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OXIDATIVE STATUS AND APOPTOSIS IN INFANTS AND CHILDREN WITH FEBRILE SEIZURE

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ABSTRACT

Objective : To assess the oxidative status and apoptosis in infants and children with febrile seizure. **Methods:** This study includes all children having a febrile seizure either simple or complex. They were 40 patients and twenty children as control. Blood sample was taken from the patients to measure serum total anti-oxidant capacity, MDA, soluble Fas-L. Data was analyzed using SPSS 16. **Results:** We found that children with FS had significantly higher oxidative stress levels (higher MDA 33.41 ± 10.36 nmol/ml and lower TAC median=0.55 Mm/L) ($p \leq 0.001$) & higher evidence of apoptosis at diagnosis (Median sFas-L 150 ng/L) ($p=0.003$) than control group. **Conclusion:** the present work provides evidence for the increase in

oxidative stress (higher MDA, lower TAC) and apoptosis (higher s Fas-L) when compared with control. Infection or fever per se may affect oxidative stress and apoptosis; which in their turn may cause and complicate FS. An inverse relationship between TAC and MDA leading to oxidative stress in FS. A correlation between oxidative stress and apoptosis.

Keywords : Febrile Seizure, Oxidative stress, Malondialdehyde, total antioxidant capacity, apoptosis.

Abbreviations : FS: Febrile seizure MDA: malondialdehyde ROS: reactive oxygen species sFas-L: soluble fas ligand TAC: total anti-oxidant capacity TNF: tumor necrosis factor TNF-R: tumor necrosis factor receptor

INTRODUCTION

Febrile seizure is the most common cause of convulsion in infants and children (*Karande, 2007*); defined as convulsion occurring between 6 months and 5 years of age (mostly at 14-18 months) (*Johnston, 2007*), associated with fever without presence of intracranial infection or a cause for the seizure (*Ganesh and Janakiraman; 2008*).

Febrile seizures are divided into simple (85% of febrile seizures) and complex/atypical types (*Ganesh and Janakiraman; 2008*).

Simple FS rarely affects the brain (*Shinnar and Glauser, 2002*). However, prolonged FS, may lead to mesial temporal sclerosis causing mesial temporal lobe epilepsy which is the most common cause of the refractory epilepsies (*Engel, 2001*).

The pathophysiology of FS is still largely unknown: The cytokines play important role in the generation of FS (*Heida et al; 2009*). Genetic factors may have a role (*Sadleir and Scheffer, 2007*), micronutrient deficiency, in addition to the effect of hyperthermia on neuronal excitability

and chemical transmitters beside reactive oxygen free radicals (*Guñes et al; 2009*) & apoptosis (*Xu et al; 2007*).

Febrile seizures diagnosis is clinically after exclusion of other causes of seizure, however; EEG & neuroimaging are requested in certain conditions (*McBride, 2012*).

Oxidative stress is defined as unbalanced equilibrium between ROS, resulting from any normal or abnormal metabolic processes in the body, and the antioxidant defense mechanisms leading to biological damage of cellular lipids, proteins, DNA or Carbohydrates & cell death (*Fiore et al; 2005*).

Free radicals are molecules containing one or more unpaired electrons in atomic orbitals (*Halliwell and Gutteridge, 1999*). Free radicals are extremely reactive, so they have a very short half-life.

Generation of ROS causes damage of polyunsaturated fatty acid residues of phospholipids, which are extremely sensitive to oxidation. The major aldehyde products of lipid peroxidation are: Malondialdehyde Hy-

droxynonenal & Isoprostanes (*Stocker and Keaney, 2004*).

Antioxidants may be enzymatic as superoxide dismutase and non-enzymatic antioxidants as Vitamin C & Selenium (*Valko et al., 2004*).

For assessment of the oxidative stress status in vivo, researchers measure molecular products resulting from the reaction of ROS with biomolecules, which are generally considered more stable than ROS themselves, including lipid peroxidation end products as MDA, or antioxidant enzymes and molecules as superoxide dismutase, selenium, total antioxidant capacity (*Dalle-Donne et al., 2006*).

Oxidative stress has a very important role in FS, proved by *Akarsu et al.; 2007* who found increased plasma & erythrocytes malondialdehyde levels in children experiencing febrile seizures; in addition to elevation of plasma nitric oxide & Glutathione peroxidase, however, decreased amounts of superoxide dismutase after febrile seizures due to its consumption. After recurrent or prolonged febrile seizures, the ultrastructure of specific organelles

(mitochondria and endoplasmic reticulum) changes, and these changes lead to brain damage (*Yang and Qin; 2004*).

Neuronal vulnerability is an important factor for seizure-induced oxidative damage (*Patel and Li; 2003*).

In conclusion neuronal cell death may be both a cause and a consequence of seizures (*Patel; 2002*).

Apoptosis is a controlled & mostly reversible process of programmed cell death that usually doesn't induce inflammatory reaction, it occurs through genetically defined & sequential series of events that terminate cell survival by 'cellular suicide' which differentiate it from necrosis (*Ziegler and Kung, 2008*).

Apoptosis is an essential physiological process throughout the life important both in development and in the maintenance of tissue homeostasis (*Testa, 2004*). The defect in apoptosis can result in various pathological states, as malignant transformation and neurodegenerative diseases (*Okada and Mark, 2004*).

Apoptosis is controlled by numer-

ous proteins and protein complexes that when activated by various stimuli (initiator caspases), induce sequential activation of the effector caspases. There are at least 2 major pathways of caspase activation; the receptor-mediated (outer/extrinsic) apoptosis pathway where the TNF family of death receptors as TNF-R & Fas, activate upstream caspase-8 (*Hengartner, 2000*). The TNF-R family proteins are characterized by the presence of cysteine-rich extracellular domains that mediate binding between ligands as (TNF- α & Fas ligand) and these receptors (*Ashkenazi and Dixit 1998*).

The second pathway is the mitochondrial-mediated (intrinsic) apoptosis pathway where cytochrome C is released from the mitochondria and activates upstream caspase-9. Both pathways culminate in the activation of a major downstream effector caspase—caspase-3 (*Hengartner, 2000*). A third minor pathway of caspase activation involving granzyme B / perforin (*Hengartner, 2000*).

The most sensitive and surest way to detect apoptosis is the measurement of enzymes and proteins in-

involved in the apoptotic process (*Distelhorst and Shore; 2004*).

Xu et al; 2007 studied the role of apoptosis in the genesis and epileptogenesis of MTS on a molecular level, through studying the expression of bcl-2, p53, fas and caspase-3 genes in resected sclerotic hippocampi from patients with refractory MTLE, which could be a process of the disease itself or may be induced by seizures. Ten of them had febrile convulsions in early childhood.

There is a great relation between apoptosis & oxidative stress; the cellular redox environment plays an important role in signal transduction, enzyme activation, DNA and RNA synthesis, cell proliferation, differentiation and apoptosis (*Moriai et al., 2001*). Induction or inhibition of cell proliferation seems to be dependent on levels of oxidants/antioxidants in the cell. Apoptosis is induced by moderate oxidizing stimuli and antioxidant acting as defense mechanisms preventing apoptosis (*Valko et al., 2006*).

Oxidative stress following ischemia or seizures can cause severe endothelial cell injury (*Lin et al;*

2006). Exposure of endothelial cells to TNF- α may result in endothelial dysfunction. TNF- α induce endothelial death through generation of ROS especially hydrogen peroxide and peroxynitrite (*Corda et al; 2001*).

SUBJECTS AND METHODS

This study includes all children who, within the preceding 6 hours, had experienced a febrile seizure either simple or complex, attending the outpatient clinic and emergency department of Mansoura University children's hospital & fulfilling the inclusion criteria in the period from February 2011 to December 2012. They were 40 patients; whose ages ranging from 6 months to 5 years. Twenty children of matched age, sex and socioeconomic status were included in the study as a control group, with no history of seizures or neurological disorders. Blood sample was taken from the patients to measure serum TAC, MDA, soluble Fas-L.

STATISTICAL ANALYSIS

Data was analyzed using SPSS 16; parametric data were expressed in mean \pm standard deviation. Non

parametric data were expressed in median, minimum and maximum. Normality of data was first tested by one sample K-S test. In addition, Mann-Whitney was used to compare continuous variables in two different groups. Chi-square tests were used to compare the categorical variables between both cases and controls. P value < 0.05 was considered as statistically significant.

RESULTS

In our study, the median age of cases was 24.66 months, ranging from 5 & 60 months. The Median age of control was 30 months, ranging from 9 & 54 months. There was male predominance in cases (60%) & in control (65%). There was no statistically significant difference between case and control group as regards age and sex.

We found that children with FS had significantly higher oxidative stress levels (higher MDA 33.41 ± 10.36 nmol/ml and lower TAC median=0.55 Mm/L) ($p \leq 0.001$) & higher evidence of apoptosis at diagnosis (Median sFas-L 150 ng/L) ($p=0.003$) than control group as shown in tables (1&2).

Table (1) Comparison of patients versus control as regards: basal serum sFas-L, TAC

Variable	Patients n=40	Control n=20	Tests of significance
Serum sFas-L (ng/L) (Median) (minimum -Max)	150 (30-780)	85 (30-300)	*0.003
Serum TAC (Mm/L) (Median) (minimum -Max)	0.55 (0.1-1.9)	1.55 (0.2-2.2)	* ≤ 0.001

- p value is statistically significant if < 0.05 .

Table (2): Comparison of basal serum MDA levels between patients & control:

Variable	Patients n=40	Control n=20	Tests of significance
Serum MDA(nmol/ml) Mean \pm SD	 33.41 \pm 10.36	 7.2 \pm 2.2	*p ≤ 0.001 **t=15.27

- * p value is statistically significant if < 0.05 .

DISCUSSION

In our study, we found children with FS had significantly higher oxidative stress (higher MDA and lower TAC) ($p \leq 0.001$) than control. Similar finding was reported by *Akarsu et al.; 2007* who found that plasma & erythrocytes MDA increased in children with FS compared with the control group.

Tsai et al; 2010 stated that the role of MDA in the oxidative damage of seizures is uncertain.

Abuhandan et al; 2013 found that the total antioxidant status values of febrile seizure group were found to be statistically significant low compared to values of the control group.

Oxidative stress is considered a cause & result of FS; fever per se changes tissue redox state through lipopolysaccharides, the primary element of bacterial cell wall, in addition to induction of proinflammatory cytokines, activated macrophages and other leukocytes to secrete reactive oxygen/nitrogen species (*Hou et al; 2011*). Also, hyperthermia-induced disruptions of mitochondrial oxidative phosphorylation and coupling may promote apoptosis not only by ag-

gravating an energy stress, but also by increasing ROS production (*Venkataraman et al., 2004*).

The most important effect of oxidative stress is lipid peroxidation, leading to excess MDA (*Stocker and Keaney, 2004*), causing disruption and destruction of cell membrane lipids, proteins and DNA. Although the brain produces high amount of ROS, owing to high aerobic metabolism, it is very sensitive to oxidative injury (*Naziroglu et al; 2008*) due to its high polyunsaturated fatty acid content, poor repair capacity, and high iron load (*Patel; 2002*).

Elevated levels of free radicals and ROS can in turn exacerbate mitochondrial dysfunction, including inactivation of complex I (*Riobo' et al., 2001*). Free radicals can induce DNA damage that leads to apoptosis (*White et al; 2007*). Furthermore, inflammation response-associated hypoxia stimulated glutamate release, which caused excitotoxicity of cells by increasing extracellular Ca^{2+} .

Seizure itself may cause oxidative stress as it elevates brain production of ROS (*Tsai et al; 2010*) in addition to deficiency of enzymatic and non-

enzymatic antioxidants leading to oxidative stress, causing damage cellular lipids, proteins or DNA, resulting in inhibition of their normal function (Valko *et al.*, 2007).

In this study, higher evidence of apoptosis (increase sFas-L, used as apoptosis marker) was found in FS cases at diagnosis than control group ($p=0.003$). Tan *et al.*; 2001 found an increased Fas due to apoptosis in an epileptic animal model. Straussberg *et al.*; 2001 stated that in children with histories of febrile convulsions, there was evidence of apoptosis (TNF- α levels in blood were steadily elevated) due to increased its production by the brain during sustained epileptic seizures in animal models. However, Lee *et al.*; 1999 reported that no significant relationship was found between TNF- α as a marker of apoptosis in children with febrile convulsions & controls.

Apoptosis may be a cause or result of FS: Many theories explain apoptosis in FS through two pathways (Straussberg *et al.*; 2001) especially intrinsic; relative hypoperfusion (Kreisman *et al.*; 1991), pathological neuronal activity might also induce

mitochondrial dysfunction and ROS production, chronic hypometabolism (Casse *et al.*; 2002). Excessive heat exposure (Burattini *et al.*, 2010).

ROS can produce DNA damage and strand breaks. In addition, topoisomerase I, an enzyme involved in DNA repair, is heat-sensitive and its inactivation could prevent correction of DNA damage (Ciavarrá *et al.*, 1992). DNA damage can lead to apoptosis by several mechanisms:

Excessive heat exposure or heat stress (high temperature especially more than 42 °C) can induce irreversible heat damage such as necrosis, apoptosis of cells through intrinsic pathway (Burattini *et al.*, 2010).

Fas-dependent apoptosis (extrinsic pathway) is involved in heat-induced apoptosis in neurons (Jayanthi *et al.*, 2005).

The Fas receptor, a member of the tumor necrosis factor receptor family, recruits the FADD (Fas-associating protein with death domain) adapter molecule that binds procaspase-8, forming the death-inducing signaling complex (DISC), releasing neurotransmitters as gluta-

mate and glycine in CSF. While associated with the DISC, procaspase-8 and/or procaspase-10 is cleaved into its activated form, initiating a proteolytic cascade resulting in caspase-3 activation, death and hyperexcitability (*White et al; 2007*). In addition of other Caspase-independent pathways.

FS may cause apoptosis and further brain damage. One of the most important complication of febrile seizure is MTS leading to MTLE; MTS is characterized by neuronal loss and gliosis. Theoretically, two cellular mechanisms contribute to neural loss in MTS; necrosis and apoptosis (*Ananth et al; 2001*).

Xu et al; 2007 stated that there was evidence of apoptosis found in the sclerotic hippocampus of patients with drug-resistant MTLE associated with MTS compared with control (through increased expression of bcl-2, p53, Fas and caspase-3); which could be a process of the disease itself or may be induced by seizures.

In our study, there was significant negative correlation between MDA & TAC in cases, there was insignifi-

cant positive correlation between MDA and Fas; and insignificant negative correlation between TAC and Fas

CONCLUSION

In conclusion, the present work provides evidence for the increase in oxidative stress (higher MDA, lower TAC) and apoptosis (higher s Fas-L) when compared with control. Infection or fever per se may affect oxidative stress and apoptosis; which in their turn may cause and complicate FS. An inverse relationship between TAC and MDA leading to oxidative stress in FS. A correlation between oxidative stress and apoptosis.

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