Hambridge et al., 2014).*** The second dose of MMR/ MMRV, administered to children between four to six years of age, has not been associated with an increased risk of febrile seizures ***(Davis et al., 1997; Klein et al., 2010).***

- ***Genetic susceptibility***

A genetic predisposition to febrile seizures has long been recognized, although the exact mode of inheritance is not known in most cases. Among first-degree relatives of children with febrile seizures, 10 to 20 percent of parents and siblings also have had or will have febrile seizures. In addition, monozygotic twins have a much higher concordance rate than do dizygotic twins, in whom the rate is similar to that of other siblings.

Susceptibility to febrile seizures has been linked to several genetic loci in different families, including the long arm of chromosome 8q13-21 (FEB1) ***(Wallace et al., 1996)***, chromosome 19p (FEB2) ***(Johnson et al., 1997 Kugler et al., 1998),*** chromosome 2q23-24 (FEB3) ***(Peiffer et al., 1999)***, and other loci ***(Nakayama et al., 2002; Nakayama et al., 2004).*** The trait is transmitted in an autosomal dominant pattern with reduced penetrance or as a polygenic or multifactorial model ***(Feenstra et al., 2014).*** In one study, heterogeneous R43Q mutations of the *GABRG2* gene, located on the long arm of chromosome 5, occurred significantly more often in patients with febrile seizures than controls (36 versus 2 percent). Family history of febrile seizures and epilepsy was significantly higher

in the study group than in controls, but the homozygous mutation carrier status was not different ***(Hancili et al., 2014).***

In a large genome-wide association study, isolated febrile seizures were associated with common genetic variants in loci containing the sodium channel genes, *SCN1A* and *SCN1B,* among others. In the same study, two loci were specifically associated with MMR-related febrile seizures, including one locus containing an interferon-stimulated gene and another correlating with the measles-specific immune response ***(Feenstra et al., 2014).***

In some patients and families, the propensity for febrile seizures is an early manifestation of generalized epilepsy with febrile seizures plus (GEFS+), a genetic epilepsy for which a variety of causative mutations have been identified. Severe myoclonic epilepsy of infancy (Dravet syndrome) is another genetic epilepsy with a well-known preponderance for seizures with fever in early childhood.

Hippocampal abnormalities are identified in some patients and families with febrile seizures and may be a link to genetic factors and risk of future temporal lobe epilepsy ***(Fernández et al., 1998).*** Developmental abnormalities of the hippocampus, including hippocampal malrotation, have also been reported in 10.5 percent of children presenting with febrile status epilepticus ***(Scheffer et al., 2007).***