LOW SERUM ZINC & MAGNESIUM– A POSSIBLE RISK FACTOR FOR FIRST EPISODE SIMPLE FEBILE SEIZURES

Submitted in partial fulfillment for

M.D. DEGREE EXAMINATION

MD BRANCH VII

PAEDIATRIC MEDICINE

Stanley Medical College, Chennai

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU.

APRIL 2012

CERTIFICATE

Certified that this dissertation entitled "**LOW SERUM ZINC & MAGNESIUM –A POSSIBLE RISK FACTOR FOR FIRST EPISODE SIMPLE FEBRILE SEIZURES"** is the bonafide work done by **Dr.L.G.AISHWARYA LAKSHMI,** Post graduate student of Pediatric Medicine, Stanley Medical College Hospital, Chennai-1, during the academic year 2009-2012.

Dr.AMBIGAPATHY, MD, DCH,
Professor and The Director I/C,
Institute Of Social Pediatrics,
Stanley Medical College,
Chennai-1.

Prof. Dr.S.GEETHA LAKSHMI,MD,Ph.D,
DEAN,
Stanley Medical College,
Chennai-1.

CERTIFICATE

Certified that this dissertation entitled "**LOW SERUM ZINC & MAGNESIUM –A POSSIBLE RISK FACTOR FOR FIRST EPISODE SIMPLE FEBRILE SEIZURES"** is the bonafide work done by **Dr.L.G.AISHWARYA LAKSHMI,** Post graduate student of Pediatric Medicine, under the guidance of **Dr. AMBIGAPATHY, MD, DCH**. Professor and The Director I/C, Institute Of Social Pediatrics, It is submitted in part of fulfillment of the award of the degree of M.D (pediatrics) for the April 2012 examination to be held under the Tamil Nadu DR.M.G.R Medical University, Chennai., during the academic year 2009-2012.

Dr.AMBIGAPATHY, MD,DCH,
Professor and The Director I/C,
Institute of Social Pediatrics,
Stanley Medical College,
Chennai-1.

DECLARATION

I declare that this dissertation entitled **"LOW SERUM ZINC & MAGNESIUM – A POSSIBLE RISK FACTOR FOR FIRST EPISODE SIMPLE FEBRILE SEIZURES"**, has been conducted by me at the Institute of Social Pediatrics, Stanley Medical College. It is submitted in part of fulfillment of the award of the degree of MD (Pediatrics) for the April 2012 examination to be held under the Tamil Nadu Dr. M.G.R. Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

Place :

Date : **(Dr.L.G.AISHWARYA LAKSHMI)**

ACKNOWLEDGEMENT

I express my sincere thanks to Prof.**Dr.S.GEETHA LAKSHMI, MD, Ph.D,** the **DEAN**, Stanley Medical College for allowing me to conduct this study in our Institute Of Social Pediatrics, Stanley Medical College.

I am greatly indebted to our Professor **Dr.AMBIGAPATHY, MD,DCH**, Professor of Pediatrics, Institute Of Social Pediatrics, Stanley Medical College for his unstinted guidance, encouragement, support given to me throughout the study.

I am grateful to **Dr.G.KARUNAKARAN, MD, DCH**, Professor of Pediatrics, Institute Of Social Pediatrics, Stanley Medical College for his valuable guidance and suggestions for the study.

I am grateful to **Dr. AMUTHA RAJESWARI, MD, DCH**, former Director , Institute Of Social Pediatrics, Stanley Medical College, for her valuable guidance and suggestions throughout the study.

I am grateful to **Dr.M.L.VASANTHAKUMARI, MD, DCH**, former Director, Institute Of Social Pediatrics, Stanley Medical College, for her valuable guidance and help for the study.

I thank our Professor of Pediatric Neurology **Dr.VELUSAMY, MD, DM**, for his valuable suggestions and help for the study.

I thank our Assistant Professor **Dr.M.A.ARAVIND, MD, DCH**, for his valuable guidance, suggestions and help throughout the study.

I thank our Assistant Professors of the Department of Pediatrics at Stanley Medical College, **Dr.GANESH , MD, DCH, Dr. RATHINAVEL , MD, DCH, Dr. ANBU, MD, DCH, Dr. ELANGO, MD, DCH, Dr. RATHIKA, MD, Dr. RAJA , MD** and **Dr. KUMAR, DCH** for their valuable help and guidance.

I wish to express my sincere thanks to the parents of the children for allowing their children to participate in this study.

I express my sincere thanks to my postgraduate colleagues and ward staff nurses for their help and cooperation.

INDEX

INTRODUCTION

INTRODUCTION

FEBRILE SEIZURES

Seizures that occur in neurologically healthy infants between the age 6 months to 5 years with a temperature of 38 ºC or higher that are not the result of CNS infection or any metabolic imbalance, and that occurs in the absence of a history of prior afebrile seizures[1]. They are brief (1 to 2 mins), generalized tonic-clonic self limited seizures, followed by brief post ictal period of drowsiness.

They are most common seizure disorder during childhood[2] with an excellent prognosis

Febrile seizures have multiple etiological factors like genetic factors, environmental factors, family history of febrile seizures among parents or sibling, iron, zinc, copper, magnesium, GABA deficiencies.

Febrile seizures occur in 3-4% of children under the age of 5 years [3].

ZINC is an important element for growth, development & normal brain function and an essential cofactor for various enymes like DNA , RNA polymerases. The mechanism by which zinc is involved in cellular growth and differentiation, enzymatic activity of different organs, proteins and cellular metabolism is well known [4,5]

It is an essential micronutrient found to play a critical role in regulating communication between brain cells and controlling the occurrence of febrile

seizures. Zinc directly raises the threshold level of seizures. Zinc deprivation may play a role in pathogenesis of febrile seizures [6].

MAGNESIUM an essential nutrient for humans, shares many characteristics with calcium and plays a role in membrane stability. Hypomagnesemia leads to nerve and muscle excitability [7,8].

REVIEW OF LITERATURE

CHILDHOOD SEIZURES

Seizures are paroxysmal, time limited change in motor activity and / or behavior that results from abnormal electrical activity in the brain [1]. Seizures are common in pediatric age group and occurs in 10 % of children [1].

The International Classification of Epilepsy divides seizures into 2 broad categories. Focal (Partial) Seizures and Generalised Seizures [1].

Focal seizures : The first clinical and EEG changes suggest initial activation of a system of neurons limited to part of cerebral hemisphere. Partial seizures are classified as simple or complex. Consciousness is maintained in simple partial seizures and is impaired in patients with complex partial seizures [1].

Generalised seizures: The first clinical and EEG changes indicate synchronous involvement of all of both cerebral hemispheres.

Convulsions are the most common neurological finding in children, about 10% of children experience convulsions in their life. The most common type observed in children is febrile seizures.

EPILEPSY

A condition in which seizures are triggered recurrently from within the brain. Epilepsy is considered to be present when 2 or more unprovoked seizures occur at an interval greater than 24 hours apart . Prognosis is generally good for children with

epilepsy, but 10-20% have persistent seizures refractory to drugs and pose a diagnostic and management challenge.

MECHANISM OF SEIZURES

To initiate a seizure, there must be a group of neurons that are capable of generating burst discharge and impairment of the γ-aminobutyric acid (GABA)-ergic inhibitory system. Seizure discharge transmission ultimately depends on excitatory glutaminergic synapses. Excitatory aminoacids (Glutamate, Aspartate) produce neuronal excitation by acting on specific receptors [1].

Seizures are more common in infants, certain seizures in the pediatric population are age specific (infantile spasms), suggesting that the underdeveloped brain is more susceptible to specific seizures than older children or adults. The actions of GABA, the major inhibitory neurotransmitter, are often paradoxically excitatory in the immature brain. The GABA sensitive substanti anigra pars reticulate neurons play a role in preventing seizures. Functional immaturity of Substanti anigra has an integral role in development of generalised seizures [1].

Febrile seizures are the most common type of seizure disorder in children. Febrile seizures occur when the temperature is rising too rapidly to more than 39 ^{o} C. The definition by National Institute Of Health (NIH) Consensus development conference emphasis the age specificity and absence of underlying brain abnormalities in a child with febrile seizures. Febrile seizures often occur early in the course of febrile illness and is often the first sign [9].

CLASSIFICATION OF FEBRILE SEIZURES : Classified as simple (70-75 %) and complex (9-35 %) febrile seizures.

1) **SIMPLE FEBRILE SEIZURES :** A generalised tonic clonic seizure associated with fever, lasting for maximum 15 minutes and does not recur within a 24 hour period without postictal neurological abnormalities.

2) **COMPLEX FEBRILE SEIZURES :** A generalised or focal and prolonged seizure lasting for more than 15 minutes or recurring within 24 hours, with or without postictal neurological abnormalities.

3) **FEBRILE STATUS EPILEPTICUS :** A febrile seizure lasting for > 30 minutes, either one prolonged seizure or series of shorter seizures without regaining consciousness in the interictal period.

Febrile seizures typically are associated with common childhood infections, most frequently upper respiratory tract, middle ear, and gastrointestinal infections. Viral infections are the most common cause of illness in children admitted to the hospital with a first episode febrile seizures[10].

1) Human Herpes Virus 6 (Roseola),Human Herpes virus 7.
2) Influenza A, B.
3) Parainfluenza
4) Respiratory Syncitial Virus
5) Adenovirus.

6) Acute Otitis Media, Shigella gastroenteritis, lower respiratory tract infections, Urinary tract infections.

7) Seizures after immunisation are likely to be febrile, particularly those occurring within 48 hours of DPT vaccination& 7 – 10 days after Measles vaccination[11].

Febrile seizures occur during early phase of rising temperature and are uncommon after 24 hours of onset of fever .Febrile seizures should be distinguished from convulsions with fever, which includes any convulsion in a child with fever of any cause like children with meningitis, encephalitis or cerebral malaria.

ETIOPATHOGENESIS

A number of hypothesis have been suggested for the occurrence of febrile seizures,

1. **Age of onset of seizures :**

   Febrile seizures are age dependent .Most febrile seizures occur between 6 months and 3 years. The peak age of onset is between 14 – 16 months onset after 6 years is unusual, this is due to specific vulnerability of young children to fever as a precipitant and the maturing brain's sensitivity to fever. Febrile seizures occurring before 6 months should raise a suspicion of CNS infection and excluded by a lumbar puncture.

2. Temperature :

Hyperthermia can result in decrease in GABA-A (Gamma Aminobutyric acid A) receptor mediated inhibition which shifts the balance towards excitation and causes seizure generation[12]. The direct effect of heat on sodium ion channel of Hippocampus and Cortical neurons cause a profound increase in neuronal Excitability[13]. The electrical systems of the brain have not yet matured sufficiently in a child to cope with the stress of high temperature.

3. Genetic factors :

There is a significant genetic component for susceptibility of febrile seizures. 2 febrile seizure loci are mapped, FEB1 in chromosome 8q13-q21 and FEB2 in chromosome 19p. A mutation in voltage gated sodium (Na+) channel beta subunit gene (SCN1B) at chromosome 19q13.1 is identified and termed as Generalised Epilepsy With Febrile Seizure Plus Syndrome (GEFS(+)). GEFS + has a spectrum of phenotypes in febrile seizures, febrile seizures plus (this comprised childhood onset of multiple febrile seizures, but unlike typical febrile seizures, attacks continue with fever beyond 6 years or afebrile seizures occurred. Studies have linked the susceptibility of febrile seizures to a gene on chromosome 5q14-5q15 (FEB4) [14].

4. **Family history of seizures:**

   Family history of seizures in first degree relative is the most consistently identified risk factor for febrile seizures. Family history is positive in 25-40% of children with febrile seizures. The risk of another child having febrile seizures with 1 affected sibling is 1 : 5. The risk is 1: 3 if both parents and a previous child had febrile seizures[15]. Polygenic inheritance or autosomal dominant inheritance[1] with reduced penetrance are most likely modes of inheritance.

5. **Respiratory Alkalosis :** Fever increases the respiratory rate, which produces Respiratory Alkalosis. The respiratory alkalosis may increase the neuronal excitability and precipitate seizures.

6. **Inflammatory Mediators :**

   An enhanced IL-1β response in children with fever plays a role in occurrence of febrile seizures. During the acute phase of febrile seizures, the children had significantly elevated levels of plasma IL-1 β and prostaglandins and decreased levels of serum zinc. These changes may be responsible for febrile seizure pathogenesis[16].

7. **Iron deficiency :**

   Monoamine oxidase, an iron dependent enzyme has a crucial role in neurochemical reactions in the central nervous system. Iron deficiency produces decreases in the activities of enzymes such as catalase and

cytochromes. Catalase and peroxidase contain iron, but their biologic essentiality is not well established. Iron deficiency alters the electron transport and neurotransmitter synthesis in the brain thereby affecting the normal function of neural tissue[17,18].

8. Specific nutrient deficiency :

Low levels of zinc, selenium and other vital minerals are involved in precipitating seizures. Zinc, calcium and magnesium are called as sedative minerals as they calm and relax the central nervous system. Many seizures are associated with some degree of biologically unavailable calcium and magnesium.

The incidence of febrile seizures in children is 2-5 % in developed countries, in India the incidence is 5-10 % [19].

Age wise incidence of febrile seizures in children :

< 6 months – 4 %

6 months to 3 years 90 – 94 %

>3 years – 6 %.

Boys have a higher incidence than girls [20].

RECURRENCE RISK OF FEBRILE SEIZURES :

Most children do not get recurrence of febrile seizures. 30 – 50 % 0f children develop recurrent febrile seizures[1]. About one third of the children would experience

recurrence. In more than 50 % children febrile seizures recurs within 1 year. More than 90 % children, febrile seizure recurs within 2 years. Recurrent febrile seizures more than 3 episodes is unusual and suggests the child may have a non febrile seizure later.

Incidence of recurrent febrile seizures depends on,

1. Age of onset is the strongest and consistent predictor of recurrence. The younger the age of onset of first febrile seizure (< 15 months), higher the chance of recurrence. 50 % risk if the onset was < 1 year, compared to 20 % risk if the onset was after 3 years[21].

2. Febrile seizure or epilepsy in a first degree relative.

3. First complex febrile seizures.

4. Many subsequent febrile episodes in the past.

5. Lower the temperature at the time of febrile seizure[22] and shorten the duration between the onset of fever and febrile seizures.

OUTCOME OF FEBRILE SEIZURES :

Studies have shown that febrile seizures in early childhood do not have any adverse effects on behaviour, scholastic performance and neurocognitive functions or specific memory impairement[23].

RISK OF EPILEPSY:

2 to 10 % of children with febrile seizures will subsequently develop epilepsy. Incidence of epilepsy is more than 9% when several risk factors are present, compared with an incidence of 1 % in children with febrile seizures without any risk factors[1].

2 % of children with simple febrile seizures develop epilepsy in later age

5-10% of children with complex febrile seizures develop epilepsy in laterage.

Generalised epilepsies tend to follow when there is a family history of nonfebrile seizures or multiple simple febrile seizures, focal epilepsies are common if there have been prolonged lateralised seizures.

DEFINITE RISK FACTOR: A family history of epilepsy, pre existing neurological or developmental abnormalities and complex febrile seizures.

NOT A RISK FACTOR: Family history of febrile seizures, age at first febrile seizures, peak temperature, sex, race & ethnicity.

MESIAL TEMPORAL LOBE EPILEPSY (MTLE):

Temporal lobe epilepsy is one of the refractory epilepsy and most common focal epilepsy in adults often caused by hippocampal sclerosis.

Current opinion suggests an association between prolonged febrile seizures and pre existing lesions within the temporal lobe may subsequently facilitate the development of hippocampal atrophy[24]. The severity or extent of hippocampal

atrophy depends on the frequent generalised tonic clonic seizures or the duration of epilepsy [25].

The association of complex febrile seizures with hippocampal atrophy and Temporal Lobe Epilepsy is likely to be multifactorial (genetic and environmental factors) and also involves cytokines specifically Interleukins 1.

There is evidence demonstrating that Mesial Temporal Sclerosis is both a result and cause of seizures [26].

There is currently no evidence that simple febrile seizures produce structural damage to the brain. The increased risk of epilepsy is due to genetic predisposition and underlying brain heterotropia.

MORTALITY :

There is no increased risk or evidence of mortality in febrile seizures as such including febrile status epilepticus[27].

DIAGNOSIS :

Seizures are manifestation of a number of underling conditions, one of the most important differential diagnosis is meningitis, hence a careful history, neurological examination is essential. History should include presence of recent or chronic illness, recent antibiotic therapy, recent immunisation & day care attendance [28].

The prevalence of meningitis in a febrile child with seizures is 1 – 2 %[29]. Meningitis should be ruled out by a thorough clinical examination and CSF analysis.

INVESTIGATIONS IN FEBRILE SEIZURES :

FEATURES	LUMBAR PUNCTURE	EEG	NEUROIMAGING	BIOCHEMICAL STUDIES
Febrile status epilepticus	Yes	No	No	None
Complex febrile seizures	Consider	No	No	None
Simple febrile seizures>18 months	No	No	No	None
Age < 18 months	Consider	No	No	None
Neuro developmental abnormality	No	No	Possibly (not urgent)	None
Symptoms and signs of meningitis	Yes	No	No	None

LUMBAR PUNCTURE : Routine CSF analysis is not indicated in all children with simple febrile seizures.

INDICATIONS OF LUMBAR PUNCTURE (when used in combination, these risk factors are very helpful in identifying children with meningitis and their negative predictive value was 100%[30]) :

1) Suspicious findings on physical and neurological examination suggestive of meningitis[31] (suspicious physical findings like rash, petechiae, cyanosis, hypotension, grunt and abnormal neurological examination, especially meningeal signs).
2) Prolonged lethargy or altered consciousness after a simple febrile seizures.
3) Focal seizures.
4) Febrile status epilepticus.
5) Strongly consider LP < 12 months and consider LP <18 months [32].
6) Also in young infants less than 6 months of age, children who had received antibiotics during the course of fever or before the episode of seizures, as meningeal signs are less reliable in this group[32].

NEUROIMAGING :

Neuroimaging is not routinely indicated in all children with simple febrile seizures[33].

It is considered in a child with febrile seizures who also has the following features,

a) Microcephaly / Macrocephaly[34],

b) Neurocutaneous syndrome,

c) Pre existing neurological deficits[34],

d) Post ictal neurological deficits persisting for more than a few hours following a febrile seizure,

e) Recurrent complex febrile seizure, or when a doubt occurs whether it is a febrile seizure.

Magnetic Resonance Imaging (MRI), is superior compared to a CT (Computed Tomography) Scan, specifically when a underlying inflammation of meninges or structural abnormality is suspected as a cause for seizures.

ELECTROENCEPHALOGRAM (EEG) :

- Routine EEG is not recommended in all cases of febrile seizures. Routine EEG in neurologically normal children with complex febrile seizure is not indicated [35]

- Useful for evaluating children with complex or atypical features or with other risk factors for later epilepsy.

EEG ABNORMALITIES IN A CHILD WITH HISTORY OF FEBRILE SEIZURES[36]:

1) ICTAL (Rarely reported) – Generalised spiking, lateralised spike wave discharge.

2) POSTICTAL - slow activity, spike wave or spikes.

3) SERIAL EEG's - bisynchronous theta activity, bisynchronous spike wave at rest and during over breathing, focal spikes or sharp waves.

Within a week of attack, a variety of nonspecific abnormalities may be seen. Various generalised or focal epileptiform abnormalities seen are of poor prognostic significance.

EEG lacks the predictive value for later occurrence of either febrile or afebrile seizures[36].

MANAGEMENT :

DURING THE SEIZURE :

The child needs to be managed as for any other seizure,

a) Airway management.

b) Semi prone position to decrease the risk of aspiration

c) Monitoring of vital signs

d) Termination of seizures immediately by intravenous Diazepam or Lorazepam, Rectal Diazepam is also found to be safe and effective in the dose of 0.5 mg /kg. Recent studies showed that Midazolam (o.2 mg/kg) given intranasally is as safe as effective as Diazepam.

e) Treatment of fever : Antipyretics are not effective in preventing recurrent febrile seizures when administered regularly (every 4 hours) or sporadically[37] , but are useful in making the child more comfortable.

Simple febrile seizures with a benign prognosis and a tendency to spontaneously remit with age and while considering the potential side effects of antiepileptic drugs, prophylaxis for simple febrile seizures are not required [38,39]

INDICATIONS FOR HOSPITALISATION IN A CHILD WITH FEBRILE SEIZURES :

1) Age < 18 months of first episode of febrile seizures.
2) Suspicion of meningitis.
3) Child who had received antibiotics in the previous 48 hours.
4) Complex or atypical febrile seizures.
5) Child drowsy or irritable.

LONG TERM MANAGEMENT:

The primary goal is to prevent recurrences, 2 treatment options are available, intermittent and continuous prophylaxis with antiepileptic drugs.

- International League Against Epilepsy (ILAE) Recommendations for prophylaxis have changed from continuous to intermittent prophylaxis. The potential toxicities associated with antiepileptic drugs outweigh the relatively minor risks associated with febrile seizures. (AAP Guidelines)

INTERMITTENT PROPHYLAXIS :

- Diazepam administered either orally or rectally at the onset of fever has been shown to be effective in preventing recurrence of febrile seizures[40].

- Diazepam administered in a dose of 0.3 to 0.5 mg/kg (max 10 mg) used and repeated every 8 – 12 hours if the temperature >38 º C . The side effects are minor like lethargy, drowsiness and ataxia, by adjusting the dose,it can be prevented.

- Clobazam 0.75mg/kg/day in 2 divided doses for 2 – 3 days during fever is found to be effective and is used to prevent recurrence of febrile seizures[41].

- The sedation associated with this therapy could mask the evolving signs of meningitis.

- This therapy does not decrease the incidence of later epilepsy in children with febrile seizures who are prone to develop epilepsy[42].

CONTINUOUS PROPHYLAXIS :

- When simple febrile seizures are recurrent despite intermittent prophylaxis and particularly when the parents are unable to promptly recognise the onset of febrile seizures, continuous prophylaxis with antiepileptic drugs are used.

- Drugs like Phenobarbitone or Sodium Valproate are used for 1 – 2 years to prevent recurrence of febrile seizures .

- Phenobarbitone in a dose 3-5mg/kg/day in 1-2 divided doses is effective, it decreases the rate of subsequent febrile seizures from 25 % to 5 % subjects per year[43].

- Long term Phenobarbitone appears to influence cognition and behaviour. The behavioural adverse effect may occur in 20-40% patients and may be severe enough to discontinue the drug [44]. Also causes hypersensitivity rarely.

- Sodium Valproate in a dose of 20 – 30 mg/kg/day in 2-3 divided doses is also used. When used in children less than 2 years ,it has a rare association of fatal hepatotoxicity, other side effects are thrombocytopenia, weight loss and weight gain, gastrointestinal disturbances and pancreatitis.

- Neither Phenobarbitone or Sodium Valproate is effective in reducing the risk of Epilepsy in children with febrile seizures.

- Phenytoin and Carbamazepine are not effective in preventing the recurrence of febrile seizures.

PARENTAL COUNSELLING :

The most important part in the management of febrile seizures is to counsel the parents. They are reassured and counselled properly with particular emphasis on:

- The benign nature of the disease.

- Febrile seizures do not lead to developmental delay or neurological problems.

- Advice should also be given regarding the initial first aid to be given in case of a seizure at home and about hospitalisation for fever or if prolonged seizures or post ictal drowsiness if present[39].

- Parents are advised to observe the type and duration of seizures if recurrence of febrile seizure occurs[39].

- Instruction regarding the need of appropriate anticonvulsive therapy , including the relevant side effects [39].

ZINC AND MAGNESIUM:

Recent studies indicate that the deficiency of trace elements such as zinc and magnesium can play a significant role causing febrile seizures[45].

ZINC :

- Zinc is an essential mineral. A metallic chemical element with atomic number 30.
- Physical properties: zinc has a hexagonal crystal structure. It has low melting point among transition metals (apart from mercury, cadmium)
- Chemistry :Zinc is chemically similar to Magnesium because of the similar size of the ions and the common oxidation state of both as +2. The ionic radii of zinc and magnesium are nearly identical.

Biological role of Zinc :

- Zinc is an essential trace element, found in many specific enzymes in our body, serves as structural ions in transcription factors and is stored & transferred in metallothienes. Zinc is the only metal which appears in all enzyme classes.

- 2-4 grams of Zinc is distributed throughout our human body. Most Zinc is present in our brain, muscles, bones, liver, kidney and in higher concentrations in prostate, seminal fluid and parts of the eye.

- Zinc, a largest component of metalloenzymes is an essential micronutrient that can be found in almost every cell [46].

- Zinc interacts with a wide range of organic ligands, has role in the metabolism of RNA & DNA, signal transduction, gene expression and also regulates apoptosis.

- In the Brain, Zinc is stored in specific synaptic vesicles by the Glutaminergic neurons. It modulates the Brain's excitability. Zinc plays a key role in synaptic plasticity and is also called as the Brain's Dark Horse. Zinc homeostasis plays a critical role in normal functioning of the brain and CNS.

- Zinc rich foods : oysters, lobsters, red meat- beef, lamb ,liver, wheat, seeds (sesame, poppy, celery, mustard, nuts, almonds, pumpkin seeds, sunflower seeds)

- Zinc as a dietary supplement:

    a) Antioxidant properties – protects against aging of skin and muscles of the body.

    b) Speeds up healing process after an injury.

c) Gastroenteritis attenuated by zinc due to the direct antimicrobial action of zinc ions in the gut, or by the absorption of zinc and rerelease from immune cells (granulocytes release zinc).

ZINC DEFICIENCY:

- Zinc deficiency occurs mainly due to insufficient dietary intake.
- Also occurs in association with malabsorption, acrodermatitisenteropathica, chronic liver disease, chronic renal disease, diabetes and malignancy.
- Phytates in whole grains and fibres interfere with its absorption.
- In children zinc deficiency is aggravated during infections and diarrhoea.

EXISTENCE OF INTRACELLULAR ZINC IN OUR BODY :

- There are 2 pools of intracellular zinc, the first pool contains zinc that is tightly complexed to proteins and thus invisible to most cytological stains.
- Second, a pool of free ionized zinc is found within vesicles containing Glutamate or Aspartate and can be visualised histochemically by staining. The free zinc pool constitutes 5-15% of the total cellular zinc, the balance is tightly maintained. Highest concentration of this ion in the synaptic vesicles (200 – 300 µm) shows its significant role in neuronal economy[47].

- The highest concentration of free ionic zinc in the synaptic vesicles is a prominent feature of some of the excitatory pathways in forebrain[47,48].

ZINC AND ITS ROLE IN NEUROPSYCHOLOGICAL DEVELOPMENT:

- It has long been recognised that the essential trace element zinc is needed for human growth and development. In the recent years, there is increasing awareness of the essentiality of zinc not just for normal physical growth in infants and children but also for normal neuropsychological development[49].

- Zinc plays a critical role in communication between brain cells, governing the formation of memories and controlling the occurring of epileptic seizures[50].

ZINC HOMEOSTASIS IN THE BRAIN :

- The mammalian central nervous system contains an abundance of the transition metal zinc, which is highly localised in neuronal parenchyma. Zinc is actively taken up and stored in the nerve terminals and stimulation of hippocampus can induce its release, suggesting that it may act as a neuromodulator. Zinc acts as a neurotransmitter and improves communicating, locomotive function and the evolution of neurological system [5]

- The brain barrier system (i.e), the blood brain and the blood cerebrospinal fluid barrier is implemented for zinc homeostasis in

brain. Zinc is supplied to the brain via both barriers. A large portion of zinc serves as zinc metalloproteins in neurons and glial cells[51].

- About 10 % of total zinc in the brain in the the form of ionic zinc exists in the synaptic vesicles, may serve as an endogenous neuromodulator in synaptic neurotransmission[51]. The turnover of zinc in brain is much lower than in peripheral tissues such as the liver.

- Dietary zinc deprivation affects zinc homeostasis in the brain. Vesicular zinc enriched region, the hippocampus are responsible to dietary zinc deprivation which causes brain dysfunction such as learning impairment and olfactory dysfunction[51].

- Zinc deficiency diminishes the hippocampal zinc and enhances the susceptibility to epileptic seizures [52].

- Therefore zinc homeostasis in brain is closely related to neuronal activity, so adequate zinc supply is important for brain function and prevention of neurological disorders[51].

HYPOZINCEMIA DURING INFECTIONS :

- During infections, in acute phase response, zinc is redistributed from plasma to the liver and lymphocytes. This is due to the liberation of endogenous mediators from polymorphonuclear leukocytes, which causes a netflow of aminoacids and zinc to the liver for the synthesis of acute phase reactants including metalloenzymes, thereby causing Hypozincemia.

- Secondly zinc may be utilised by the infecting organisms for their growth and multiplication thereby resulting in Hypozincemia.

- The release of Tumour Necrosis Factor (TNF) and Interleukins during fever or tissue injury may result in reduction of serum zinc levels.

HYPOZINCEMIA DURING FEVER MAY TRIGGER FEBRILE CONVULSIONS:

- Zinc suppresses some of the excitatory mechanism in the central nervous system. Zinc directly raises the threshold level of seizures by inhibiting the NMDA receptors and by improving the calcium inhibitory functions[49].

- Hypozincemia activates the N-methyl D- aspartate (NMDA) receptors, one of the glutamate family receptors(the excitatory receptors), which plays an important role in induction of epileptic discharges. Normal serum zinc would suppress these excitatory receptors and prevents occurrence of seizures.

REGULATORY EFFECT OF ZINC ON GABA:

- Gamma amino butyric acid (GABA) is an important inhibitory neurotransmitter.

- Zinc has an important role in GABA synthesis. Zinc has a regulatory effect on Glutamic acid decarboxylase synthesis, a rate limiting enzyme in GABA synthesis. So a low serum zinc level causes a decrease in GABA concentration and facilitates the occurrence of seizures[49,53]

MAGNESIUM:

The fourth most abundant cation and second most abundant intracellular cation. The total magnesium content of our body is 20 – 28 grams. As a divalent cation, it shares many characteristics with calcium. Magnesium is unique in that it has high binding affinity and a small ion radius. It co ordinates with 6 molecules of water as a solute and forms the largest hydrated radius among biological cations. These characteristics allows flexibility and stability of magnesium in biological systems.

MAGNESIUM HOMEOSTASIS :

60 % of the body's magnesium is adsorbed to hydroxyapatite in the bone, 38 % in muscle, organ systems and < 1 % in blood. 3 systems, the gastrointestinal tract, kidneys and bone work in concert to maintain the magnesium homeostasis.

ROLE OF MAGNESIUM IN THE BODY :

Magnesium functions as an essential cofactor to mediate enzyme substrate interactions, stabilise intermediate metabolite, bridge reactive species, directly bind to enzymes or form part of active substrates.

Magnesium is used in many enzymatic reactions in the human body, particularly all reactions requiring ATP (Adenosine Tri Phosphate). 40 – 60 % of total magnesium in muscle cells is bound to ATP.

Magnesium is involved in gluconeogenesis, lipid metabolism, amino acid activation via RNA and DNA, cellular and membrane stabilisation, calcium channel activity and other essential metabolic reactions. It activates enzymes in glycolytic

pathway and TCA cycle. DNA and RNA synthesis were not affected until > 50 % magnesium was reduced, whereas glycolysis was affected only when cellular magnesium was reduced to 10 % of the total value.

MAGNESIUM RICH FOODS :

Whole grains, green vegetables, nuts, seeds, legumes, seafood, fruits like avocado. A dietary ratio of 2:1 of calcium to magnesium is considered optimal for magnesium absorption. Phytate, may bind magnesium and thereby decreasing its bioavailability.

HYPOMAGNESEMIA :

The total serum magnesium concentration of < 0.74 mmol/l (< 1.8 mg/dl) is defined as hypomagnesemia. It is often asymptomatic.

Clinical signs and symptoms are, arrhythmia, dysphagia, tremulousness, disorientation, ataxia, nystagmus, hyper reactive deep tendon reflexes, convulsions, hypertension or coma.

Often hypomagnesemia results from renal dysfunction, drug interactions, gastrointestinal related decreased intake or increased losses.

ROLE OF MAGNESIUM IN FEBRILE SEIZURES :

Magnesium is required for the enzymes to maintain the cell membrane stability and nerve conduction. Low magnesium level leads to cell and membrane excitability thereby causing seizures[7,8].Magnesium may be an endogenously occurring neuromodulator in epilepsy and seizures would be caused by magnesium depletion.

Ahmad Talebian, et al in a case control study at Kashan university of medical sciences,Iran studied the relation between serum zinc & magnesium levels in children with simple febrile seizures with children with fever without seizures in a sample of 60 children. It was found that the mean serum zinc among febrile seizure group as 116.28 mg/dl, controls as 146 mg/dl. The serum magnesium among cases as 2.21 mg/dl, controls as 2.39 mg/dl with a p value< 0.005. Concluded that serum zinc & magnesium were lower in febrile seizure group than the controls.

HeydarianFarhad ,et al in a case control study at Mashad university of medical sciences,Iran studied the level of serum zinc among children with simple febrile seizures and children without seizures in a sample of 30 cases & 30 controls. It was found that the mean serum zinc 663.7µg/dl among febrile seizures lower than the control group 758.33µg/dl, the difference was statistically significant p<0.001.

Lalitkumar et al in a prospective study of serum zinc level in febrile seizures ,idiopathic epilepsy & CNS infection at MLB Medical college , Jhansi on 120 children, found that the mean serum zinc among febrile seizures group 79.55± 40.84 µg/dl and among controls as 120 ± 37.79 µg/dl. The difference was statistically significant with a p value < 0.005.

MojitabaAmiri, et al in a study regarding serum trace element levels in febrile convulsions, a case control study on 60 children, found a mean serum zinc level among febrile seizure group as 66.13 ± 18.97 µg/dl and among the controls as 107.87 ± 28.79 µg/dl. The difference was statistically significant with a p value< 0.001.

LusianaMargaretta, et al in a study correlation between serum zinc level and simple febrile seizures in children, a cross sectional study at R.D.Kandou, PancaraKasih& Telling hospitals, Mando,Indonesia, among 50 children, found the mean serum zinc among febrile seizure group as 8.83 µmol/l and anong the controls as 13.72 µmol/l. The difference was statistically significant with a p value < 0.001. Concluded that low serum zinc is associated with simple febrile seizures and lower the serum zinc, longer the duration of seizures.

Ganesh, et al in a prospective case control study , serum zinc level in children with simple febrile seizures, at KKCTH, Chennai on 76 children, found the mean serum zinc level in cases as 32.17 µg/dl and among controls as 87.6 µg/dl. The difference was statistically significant with a p value <0.001. Concluded that children with febrile seizures had low serum zinc levels.

FahmehEhsanipour ,et al in a study serum zinc level in children with febrile convulsions & its comparison with that of control group at Iran university of medical sciences, Tehran, Iran, a prospective analytical case control study on 92 children 6 months to 5 years. The mean serum zinc level among febrile seizure group was 76.82 ± 24.36 mg/l and the controls 90.1 ±14.6 mg/l. Concluded that p value < 0.006 and there was a significant relation between low levels of serum zinc & febrile convulsions.

A Mayhar, A Pahlavan,VarasethNejad, school of Medicine Qazain university of Medical Sciences, Qazain, Iran. Case control study was done in Qazain university of Medical Sciences, Qazain, Iran.52 children with simple febrile

convulsions were taken as cases and 52 healthy children as controls. Average serum Zn level was 62.8±18.4µg/dl in cases and 85.7±16.76µg/dl in controls.

Y.Izumi, et al from Yamagata university school of Medicine, Japan, found that Hypozincemia during fever may trigger febrile convulsions. The hypothesis was that hypozincemia activates NMDA receptors (one of glutamate receptors) plays an important role in induction of epileptiform disharges.

Amiri et al from GhazvinHospital, in a case control study on 60 children to know about the serum levels of zinc, selenium and copper in children with febrile seizures, found a statistically significant low levels of serum zinc, selenium and copper levels among the children with febrile seizures.

Sadinejad M et al in a study for determination of serum magnesium level in children with febrile seizures in Tokyo, found a significant low level of magnesium among children with febrile seizures.

OBJECTIVES OF THE STUDY

OBJECTIVES OF THE STUDY

1) To study the association between low serum zinc & magnesium and first episode simple febrile seizures.

2) To find out whether age and gender has any relation with the occurrence of simple febrile seizures.

3) To find out whether family history of febrile seizures has a role in predisposition to simple febrile seizures.

STUDY JUSTIFICATION

STUDY JUSTIFICATION

Febrile seizures is a common problem in our country, the incidence in India being 5-10 %, and many studies have shown the association of low serum trace elements have been a cause for febrile seizures.

In India the association between serum zinc and febrile seizures was done in the year 2006, this study is conducted to determine the association between serum zinc &magnesium and children with simple febrile seizures hospitalised in our Institute of Social Pediatrics .

Study regarding the administration of zinc & magnesium to prevent recurrence of febrile seizures shall be conducted in the future.

MATERIALS AND METHODS

SUBJECTS AND METHODS

STUDY DESIGN	**:**	Case control study
STUDY PLACE	**:**	Institute Of Social Pediatrics, Govt Stanley Hospital & Medical college.
STUDY PERIOD	**:**	August 2010 – August 2011.
STUDY POPULATION	**:**	Children admitted at the Institute Of Social Pediatrics satisfying the criteria for simple febrile seizures & children attending the op satisfying the criteria as controls

CASES:

Inclusion Criteria :

Age 6 months to 5 yrs

Simple febrile seizures with seizure attack < 15 minutes

Generalised tonic clonic seizures

1 seizure episode during the febrile illness

Normal growth and development.

Exclusion Criteria :

Age < 6 months or > 5 years

H / O previous seizures

Children on mineral supplement therapy

Acute CNS infection

Children with chronic neurological deficits

CONTROLS :

Inclusion Criteria :

Children with acute febrile illness without seizures attending the out patient department who needed blood investigations for fever, matched by age and sex.

Exclusion Criteria :

Children with h/o previous seizures

Children on mineral supplement therapy

Children with neurological deficit

Ratio of cases and controls : 1 : 1.

Sample size :

40 cases and 40 controls.

Method :

- All the children fulfilling the inclusion criteria of cases admitted in our hospital and controls attending the pediatric out patient department were selected for our study.
- Informed consent was obtained from the parents.
- Detailed history and clinical examination was done and the findings were entered in the proforma.
- The blood sample was collected, serum zinc & magnesium was estimated and analysed using appropriate statistical methods.

SERUM ZINC LEVEL ESTIMATION :

- Calorimetric method using NITRO PAPS was used for the estimation of serum zinc. NITRO PAPS (5-Nitro 2 Pyridoxylazo) 5 NPropyl-3 Sulfopropyl amino Phenol disodium salt) is a chromogenic reagent for the calorimetric assay of serum zinc in microamounts.

- Zinc in an alkaline medium reacts with NITRO PAPS to form a purple coloured complex.

- The amount of zinc present in the sample is directly proportional to the intensity of purple coloured complex.

- The normal reference value is 60 – 120 µg/dl.

SERUM MAGNESIUM LEVEL ESTIMATION :

- Calorimetric assay with Chlorphosphonazo III method. Chlorphosphonazo (2,7- bis (4-chloro-2phosphonophenylazo)-1,8-dihydroxy-3,6-napthalenedisulphonic acid disodium salt)reacts with magnesium in the blood sample.

- The colour developed is spectrophotometrically analysed, is directly proportional to the amount of magnesium present in blood sample.

- The normal reference value is 1.7 – 2.5 mg/dl.

STATISTICAL ANALYSIS :

- The results were entered and were analysed by using the Independent Sample T Test, using the SPSS software version 16.0 .

- The mean value of serum zinc and magnesium among cases and controls were 35.08 and 1.35 respectively, they were statistically significant with a p value <0.001 and low compared to the controls with a mean serum zinc and magnesium value as 70.23 and 1.68 respectively.

RESULTS
AND
OBSERVATION

RESULTS

Total number of cases : 40

Total number of controls : 40

TABLE 1 - INCIDENCE OF FEBRILE SEIZURES WITH RESPECT TO AGE:

AGE	FREQUENCY	PERCENT
6 Months – 1 year	9	22.5 %
1 year – 2 years	15	37.5%
2 years – 3 years	10	25 %
3 years – 4 years	2	5 %
4 years – 5 years	4	10 %

In our study the maximum incidence of febrile seizures is among the age group 1-2 years.

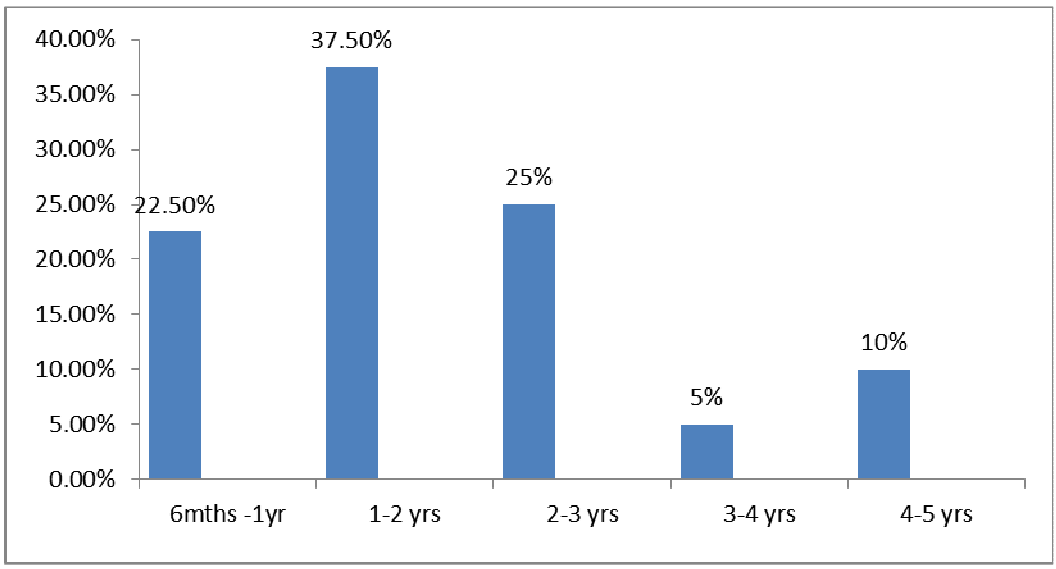


Figure 1 - INCIDENCE OF FEBRILE SEIZURES WITH RESPECT TO AGE

TABLE 2 – INCIDENCE OF FEBRILE SEIZURES WITH RESPECT TO GENDER

SEX	FREQUENCY	PERCENT
MALES	22	55 %
FEMALES	18	45 %

In our study , incidence of febrile seizures was found to be higher among male children. The ratio of male : female is 1.2 : 1.

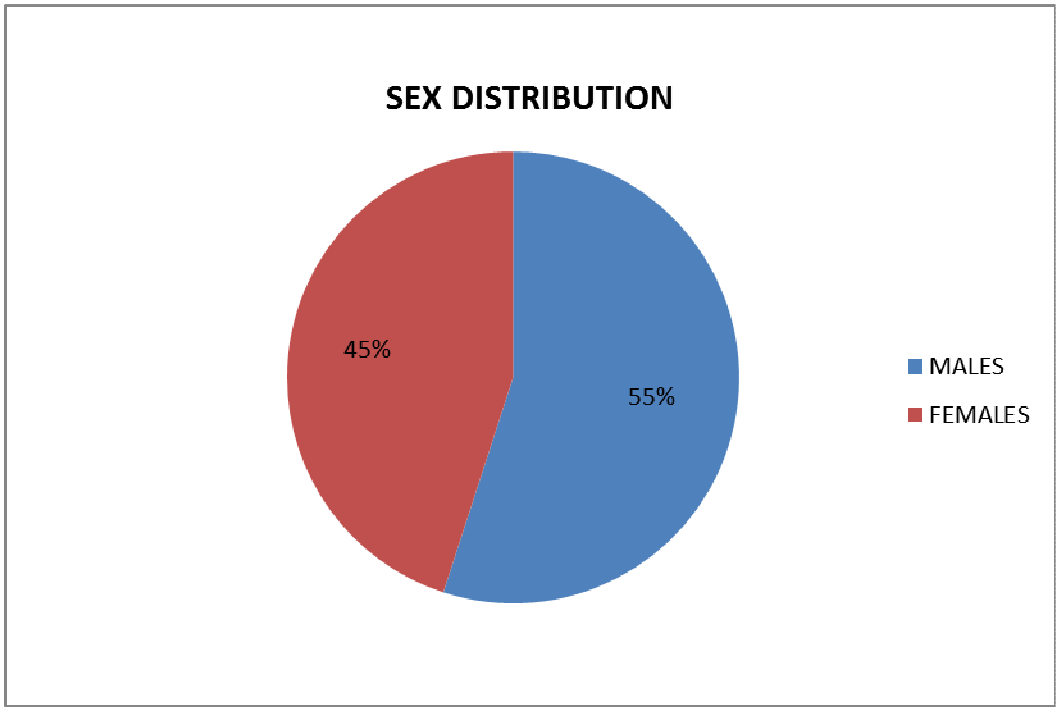


Figure 2 - INCIDENCE OF FEBRILE SEIZURES WITH RESPECT TO GENDER

TABLE 3 – FAMILY HISTORY OF FEBRILE SEIZURES AMONG BOTH GROUPS

GROUP	CASES		CONTROLS	
	NUMBER	PERCENT	NUMBER	PERCENT
WITH POSITIVE FAMILY HISTORY	11	22.5 %	0	0
WITH NEGATIVE FAMILY HISTORY	29	77.5 %	0	0

Eleven (11) children out of 40 children with simple febrile seizures have a positive family for simple febrile seizures.

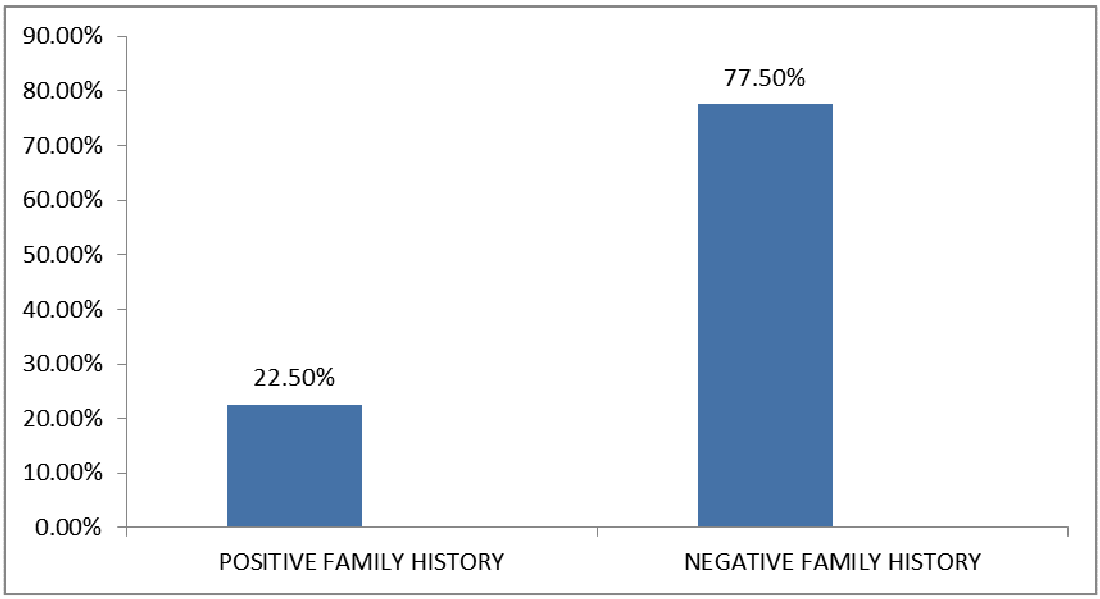


Figure 3 - FAMILY HISTORY OF FEBRILE SEIZURES AMONG THE CASES

TABLE 4 – NUTRITIONAL STATUS AMONG BOTH THE GROUPS :

NUTRITIONAL STATUS IAP GRADE	CASES NUMBER	CASES PERCENT	CONTROLS NUMBER	CONTROLS PERCENT
NORMAL > 80 %	8	20%	17	42.5%
GRADE 1 – 71 – 80 %	25	62.5%	21	52.5%
GRADE 2 – 61 – 70 %	7	17.5%	2	5%

Among both the groups, maximum number of children were in the grade I malnutrition (71 – 80 %)

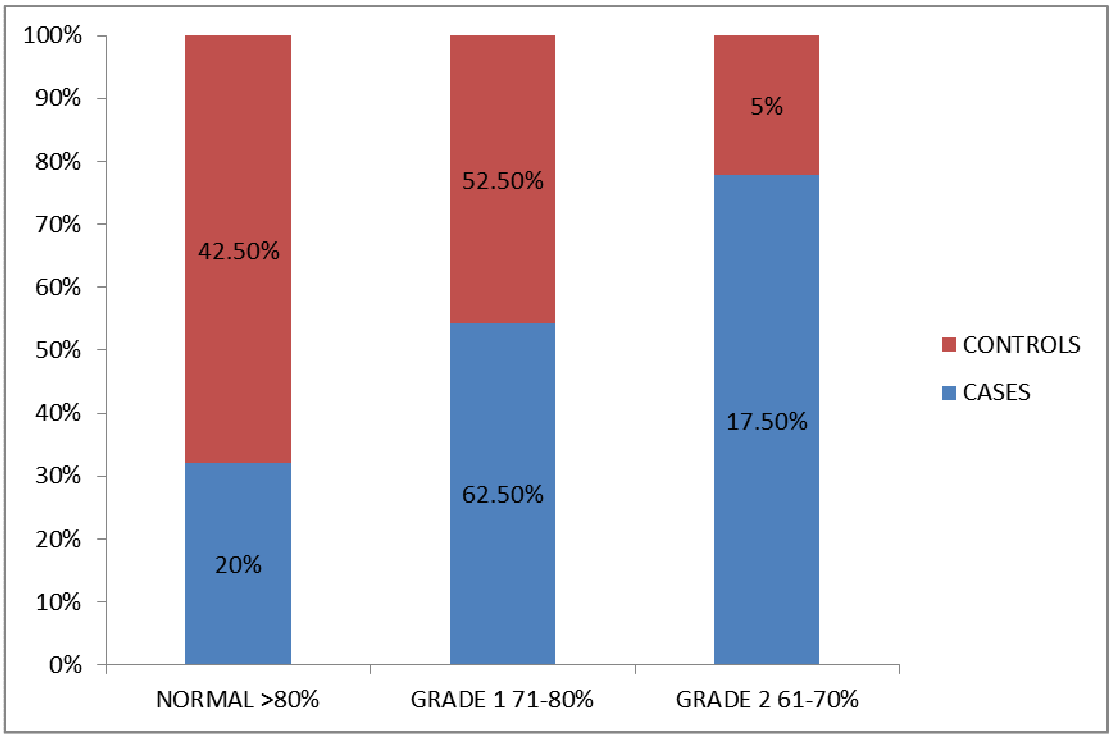


Figure 4 - NUTRITIONAL STATUS AMONG BOTH THE CASES & CONTROLS

TABLE 5 : MEAN VALUE OF SERUM ZINC AMONG CASES AND CONTROLS

	CASES		CONTROLS		T STATISTICS	P VALUE
	MEAN	SD	MEAN	SD		
SERUM ZINC	35.08	8.56	70.23	13.41	-13.96	<0.001

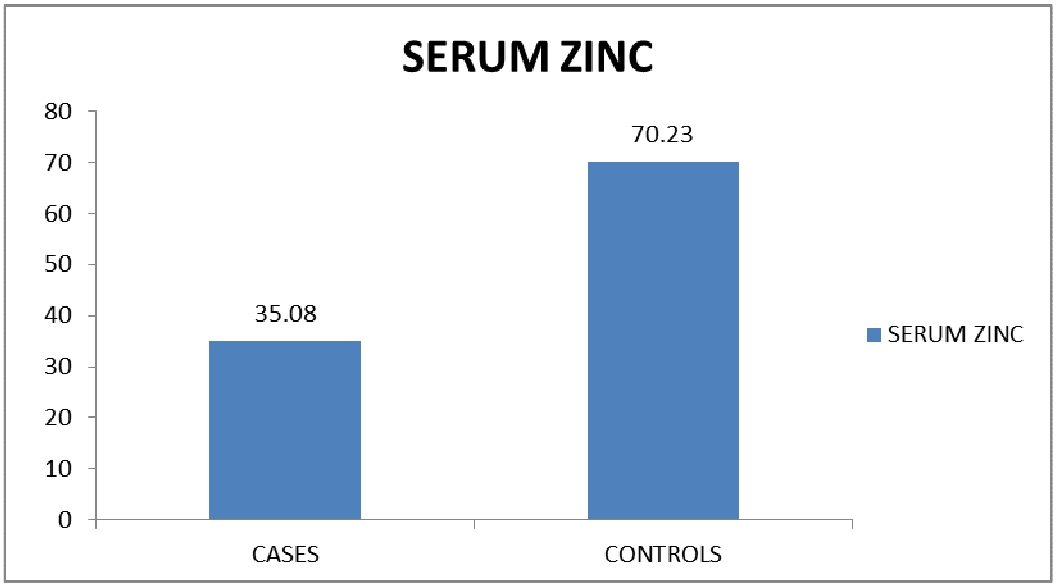
The mean serum zinc is lower among cases group than the controls. The difference between both the groups is statistically significant with a p value <0.001.

TABLE 6: MEAN VALUE OF SERUM MAGNESIUM AMONG CASES AND CONTROLS

	CASES		CONTROLS		T STATISTICS	P VALUE
	MEAN	SD	MEAN	SD		
MAGNESIUM	1.35	0.29	1.68	0.42	-3.946	<0.001

The mean value of serum magnesium is lower among the cases group than the controls. The difference between both the groups is statistically significant with a p value <0.001.

MEAN VALUE OF SERUM ZINC AMONG CASES AND CONTROLS



MEAN VALUE OF SERUM MAGNESIUM AMONG CASES AND CONTROLS

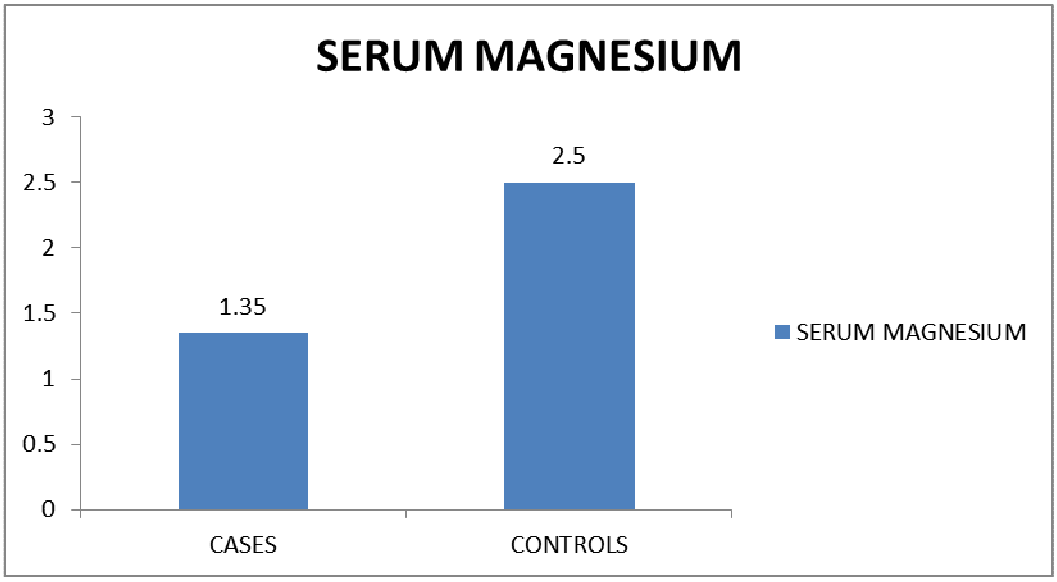


Figure 5 - MEAN VALUE OF SERUM ZINC & MAGNESIUM AMONG CASES AND CONTROLS

TABLE 7: COMPARISON OF SERUM ZINC VALUE BETWEEN THE TWO GROUPS ACCORDING TO THE AGE GROUP 6 MONTHS TO 1 YEAR.

AGE 6 MONTHS -1 YEAR	SERUM ZINC	
	MEAN	**SD**
CASES	36.33	6.42
CONTROLS	75.44	13.84

The difference is statistically significant with a p value <0.001

TABLE 8: COMPARISON OF SERUM ZINC VALUE BETWEEN THE TWO GROUPS ACCORDING TO THE AGE GROUP 1-2 YEARS

AGE 1-2 YEARS	SERUM ZINC	
	MEAN	**SD**
CASES	37.05	8.83
CONTROLS	66.87	13.11

The difference is statistically significant with a p value <0.001

TABLE 9: COMPARISON OF SERUM ZINC VALUE BETWEEN THE TWO GROUPS ACCORDING TO THE AGE GROUP 2-3 YEARS

AGE 2-3 YEARS	SERUM ZINC	
	MEAN	**SD**
CASES	33.78	9.20
CONTROLS	70.10	13.67

The difference is statistically significant with a p value <0.001.

TABLE 10: COMPARISON OF SERUM ZINC VALUES BETWEEN BOTH THE GROUPS ACCORDING TO THE AGE GROUP 3-4 YEARS

AGE 3-4 YEARS	SERUM ZINC	
	MEAN	SD
CASES	29.5	9.19
CONTROLS	66	9.90

No significant difference was observed for the 2 values.

TABLE 11: COMPARISON OF SERUM ZINC VALUES BETWEEN BOTH THE GROUPS ACCORDING TO THE AGE GROUP 4-5 YEARS

AGE 4-5 YEARS	SERUM ZINC	
	MEAN	SD
CASES	31.0	11.17
CONTROLS	73.50	16.42

No significant difference was observed for the 2 values.

TABLE 12: COMPARISON OF SERUM MAGNESIUM AMONG THE CASES AND CONTROLS BETWEEN AGE GROUP 6 MONTHS TO 1 YEAR

AGE 6 MONTHS – 1 YEAR	SERUM MAGNESIUM	
	MEAN	SD
CASES	1.19	0.28
CONTROLS	1.92	0.39

The difference is statistically significant with a p value <0.001.

TABLE 13: COMPARISON OF SERUM MAGNESIUM AMONG CASES AND CONTROLS BETWEEN THE AGE GROUP 1-2 YEARS

AGE 1-2 YEARS	SERUM MAGNESIUM	
	MEAN	SD
CASES	1.53	0.28
CONTROLS	1.71	0.43

No significant difference was observed for the 2 values.

TABLE 14: COMPARISON OF SERUM MAGNESIUM AMONG CASES AND CONTROLS BETWEEN THE AGE GROUP 2-3 YEARS

AGE 2-3 YEARS	SERUM MAGNESIUM	
	MEAN	SD
CASES	1.29	0.26
CONTROLS	1.47	0.42

No significant difference was observed for the 2 values.

TABLE 15: COMPARISON OF SERUM MAGNESIUM AMONG CASES AND CONTROLS BETWEEN THE AGE GROUP 3-4 YEARS

AGE 3-4 YEARS	SERUM MAGNESIUM	
	MEAN	SD
CASES	1.40	0.28
CONTROLS	1.50	0.14

No significant difference was observed for the 2 values.

TABLE 16: COMPARISON OF SERUM MAGNESIUM AMONG CASES AND CONTROLS BETWEEN THE AGE GROUP 4-5 YEARS

AGE 4-5 YEARS	SERUM MAGNESIUM	
	MEAN	SD
CASES	1.23	0.30
CONTROLS	1.63	0.46

No significant difference was observed for the 2 values.

LINEAR CORRELATION FOR THE SERUM ZINC, SERUM MAGNESIUM VALUES FOR THE AGE GROUPS

- The relationship between serum zinc and age is -0.240 which indicates a 24% negative relation between serum zinc and age.

- The relationship between serum magnesium and age is -0.038, which indicates a 4% negative relation between serum magnesium and age.

TABLE 17 – COMPARISON OF SERUM ZINC & MAGNESIUM AMONG THE TWO GROUPS ACCORDING TO THE GENDER :

MALES	SERUM ZINC		SERUM MAGNESIUM	
	MEAN	SD	MEAN	SD
CASES	33.93	9.04	1.34	0.23
CONTROLS	73.70	14.67	1.81	0.44

The difference between serum zinc & magnesium values among the male children in the 2 groups is statistically significant with a p value < 0.001.

FEMALES	SERUM ZINC		SERUM MAGNESIUM	
	MEAN	SD	MEAN	SD
CASES	36.51	7.96	1.38	0.37
CONTROLS	65.53	10.12	1.50	0.35

The difference between serum zinc value among the female children in the 2 groups is statistically significant with a p value < 0.001, the difference between serum magnesium value is not significant.

SUMMARY OF THE RESULTS

SUMMARY OF THE RESULTS

1) The mean serum zinc & magnesium levels were lower in the cases group than the controls with a statistically significant p value < 0.001.

2) The incidence of febrile seizures in our study was maximum among the age group 1 – 2 years.

3) The incidence of febrile seizures in our study was slightly higher among male children than the female children with a male to female ratio of 1.2:1.

4) Family history was positive in 11 out of 40 children (cases), i.e 22.5% of the cases.

5) Among the 2 groups the maximum number of children were in the grade 1 malnutrition (71 – 80%).

6) Comparing the mean serum & magnesium values among both the groups according to age, statistically significant low levels with a p value <0.001 was found in the age group 6 months – 1 year. Among 1 – 2 years, the serum zinc level was lower with a significant p value <0.001. Among 3-4, 4-5 years age, no significant difference was observed for the serum zinc & magnesium values.

7) Linear correlation between serum zinc & magnesium with age is negative, with a value of -0.240 for zinc and -0.038 for magnesium.

DISCUSSION

DISCUSSION

Febrile seizure is the most common type of seizure in children. The exact etiopathogenesis is unknown. Multiple etiological factors are considered in the pathogenesis of febrile seizures, such as genetic factors, family history, following immunisation, deficiency of specific nutrients like iron, zinc, magnesium, selenium and copper and some changes in the level of pro inflammatory cytokines have been suggested to be responsible.

In our study to detect low serum zinc & magnesium a possible risk factor for first episode simple febrile seizures, 40 cases and 40 age and sex matched controls were studied and analysed.

In the present study we found that the peak incidence of febrile seizures was occurring between 1 to 2 years. This is comparable to the previous studies. The peak age of onset being 14 – 18 months as per Nelson Textbook of Pediatrics. Berg et al. in his study found that the peak incidence is between 18 to 24 months. Similarly Naveedur Rehman .et al. from their study reported a peak incidence of febrile seizures at 22 months.

In our study the incidence of febrile seizures was slightly higher among the boys than the girl children, with a male to female ratio of 1.2 : 1. This is similar to the study done by Berg et al. but in the study by Naveedur Rehman et al. no gender difference was observed for incidence of febrile seizures.

In our study children with positive family history developing febrile seizures were 22.5 %, Forfar textbook of Pediatrics says about 50 % of febrile seizures children will have a positive family history. Van Esch et al. in Prediction of Febrile seizures in children, a practical approach. Neuropediatrics 1998;157:340 – 4 . says a risk of 10 – 45 % exists for occurrence of febrile seizures if a first degree relative or a sibling has febrile seizures. The results of our study revealed significantly low serum zinc & magnesium level among cases than the controls, this was comparable to many studies done previously.

STUDY	**SERUM ZINC (CASES)**	**SERUM ZINC (CONTROLS)**	**SERUM MAGNESIUM (CASES)**	**SERUM MAGNESIUM (CONTROLS)**
Our study	35.08 µG/dl	70.23 µg/dl	1.35mg/dl	1.68mg/dl
Study by Ahmed Talebian et al.	116.28 mg/dl	146mg/dl	2.21mg/dl	2.39mg/dl

STUDY	**SERUM ZINC (CASES)**	**SERUM ZINC(CONTROLS)**
Our study	35.08µg/dl	70.23µg/dl
HeydarianFarhad et al	663.7µg/dl	758.33µg/dl
LusianaMargaretha et al	8.83µmol/L	13.72µmol/L
MojitabaAmiri et al	66.13 ±18.97µg/dl	107.87±28.79µg/dl
Lalit Kumar et al	79.55±40.84µg/dl	120±37.79µg/dl
FahmehEhsanipour et al	76.82±24.36mg/dl	90.1±14.6mg/dl
Ganesh et al	32.17µg/dl	87.6µg/dl

Among the various studies done previously, the serum zinc values among cases and controls are more comparable with the study done by Ganesh et al, in India.

Many reasons have been proposed for the reduction of serum zinc and magnesium levels among children with febrile seizures. Izumi et al. proposed that the hypozincemia during fever trigger the NMDA receptor, which plays an important role in the initiation of epileptic discharge during febrile seizures. Zinc acts as a neurotransmitter and improves the communicating function and evolution of neurological system[5]. Zinc deficiency diminishes hippocampal zinc and leads to seizure discharge [52].

CONCLUSION

CONCLUSION

In our study a significant difference existed between the levels of serum zinc and magnesium in children with febrile seizures and children with fever without seizure, it is concluded that there is a relationship between levels of serum zinc & magnesium and incidence of febrile seizures in children.

The maximum age of onset of febrile seizures was between 1 – 2 years and male children had slightly higher incidence of febrile seizures than the female children.

A positive family history was present in 22.5 % of children in our study.

LIMITATIONS AND RECOMMENDATIONS

LIMITATIONS AND RECOMMENDATIONS OF THE STUDY

All children with simple febrile seizures were included in the study,children with undernourishment were not excluded from the study.

The duration of fever, nutritional status of the cases and controls were not matched.

Previous studies have shown low CSF zinc in children with febrile convulsions, we could not do the CSF zinc.

In future, studies regarding administration of supplementary zinc and magnesium in preventing recurrences of febrile seizures would be of great value.

BIBLIOGRAPHY

BIBLIOGRAPHY

1) Johnston MV. Seizures in Childhood. Behrman RE, Kleigman RM, Jenson HB, editors, Nelson Textbook of Pediatrics 18 th edition ch 593;p:2457-75.

2) Campbell A, McIntosh C (eds). Forfar and Arneil's Textbook of Pediatrics. 4th ed. Churchill Livingstone :1992;p 754-755.

3) Aicardi J. febrile convulsions. In : Epilepsy in children : International review of Child Neurology series. New York, Raven Press, 1994;pp 253-275.

4) Hambidge M. Human zinc deficiency. *J Nutr.2000 May*; 130 (5s Suppl):1344S-1349S.

5) Mahyar A. The preventive role of zinc from communicable and noncommunicable diseases in children,NCD Malaysia, 2005;4:21-25.

6) Burhanoglu M, Tutuncuoglu S, Coker C. Hypozincemia in Febrile Convulsions. *Eur T Pediatr* 1996;155: 498-501.

7) Hamed SA, Abdellah MM. Trace elements and electrolytes homeostasis and their relation to antioxidant enzyme activity in brain hyperexcitability of epileptic patients. *J PharmacolSci* 2004;96(4)349-59.

8) Om Prakash m, Deepak s, ram sanmukh U, Ranjiti P, Divya A. Cerebrospinal fluid zinc, magnesium, copper and gamma aminobutyric acid levels in febrile seizures. *J pedNeurol* 2005;7(1)39-44.

9) Hirtz DG. Febrile seizures .In : American Academy of Pediatrics. Pediatrics in Review, Arab World Edition, Amman : Aram Publishing House ; 1997 p. 5-8.

10) Lewis MH, Parry JV, Parry RPetal. Role of Viruses in Febrile convulsions. *Arch DisChild*1979 ; 54 : 869-876.

11) Hirtz DG, Nelson KB, Ellenbery JH. Seizures following children immunisation. *J Pediatr1983* ; 120:14 – 18.

12) Qu L, Leung LS. Mechanism of Hyperthermia – induced depression of GABA ergic synaptic transmission in the immature rat hippocampus. *J Neurochem* 2008; 106:2158-69.

13) Thomas EA, Hawkins RJ, Richards KL, Xu R, Gazina EV, Petrou S. heat opens axon initial segment sodium channel: a febrile seizure mechanism*? Ann Neurol* 2009;66:219-26.

14) Nakayan J, Hassano K, Iwasaki N. Significant evidence for the linkage of febrile seizures to chromosome 5q14-q15. *Hum Mol Gene* 2000; 87-91.

15) Baraister M. Relevance of Family History of Seizures. *Arch Dis Child* 1983;58:404-405.

16) Tutuncuoglu S, Kutukcuker N, Kepe L, Coker C, Berdeli A and Tekgul H (2001), Proinflammatory cytokines, prostaglandins and zinc in febrile convulsions. *PediatricsInternational*, 43:235-239.

17) AAp Grand rounds , iron deficiency , a risk factor for febrile seizures.2002,8(16);62-63.

18) Febrile seizures review and update – *J pediatrNeurol* 2002;2(1);22-24.

19) Waruiru c, r Appleton , Febrile seizures an update, arch Dis child, 2004;89:751-756

20) Berg AT, Shinnar S, Darefsky AS, et al. Predictors of recurrent febrile seizures.
A prospective cohort study, *Arch Pediatraddex med* 1997;151:35-378.

21) Hirtz DG, Generalised Tonic Clonic and febrile seizures. *Pediatric clinic of NorthAmerica*. 1989;36:365-382.

22) El Radhi As, Withana K, Banajih S. Recurrence rate of febrile seizures related to the degree of pyrexia during first attack. *Clinpediatr* 1986; 25:311-13.

23) Verity CM, Greenwood R, Goldng J. Long term intellectual and behavioural outcome of children with febrile convulsions . *N. Engl J Med* 1998;338:1723-1725.

24) Mitchell TV, Lewis Dv, Do prolonged febrile seizures injure the hippocampus? Human MRI Studies . In: Baram TZ, Shinnar S, eds. Febrile seizures. San Diego: Academic Press, 2002:103-21.

25) Theodore WH, Bhatia S, Hatta J, et al. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. *Neurology* 1999;52:132-6.

26) Liv Z, Mikate M, Holmes GL. Mesial temporal sclerosis: Pathogenesis and significance. *PediatrNeurol* 1995; 12:5-16.

27) Callenbach PM, Westendrop RG, Geerts AT et al. Mortality results in children with epilepsy: the Dutch study of epilepsy in childhood Pediatrics 2001;107:1259-63.

28) Vestergaard M, Hviid A, Madsen KM,Wohlfarht J, Thorsen P, Schendel D , et al. MMR vaccination and febrile seizures : evaluation of susceptible subgroups and long term prognosis. *JAMA* 2004; 292:351-7.

29) Offringa M, Moyer VA. An evidence –based approach to managing seizures associated with fever in children. *West J Med 2001;* 175: 254-9.

30) Joffe A, McCormick M, DeAngelis C. Which children with febrile seizures need lumbar puncture? A decision analysis approach. *Am J Dis Child 1983*; 1153-1156.

31) Joint Working Group of the Research unit of the Royal College of Physicians and the British Pediatrics Association. Guidelines for the management of convulsions with fever. *BMJ 1991*; 303: 634-6.

32) Mcbee GN, Wark JE. A practical approach to uncomplicated seizures in children.*Am Fam Physician 2000*; 62;1109-16.

33) Boniha L, Montenegro MA, Cendes F, Li LM. The role of neuroimaging in the investigation of patients with single seizures, febrile seizures, or refractory partial seizures. *Med Scimonit 2004*; 10: 40-6.

34) Rosman NP. Evaluation of the child who convulses with fever. *Pediatr drugs 2003*; 5: 457-61.

35) Maytal J, Steele R, Eviate L, Novak G. the value of postictal EEG in children with complex febrile seizures.

36) Gregory Stores. When does an EEG contribute to the management of febrile seizures.*Arch Dis Child 1990*;66:554-557.

37) Schnaiderman D, Lahat E, Shefeer T, Aladjem M. Antipyretic effectiveness of acetaminophen in febrile seizures: ongoing prophylaxis versus sporadic usage. *Eur J Pediatr 1993*; 152: 747-9.

38) Steering committee on Quality Improvement and Management, Subcommittee on Febrile seizures. Febrile seizures: clinical practice guideline for the long term management of the child with simple febrile seizures. *Pediatrics 2008*; 121 :1281-6.

39) Adhoc Task force of Lice Guidelines Commission .recommendations for the management of febrile seizures.. *Epilepsia2009*; 50: 2-6.

40) Rosman NP, Colten T, Labazz P, Gilbert PL, Gasdella NB, Kaye Fm et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993; 329: 79-84.

41) Manreza ML, Gherpelli JL, Machado Hairtel LR, Pedreira CC, Heise CO, Diament a. Treatment of febrile seizures with intermittent clobazam. *ArqNeuropsiquiatr* 1997; 55: 757-761.

42) Knudson FU, Paerregaard A, Anderson R, Anderson J. Long term outcome of prophylaxis for febrile convulsions. *Arch Dis Child* 1996; 74: 13-18.

43) Camfield RR, Camfield CS, Shapiro SH, Cumming C. The first febrile seizure anti-pyretic instruction plus either Phenobarbitone or placebo to prevent recurrence. *J Pediatr* 1980; 97:16-21.

44) Antony JH, Hawke SHB. Phenobarbitone compared with carbamazepine in prevention of recurrent febrile convulsions. *Am J Dis Child* 1983; 137:892-5.

45) Papierkowski A, Mroczkowska-Juchkiewicz A, Pawlowska-Kamieniak A, Pasternak K. magnesium and zinc levels in blood serum and cerebrospinal fluid in children with febrile convulsions. Pol MerkurLekaski 1999;6(33):138-40.

46) Cousins RJ. Zinc. In: Ziegler EE, Filer LJ Jr, editors. Present knowledge in nutrition. 7th Ed. Washington Dc: ILSI Press, 1996;p. 40-50.

47) Fredrerickson C.J and Moncrieff D.N(1994), Zinc containing neurons. *Biological signals 3*, 127-139

48) Frederickson C.J (1989) Neurobiology of zinc & zinc containing neurons. *Int. Rev. Neurobiol.* 31,145-238.

49) Peters S, Koh J, Choi W. Zinc selectively blocks the action of NMDA on cortical neurons .*Science* . 1987; 236(4801): 589-93.

50) Enhui Pan et al. Vesicular Zinc Promotes Presynaptic and Inhibits Postsynaptic Long Term Potentiation of Mossy Fibre- CA3 Synapse. *Neuron*, 2011; 71(6):

51) "Zinc Homeostasis and Function of Zinc in the brain" Department of Radiobiochemistry, School of Pharmaceutical Sciences, University of Shizuka, Japan, *Biometals*. 2001 sep-dec; 14(3-4): 343-51.

52) Tapiero H, Tew KD. Trace elements in human physiology and pathology: zinc and metallothioneins. *Biomed Pharmacother*. 2003 Nov; 57 (9):399-411.

53) Izumi Y, Ishii K, Akiba K, et al. Hypozincemia during fever may trigger febrile convulsion. *Med Hypothesis*. 1990; 32(1):77-80.

ANNEXURES

PROFORMA

CASE

SERIAL NO:

NAME: INFORMANT:

AGE: RELIABILITY:

SEX:

NUTRITIONAL STATUS:

TYPE OF SEIZURE:

DURATION OF SEIZURE:

DURATION OF FEVER:

PREVIOUS H/O FEBRILE SEIZURE:

FAMILY H/O SEIZURES:

DEVELOPMENTAL H/O :

H/O SUPPLEMENTS INTAKE:

EXAMINATION :

GENERAL EXAMINATION,

HEAD TO FOOT EXAMINATION

CNS EXAMINATION:

HIGHER MENTAL FUNCTIONS

CRANIAL NERVES

MOTOR SYSTEM:

BULK

POWER

TONE

REFLEXES- SUPERFICIAL, DEEP

B/L PLANTAR RESPONSE

SIGNS OF MENINGEAL IRRITATION:

ANTERIOR FONTANELLE:

SPINE & CRANIUM:

GAIT:

CEREBELLAR SIGNS:

INVESTIGATIONS:

SERUM ZINC :

SERUM MAGNESIUM :

MASTER CHART

CASES

Sl. No.	Name	Age	Sex	Nutritional Status	Serum Zinc	Serum Magnesium	Family H/O Febrile Seizures
1.	Arunashri	1	2	1	44	0.7	2
2.	Gopika	1	2	2	29	1.2	2
3.	Anushka	1	2	2	33	1.1	2
4.	Joshua	1	1	1	38	1.5	1
5.	Rivashree	1	2	2	36	1.2	2
6.	Naveen Raj	1	1	2	28	1	1
7.	Ranjini	1	2	1	46	1.6	1
8.	Mohammed	1	1	1	41	1.4	2
9.	Vignesh	1	1	2	32	1	2
10.	Nithisri	2	2	2	46	1.5	2
11.	Jeshwanth	2	1	2	35.2	1.3	2
12.	Afrin Fathima	2	2	1	48.4	1.5	1
13.	Yuvanshankar	2	1	3	27	1.3	2
14.	Vikki	2	1	1	42	1.7	2
15.	Madhumitha	2	2	2	31	2	2
16.	Logesh	2	1	2	33	1.6	2
17.	Gowtham	2	1	1	45	1.5	1
18.	Kamaeesh	2	1	3	18	1.4	2
19.	Vishnuvardhan	2	1	2	34	1.3	2
20.	Akshaya	2	2	2	39	1	2
21.	Karthikeyan	2	1	2	43.2	1.5	1
22.	Sabitha	2	2	2	27	1.4	2
23.	Kalaivani	2	2	2	39	1.8	2

24.	Priya	2	2	2	47.9	2.1	2
Sl. No.	**Name**	**Age**	**Sex**	**Nutritional Status**	**Serum Zinc**	**Serum Magnesium**	**Family H/O Febrile Seizures**
25.	Vijaya Kumar	3	1	2	48	1.5	2
26.	Vishnu	3	1	2	37	1.4	2
27.	Selvam	3	1	3	24	1	1
28.	Bhargath Nisha	3	2	2	35	1	2
29.	Subash	3	1	2	37	1.4	2
30.	Dhanush	3	1	3	22	1	2
31.	Anitha	3	2	2	32.8	1.5	1
32.	Dhanasekar	3	1	2	43	1.6	2
33.	Tamilarasi	3	2	3	20	1	2
34.	Yuvashri	3	2	2	39	1.5	2
35.	Ramya	4	2	1	36	1.6	2
36.	Mohammed	4	1	2	23	1.2	1
37.	Adithya	5	1	3	17	0.9	2
38.	Irfan	5	1	2	43	1.6	2
39.	Beula	5	2	2	28	1.1	2
40.	Saravanan	5	1	3	36	1.3	2

CONTROLS

Sl.No	Name	Age	Sex	Nutritional Status	Serum Zinc	Serum Magnesium	Family H/O Febrile Seizures
1.	Priyadarshini	1	2	2	68	1.1	2
2.	Kavya	1	2	1	68	2	2
3.	Ramyashri	1	2	1	81	1.7	2
4.	Saravanan	1	1	1	72	1.8	2
5.	Nithya	1	2	2	57	1.9	2
6.	Babu	1	1	1	100	2.5	1
7.	Anitha	1	2	1	63	2	2
8.	Naveen	1	1	1	92	2.3	2
9.	Anand	1	1	2	78	2	2
10.	Pavithra	2	2	3	49	1.8	1
11.	Ramesh	2	1	1	88	2.1	1
12.	Pooja	2	2	1	58	1.5	1
13.	Ashok Kumar	2	1	2	69	2	2
14.	Vijay	2	1	2	61	2.2	2
15.	Divya	2	2	2	66	1.8	2
16.	Kumar	2	1	3	48	2	1
17.	Shankar	2	1	2	56	1.9	2
18.	Santhosh	2	1	1	90	2.3	2
19.	Ajay	2	1	1	70	1.8	1
20.	Jamini	2	1	1	82	1	2
21.	Koushik	2	1	2	58	1.6	2
22.	Monisha	2	2	2	66	1	2
23.	Sharmila	2	2	1	80	1.7	2
24.	Gowri	2	2	2	62	1	2
25.	Vignesh	3	1	1	96	2.3	1
26.	Gowtham	3	1	2	76	1	2

	Name	Age	Sex	Nutritional Status	Serum Zinc	Serum Magnesium	Family H/O Febrile Seizures
27.	Viswanathan	3	1	2	55	1	2
28.	Nisha	3	2	1	82	1.1	1
29.	Ramesh	3	1	2	66	1.5	1
30.	Ashwin	3	1	2	71	1.4	2
31.	Priya	3	2	2	49	1.3	2
32.	Kumaresan	3	1	2	62	2	2
33.	Ameena	3	2	2	66	1.5	2
34.	Lekhasri	3	2	1	78	1.6	2
35.	Vasuki	4	2	2	59	1.4	1
36.	Tamilvannan	4	1	2	73	1.6	2
37.	Saravanan	5	1	1	90	2.2	2
38.	Kumaravel	5	1	2	57	1.5	1
39.	Narmadha	5	1	1	62	1.1	2
40.	Selva Kumar	5	1	1	85	1.7	2

KEY TO THE MASTER CHART

SEX:

1 – Male

2 – Female

AGE:

1- 6 months to 1 year

2- 1 to 2 years

3- 2 to 3 years

4- 3 to 4 years

5- 4 to 5 years

NUTRITIONAL STATUS:

1- MORE THAN 80 % IAP CLASSIFICATION

2- 71 TO 80 % (GRADE 1 OF IAP)

3- 61 TO 70% (GRADE 2 OF IAP)

FAMILY HISTORY OF FEBRILE SEIZURES:

1- WITH POSITIVE FAMILY HISTORY OF FEBRILE SEIZURES

2- WITHOUT FAMILY HISTORY OF FEBRILE SEIZURES.

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Low serum Zinc & Magnesium – A possible risk factor For simple febrile seizures

Principal Investigator : Dr.L.G.Aishwarya Lakshmi

Designation : PG in M.D(Paed)

Department : Department of Paediatrics
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 19.11.2011 at the Modernized Seminar Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate form the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

07/12/11

MEMBER SECRETARY,
IEC, SMC, CHENNAI

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

குழந்தைகளுக்கு காய்ச்சல் காரணமாக வரும் வலிப்பு நோயில், இரத்தத்தில் தாது உப்புக்கள் (ஸின்க் & மெக்னீசியம்) குறைவாக உள்ளதா என்று கண்டறிய உதவும் ஆய்வு

ஆராய்ச்சி நிலையம் : சமூக குழந்தைகள் நல நிலையம்
சென்னை - 600 001.

பங்கு பெறும் குழந்தையின் பெயர் : வயது :

பங்கு பெறும் குழந்தையின் எண் : பாலினம் : ஆண் ☐ பெண் ☐

பெற்றோர் பெயர் / விலாசம் :

பெற்றோர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது ☐

நான் என் குழந்தையை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என் குழந்தையை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என் குழந்தையுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என் குழந்தை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் என் குழந்தையை ஈடுபடுத்த முழுமனதுடன் ஒப்புக் கொள்கிறேன். ☐

இந்த ஆய்வில், என் குழந்தைக்கு இரத்தத்தில் தாது உப்புக்கள் குறைவாக உள்ளதா என அறிந்து கொள்ள, இரத்த பரிசோதனை செய்து கொள்ள முழுமனதுடன் சம்மதிக்கின்றேன். ☐

என் குழந்தையின் நலன் கருதியே இந்த ஆய்வு மேற்கொள்ளப்பட்டது என்று தெரிந்து இந்த ஆய்விற்கு ஒப்பளிக்கின்றேன். ☐

பெற்றோரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

தகவல் படிவம்

ஜீரம் காரணமாக வரும் வலிப்பு நோயில், ஸிங்க் மற்றும் தாது உப்பு குறைவாக உள்ளதா என கண்டறிவதற்கான ஓர் ஆய்வு

தங்களின் குழந்தைக்கு காய்ச்சல் காரணமாக வலிப்பு நோய் வந்துள்ளது. காய்ச்சலுக்காக இரத்தப்பரிசோதனை செய்யும் பொழுது, உடலில் ஸிங்க் மற்றும் தாது உப்பின் அளவு குறைவாக உள்ளதா என்று கண்டறிவத்தற்காக ஓர் ஆய்வு மேற்கொள்ளப்பட உள்ளது. தங்கள் குழந்தையின் நோய் குறித்த விபரங்களை தங்கள் சம்மதத்துடன் இவ்வாய்வில் பயன்படுத்த விரும்புகிறோம்.

தாங்கள் விரும்பினால் மருத்துவ ஆய்விலிருந்து எப்பொழுது வேண்டுமானாலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் தாங்கள் தன் குழந்தையை ஆய்விலிருந்து விலகிக் கொள்ளலாம்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களும், பரிசோதனை முடிவுகளும் தங்களின் ஒப்புதலின் மூலம் மட்டுமே மருத்துவ ஆய்வில் பயன்படுத்தப்படும்.

ஆய்வாளர் கையொப்பம் :

ஆய்வாளரின் பெயர் :

இடம் :

நாள் :