DOI: 10.7860/NJLM/2017/23271:2188

Original Article

Biochemistry Section

Febrile Seizures – Can Vitamin C Act as Prophylactic Agent?

IYSHWARYA UDAYA KUMAR, ARUNA KUMARI

ABSTRACT

Introduction: Febrile convulsions are defined as seizures in children between 6 months to 5 years of age, accompanied with fever, but without evidence of underlying CNS infection. The incidence is about 2-5% in the population. The exact pathogenesis is unknown involving various factors. Febrile seizures may be caused due to significant oxidative stress, and along with oxidant status changes. This results in cell damage subsequent to febrile seizures.The high rate of oxidative metabolism, coupled with the low antioxidant defense, makes the brain highly vulnerable to free radical damage.

Aim: This study was done to evaluate the oxidative stress and antioxidant status in healthy children and children with febrile seizures.

Materials and Methods: The children were divided into two groups –

1. Children without febrile seizures
2. Children with febrile seizures.

Malondialdehyde and vitamin C levels were assessed in both groups (30 in each group).

Result: Malondialdehyde was significantly increased ($p < 0.01$) in children with febrile seizures compared to the other group and Vitamin C was significantly decreased ($p < 0.001$) in febrile seizures children compared to the other children group.

Conclusion: The antioxidants have the ability to reduce the febrile seizure manifestations and thus the accompanying biochemical changes like the markers of oxidative stress. This makes the antioxidants (vitamin C) role possible in controlling febrile seizure.

Keywords: Antioxidant, Malondialdehyde, Oxidative stress

INTRODUCTION

Febrile seizures (FS) are the most common seizures seen in the pediatric population in OPD and emergency department settings, and they account for the majority of seizures seen in children younger than 5 years old [1].

Young children are most likely to experience febrile seizures. FS are the most common type of convulsions in infants and young children. Recurrent episodes of febrile seizures are likely to occur in those children if the prophylactic therapy is not given after the first episode of febrile seizures [2].

A febrile seizure is defined as a seizure occurring in a neurologically healthy child between 6 months and 5 years of age [3]. The National Institute of Health defined febrile seizures as "an event in infancy or childhood usually occurring between 3 months to 5 years, associated with fever and not having any intracranial infection or defined cause for the seizure" [4].

Approximately, FS occurs in 2% - 4% of young children in the United States, South America, and Western Europe. The Occurrence is reported to be even more common in Asian countries. Based upon many prospective studies, it is determined that the first FS is complex in around 20% of cases and usually in 2nd year of life. Males are slightly more prone than females [5].

Febrile seizures are classified as simple and complex [Table/Fig-1].

Simple (All of the following)	Complex (Any of the following)
• Duration of less than 15 minutes • Generalized • No previous neurologic problems • Occur once in 24 hours	• Duration of more than 15 minutes • Focal • Recurs within 24 hours

[Table/Fig-1]: Classification of febrile seizures [6].

Most often whenever the temperature rises above 101°F (38.3°C), it may result in febrile seizures lasting only for few minutes. Even though the febrile seizures episode may last less than 15 minutes, and may not cause any long term health problems, but still it makes the parents very frightened [7]. Rarely febrile seizures cause brain damage. There are no documented cases of febrile seizure-related deaths on record (excluding developing countries). Numerous reviews and updates have explored the history, treatment and complications of febrile seizures [8].

Family history of febrile and of unprovoked seizures, socio-demographic characteristics, daycare use, developmental delay, discharge from a neonatal unit after 28 days, day care attendance, maternal smoking during pregnancy, viral infections, certain vaccinations, and certain mineral deficiencies (iron and zinc) are all considered as risk factors for FS.

Risk factors and risk of recurrence after an initial febrile seizures are provided in the [Table/Fig-2]. The risk of recurrence is similar between simple and complex febrile seizures [9-18].

The exact pathogenesis is not well understood but it involves several factors like genetic predisposition, changes in the levels of neurotransmitters. Generation of oxidative free radicals is increased in many pathological conditions. The cellular constituents and biomolecules are subjected to free radical attack. Polyunsaturated Fatty Acids (PUFA) present in cell membranes are readily attacked by oxygen free radicals. The oxidative destruction of PUFA is known as lipid peroxidation. Lipid peroxidation has been implicated in a wide range of tissue injuries and diseases. The free radical mediated destruction of proteins may lead to structural loss of the enzymes or enzymatic deactivation may occur. Similarly, there are changes occurring in nucleic acids like base hydroxylation, mutation or even cell death [19].

Complex febrile seizure
Family history of epilepsy
Fever duration < 1 hour before seizure onset
Neurodevelopmental abnormality (e.g., cerebral palsy, hydrocephalus)

[Table/Fig-2]: Risk factors for future epilepsy after a febrile seizure [8].

Free radicals are involved in the pathogenesis of various diseases, including atherosclerosis, stroke, epilepsy and inflammatory diseases. The most important effect of free radicals is lipid peroxidation. The effect of increased lipid peroxidation is disruption of cell membranes. Significant oxidative stress and changes in oxidant status may be a step along the way to cell damage, leading to febrile seizures [20].

OBJECTIVES

The present study was aimed to investigate the possible free radical mediated injury in children with febrile seizures by measuring the oxidative stress.

Oxidative stress is assessed by measuring Malondialdehyde (MDA), which is a marker and a product of lipid peroxidation. The study also included the assessment of the non-enzymatic antioxidant Vitamin C in children with febrile seizures, which prevent oxidative damage and scavange or neutralize free radicals which are produced in disease processes.

MATERIALS AND METHODS

It was a case-control study. This study was carried out in the Department of Pediatrics, tertiary care hospital in Andhra Pradesh, India. A pilot study was done initially, which helped us in calculating the sample size. The study duration was 6 months. Institutional ethical committee approval was obtained for the study. A total of 30 children with febrile seizures and 30 healthy children were enrolled in the study. 70% of them were girls and 30% were boys. Around 56% of children with febrile seizures were between <2 years of age, 20% were between 2-3 years, 13% between 3-4 years, 10% between 4-5 years of age. Informed consent was taken from the parents of these 60 children.

Inclusion Criteria

- Children with febrile seizures between 6 months to 5 years of age.
- Healthy children (age matched).

Exclusion Criteria

- Children with CNS infections.
- Previous history of afebrile seizures.
- Underlying CNS abnormality.
- Febrile seizures occurring < 6 months or >5 years of age.

Blood samples were collected through vein puncture under aseptic precautions, 5 ml of blood was collected in an EDTA vacutainer from the controls and the children with febrile seizures. Of which, 1 ml of blood was used for the estimation of malondialdehyde by the thiobarbituric acid method. On centrifuging the rest of the sample, plasma was obtained and separated for the analysis of antioxidant like vitamin C (ascorbic acid) by the Evelyn and Malloy method.

Estimation of Malondialdehyde (MDA) [21]: This reaction depends on the formation of a pink colored complex between malondialdehyde and thiobarbituric acid (TBA), having a maximum absorption at 532 nm using a spectrophotometer.

Estimation of Plasma Vitamin C [22]: When 2,6-dichlorophenol indophenol reacts with ascorbic acid, it forms reduced 2,6-dichlorophenol indophenol, which is colorless. The color obtained is proportional to the concentration of ascorbic acid present in the solution. Decreased color indicates low concentration of ascorbic acid. The optical density was measured at 520nm using a spectrophotometer.

STATISTICAL ANALYSIS

Statistical analysis of all the obtained parameters in children with febrile seizures and the control healthy groups were done using unpaired students 't' test.

RESULTS

[Table/Fig-3] shows the mean and standard deviation of oxidant and anti-oxidant levels in controls and in febrile seizures.

	MDA (nm/ml) (Mean ± SD)	Vitamin C mg/dl (Mean ± SD)
Controls (n = 30)	2.63 ± 1.30	0.88 ± 0.14
Cases (n = 30)	3.84 ± 1.09	0.48 ± 0.10
p-value	< 0.01	< 0.001

[Table/Fig-3]: MDA and vitamin C levels in controls and in febrile seizure groups.

Children with febrile seizures showed significantly increased levels of MDA ($p<0.01$). The mean value of MDA was 2.63nm/ml in controls and 3.84nm/ml in cases.

The levels of vitamin C were also significantly decreased in children with febrile seizures ($p<0.001$), mean value was 0.88 mg/dl (controls) and 0.48 mg/dl (cases).

DISCUSSION

Oxidative stress is a shift in the equilibrium between reactive oxidant species and antioxidant defense mechanisms in favor of reactive oxygen species. Oxidative stress is implicated in the pathophysiology of neurological disorders such as epileptic seizures, stroke, neurodegenerative disorders and neurotrauma. Disruption of cell membranes and their destruction occurs due to lipid peroxidation, which again is because of oxidative stress [23].

The high metabolic demand, high polyunsaturated fatty acid content, poor repair capacity, and high iron load makes our brain sensitive to oxidative damage. Although it is well known that epileptic seizures cause oxidative stress, the effect of febrile seizures on oxidative balance is not clear.

Malondialdehyde, an indicator of lipid peroxidation and oxidative stress, is the end product of polyunsaturated fatty acid peroxidation. PUFA are essential for cell membranes and for some organelles, including mitochondria and endoplasmic reticulum. Increased amounts of malondialdehyde reflect loss of fatty acids, which leads to cell membrane damage and cell death. In an investigation of the effects of febrile and afebrile seizures on oxidant state in children, Akarsu et al., [13] found increased plasma malondialdehyde levels in children experiencing febrile seizures.

When the balance between the free radicals produced and anti-oxidant protective defense system is damaged, it then results in tissue damage. Many antioxidants like vitamin C, vitamin E, vitamin A, uric acid, bilirubin, etc., contribute greatly to the body's defensive system [24].

The mean level of vitamin C was decreased significantly in cases compared to controls. The lowered levels of vitamin C are due to its enhanced consumption because of increased oxidantive stress caused by free radicals which indicates asynchrony between oxidants and antioxidants in febrile seizures. Vitamin C level has been found low in acute infectious diseases, fever, stress, etc. Vitamin C works on several levels to eliminate viruses, bacteria and toxins from the body, thus reducing fever and symptoms. It strengthens and nourishes the body, so it can handle the invaders. This also helps the weakened body, and thus prevents the febrile seizures. Vitamin C affects system to help prevent seizures caused by fever [25]. Vitamin C has some role in preventing febrile seizures if given during the fever or prophylactically. The supplementation of Vitamin C may prevent febrile seizures [26].

LIMITATIONS

Smaller study group and short study duration are few limitations of the study.

CONCLUSION

The children with febrile seizures have an imbalance between the oxidant-antioxidant systems.

Oxidative stress is considered as one of the mechanisms that could independently contribute to the disease progression, in addition to serving as processes that underlie neuronal injury. It could also cause mitochondrial dysfunction, cell damage and consequently seizures. Febrile seizures are due to an imbalance in the oxidants and anti-oxidants system, which causes lipid peroxidation and eventually to neuronal damages.

Vitamin C plays a promising role in the prevention of febrile seizures. It is better to give it prophylactically.

Vitamin C has the capacity to turn the invading particles into an oxidized particle inside the body. Hence, it is necessary to continue vitamin C supplementation even after the symptoms subsides, in order to remove these damaged particles. The amount of vitamin C required depends upon the amount of oxidation and infection.

Further large group studies are required to evaluate the role of vitamin C prophylaxis in the prevention of febrile seizures and its role in decreasing the episodes and subsequent cell damages caused by febrile seizures.

REFERENCES

[1] Smith R, Martland T, Lowry M. Children with seizures presenting to accident and emergency. *Emergency Medicine Journal*. 1996;13(1):54-58.
[2] Khair AE, Imagrabi D. Febrile seizures and febrile seizure syndromes: an updated overview of old and current knowledge. *Neurology Research International*. 2015;2015:01-07.
[3] Chung S. Febrile seizures. *Korean J Pediatr*. 2014; 57(9): 384–395.
[4] Donner E. Febrile seizures. *Epilepsy Research*. 2002;50(3):223-334.
[5] Deborah G. Hirtz. Febrile seizures. *Pediatrics in Review*.1997;18(1):05-09.
[6] Millar JS. Evaluation and treatment of the child with febrile seizure. *Am Fam Physician*. 2006;73(10):1761.

[7] Parmar RC, Sahu DR, Bavdekar SB. Knowledge, attitude and practices of parents of children with febrile convulsion. *J Postgrad Med*. 2001;47:19-23.
[8] Gordon KE, Dooley JM, Camfield PR, Camfield CS, MacSween J. Treatment of febrile seizures: the influence of treatment efficacy and side-effect profile on value to parents. *Pediatrics*. 2001;108:1080-88.
[9] Satish Kumar D, Vishali V, Indumati V, Kodliwadmath MV, Deveranavadgi BB. Oxidative stress and antioxidants in CRF patients before and after dialysis. *J Clin Diag Res*. 2010;(4):2752-56.
[10] Gunes S, Dirik E, Yis U. Oxidant status in children after febrile seizures. *Pediatr Neurol*. 2009;40:47- 49.
[11] Placer ZA, Linda L, Crushman JBC. Estimation of product of lipid peroxidation (MDA) in biochemical system. *Annal Biochem*. 1966;16:359-64.
[12] Evelyn KA, Malloy HT, Rosen C. The determination of ascorbic acid in urine with the photoelectric colorimeter. *J Biol Chem*. 1938;126:645-54.
[13] Akarsu S, Yilmaz S, Ozan S, Kurt A, Benzer F, Gurgoze MK. Effects of febrile and afebrile seizures on oxidant state in children. *Pediatr Neurol*. 2007;36:307-11.
[14] Berg AT, Shinnar S, Darefsky AS, et al. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med*. 1997;151(4):371-78.
[15] Gururaj A. Predictors of Febrile Seizure: A matched case-control study. *Journal of Tropical Pediatrics*. 2001;47(6):361-62.
[16] Stockman J. Which characteristics of children with a febrile seizure are associated with subsequent physician visits? *Year book of Pediatrics*. 2006;2006:353-54.
[17] Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev*. 2005;(4):CD004407.
[18] Ganesh R, Janakiraman L. Serum zinc levels in children with simple febrile seizure. *Clin Pediatr* (*Phila*). 2008;47(2):164-66.
[19] Hartfield DS, Tan J, Yager JY, et al. The association between iron deficiency and febrile seizures in childhood. *Clin Pediatr* (*Phila*). 2009;48(4):420-26.
[20] Vestergaard M, Hviid A, Madsen KM, et al. MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. *JAMA*. 2004;292(3):351-57.
[21] Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. *Indian Pediatr*. 2010;47(5):437-39.
[22] Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. *Arch Dis Child*. 2007;92(7):589-93.
[23] Laina I, Syriopoulou VP, Daikos GL, et al. Febrile seizures and primary human herpesvirus 6 infection. *Pediatr Neurol*. 2010 Jan;42(1):28-31.
[24] Machlin LJ. Free radical tissue damage: protective role of antioxidant nutrients. *FASEB J*. 1987;(1):441-45.
[25] Barlow WE, Davis RL, Glasser JW, et al. Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med*. 2001;345(9):656-61.
[26] Kruzel Thomas. Natural Medicine Pediatric Home Health Advisor. 2012.pages:78-79.

AUTHOR(S):
1. Dr. Iyshwarya Udaya Kumar
2. Dr. Aruna Kumari

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biochemistry, The Oxford Medical College, Hospital & Research Centre, Bangalore, Karnataka, India.
2. Professor, Department of Biochemistry, Karpaga Vinayaga Institute Of Medical Sciences, Madurantagam, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Iyshwarya Udaya Kumar,
The Oxford Medical College, Hospital & Research Centre,
Department of Biochemistry, Attibele,
Bangalore-562107, Karnataka, India.
E-mail: iyshwarya.fun@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Publishing: **Jan 01, 2017**