The Role of High Mobility Group Box 1 (HMGB1) in The Pathogenesis of Febrile Seizures

Thesis

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بسم الله الرحمن الرحيم

(وَعلمكَ مَا لم تكُن تعلَم وكَانَ فضلُ اللهِ عَليكَ عَظِيماً)

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CONTENTS

Abstract

Febrile seizures are the most common form of childhood seizures. Fever is induced by increased high mobility group box-1 (HMGB-1) level during infection and this may trigger the development of febrile seizures.

HMGB1 is a highly conserved, ubiquitous protein present in the nuclei and cytoplasm of nearly all cell types. HMGB1 has been shown to be a key mediator of inflammatory diseases.HMGB1 was involved in the generation of febrile seizures .

This work aimed to determine the role of HMGB1 as a proinflammatory cytokine in the pathogenesis of febrile seizures.

Our study included 50 patients with febrile seizures. Control samples were collected from children with febrile illness without seizures n=51cases, afebrile seizures children(known epileptic) n=10 cases, and afebrile healthy n=25 children.

Both patients and control groups were subjected to history taking , complete neurological examination , laboratory investigations (serum blood [sodium, potassium, calcium, blood urea nitrogen, creatinine] , C-reactive protein , complete blood count and serum HMGB-1).

Results

Serum (HMGB-1) was significantly higher in patients with febrile seizures than other groups.

In conclusion, From this study we conclude that HMGB1 were significantly higher in patients with febrile seizures . Our data suggest that HMGB1 may be contribute to the generation of febrile seizures in children.

Keywords:
Febrile seizures.
HMGB-1

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List of Abbreviations

B

BUN: Blood Urea Nitrogen .

C

Ca : Calcium .
CBC: Complete Blood Counts.
CNS: Central Nervous System.
COX-1 and COX-2: Cyclo-Oxygenase enzymes 1and 2.
CRP: C-Reactive Protein.
CS F: Cerebrospinal Fluid.
CT: Computed Tomography.

D

DCs: Dendritic Cells.
DNA: Deoxyribonucleic Acid.

E

ED: Emergency Department.
EEG: Electroencephalography.
ER: Emergency Room.

F

FS: Febrile Seizures.

G

GABA: Gamma Amino Butyric Acid.
GEFS+ : Generalized Epilepsy with Febrile Seizures plus**.**

H

HIE : Hypoxic Ischemic Encephalopathy.
HMGB1: High Mobility Group Box 1.

I

IBL: Inflammatory Bowel Disease.
IFN-γ: Interferon γ.
IL-1alfa: Interleukin–1alfa.
IL-1beta: Interleukin–1beta.
IL-6: Interleukin-6.
IL-8: Interleukin-8.
IL-1R: Interleukin-1 Receptor.
ILAE : The International League Against Epilepsy.

K

K:Potassium.

L

LBP: Lipopolysaccharide-Binding Protein.
LP: Lumbar Puncture.
LPs: lipopolysaccharides.

M

MES: Maximal Electroshock Seizure **.**
MMR: Measles, Mumps, Rubella**.**
MMRV: MMR combined with Varicella vaccine.
MRI: Magnetic Resonance Imaging.
MTS: Mesial Temporal Sclerosis.

N

Na: Sodium.
NMDA: N-Methyl-D-Aspartate.

P

PCR: Polymerase Chain Reaction.
PG: Prostaglandin.
PRR: Pattern Recognition Receptors**.**

R

RAGE : Receptor for Advanced Glycation Endproducts**.**

S

SCN1B: Sodium Channels Subunits.
SE : Status Epilepticus .
SIRS : Systemic Inflammatory Response Syndrome .

T

TLE: Temporal Lobe Epilepsy .
TLR4: Toll-Like Receptor 4 .
TNF: Tumor Necrosis Factor.
TNF-α :Tumor Necrosis Factor- alpha .

Introduction

Seizures in children

Definition of Seizure:

An uncontrolled, paroxysmal neuronal discharge in any part of the brain; it may cause physical or mental symptoms and may be convulsive or non convulsive ***(Kammerman and Wasserman.,2001)***.

It is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain ***(Fisher et al.,2005)***.

Epidemiology:

Seizures are the most common pediatric neurologic disorder. Four to ten percent of children suffer at least one seizure in the first 16 years of life. The incidence is highest in children less than 3 years of age, with a decreasing frequency in older children ***(Friedman and Sharieff.,2006)***.

Worldwide, it is estimated that 10.5 million children under 15 years have active epilepsy, representing about 25% of the global epilepsy population. Of the 3.5 million people who develop epilepsy annually, 40% are younger than 15 years, and more than 80% live in developing countries ***(Guerrini.,2006)***.

Febrile seizures are the most common form of childhood seizures, affecting 2–5% of all children and usually appearing between 3 months and 5 years of age. Despite its predominantly benign nature, a febrile seizure (FS) is a terrifying experience for most parents ***(Fetveit.,2008)***.

Causes of seizures:

Seizures are commonly encountered in patients who do not have epilepsy. Factors that may provoke such seizures include organ failure, electrolyte imbalance, medication and medication withdrawal, and hypersensitive encephalopathy. There is usually one underlying cause, which may be reversible in some patients ***(Delanty et al.,1998)***.

Only one third of the patients with newly diagnosed unprovoked seizures receive an etiologic diagnosis. In children, developmental causes are prominent, whereas in older age groups, cerebrovascular and degenerative causes have become recognized as important causes ***(Sidenvall et al.,2001)***.

Of many exogenous causes as difficult birth, neonatal asphyxia, and coiling of the umbilical cord might be identified as risk factors predicting an initial febrile convulsion. Children with febrile convulsions and exogenous causes are likely to have affected family members, and have a risk of recurrence of seizures on 5 occasions or more. Exogenous causes alone barely raise the risk of recurrence of febrile convulsions after 3 years of age or development of afebrile convulsions. The incidence of exogenous causes is highest in children who develop afebrile convulsions after febrile convulsions, and lowest in children who experience only febrile convulsions, although a little higher than in normal controls ***(Tsuboi and Okada.,2009)***.

Classification of seizures:

International classification of seizure types (1981)

This classification is based on observation clinical and electroencephalography (EEG) rather than the underlying pathophysiology or anatomy.

I <u>Partial seizures</u> (Older term: focal seizures)

A <u>Simple partial seizures</u> - consciousness is not impaired

1 With motor signs

2 With sensory symptoms

3 With autonomic symptoms or signs

4 With psychic symptoms

B Complex partial seizures - consciousness is impaired (Older terms: temporal lobe or psychomotor seizures)

1 Simple partial onset, followed by impairment of consciousness

2 With impairment of consciousness at onset

C Partial seizures evolving to secondarily generalized seizures

1 Simple partial seizures evolving to generalized seizures

2 Complex partial seizures evolving to generalized seizures

3 Simple partial seizures evolving to complex partial seizures evolving to generalized seizures.

II **Generalized seizures**

A Absence seizures (Older term: petit mal) involve an interruption to consciousness where the person experiencing the seizure seems to become vacant and unresponsive for a short period of time (usually up to 30 seconds). Slight muscle twitching may occur.

1 Typical absence seizures

2 Atypical absence seizures