"THE ASSOCIATION BETWEEN SERUM ZINC LEVEL AND FEBRILE SEIZURES IN CHILDHOOD"

BY

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IN

PEDIATRICS

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I solemnly declare that the dissertation titled **"THE ASSOCIATION BETWEEN SERUM ZINC LEVEL AND FEBRILE SEIZURES IN CHILDHOOD"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. R.H.GOBBUR**$_{MD,DCH}$**,** as a guide, Professor Department of **PEDIATRICS** and **DR.J.G.AMBEKAR**$_{MD}$, as a co-guide, Professor Department Of **BIOCHEMISTRY** BLDEU's Shri B.M.Patil Medical College Hospital and Research Centre, Bijapur.

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ABSTRACT

Background:

Febrile seizure defined by national institute of health as " an event in infancy or childhood usually occurring between 3 months to 5 years but without evidence of intracranial infection or defined cause for seizure". Simple febrile seizures are most common form and are single, brief and generalized. Complex febrile seizure is focal, last longer than 15 minutes or include more than one seizure associated with febrile illness. Peak age of febrile seizure is 18 months with recurrent episode occurring in one third of the patients. Serum Zinc levels are shown to be low in febrile seizure in some studies. Hence we want to study this association in our study group.

Objective :

To study the association between serum zinc levels and febrile seizures in childhood.

Method :

It is a prospective case control study. All children with febrile seizure between 6 months and 5 years from Pediatric ward of B.L.D.E.U's Shri. B.M.Patil medical college hospital & research centre were taken as cases and compared with age, weight (nutrition) matched 15 children with and 15 without fever as controls.

Detailed clinical history comprising of age, sex, birth weight, present weight, developmental mile stones, body temperature at admission, cause of fever, history of recent zinc supplementation, family history of febrile seizure as well as details of seizure history, duration, frequency, type of seizure (simple or complex).

All children underwent detailed physical and systemic examination. Serum zinc level was measured using zinc kit by colorimetric method between cases and controls. Normal serum zinc levels is 60-120 µgm/dl.

Results:

Out of 30 cases, 20 had low serum zinc levels and 10 had normal values. Out of 30 controls, 15 controls with fever, 3 had low serum zinc levels, 10 had normal values and 2 had high values. 15 controls without fever, 2 had low values and 13 had normal values.

Conclusion:

Serum zinc levels were found to be low in children with febrile seizure and further zinc supplementation of these children for > 1 month may reduce the recurrence rate of febrile seizure.

Key words: Febrile seizure, Serum zinc levels

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF PHOTO GRAPHS

INTRODUCTION

Febrile seizures are defined by the National Institute of Health as an event in infancy or childhood usually occurring between three months and five years but without evidence of intracranial infection or defined cause for the seizure.

Peak age of febrile seizures is 18 months. Simple febrile seizures are most common form and are single, brief, and generalized tonic clonic in nature last upto 15 min, occurs once in 24 hrs Complex febrile seizures , last longer than 15 minutes, or include more than 1 seizure associated with febrile illness in 24 hrs and focal findings are present during post ictal period.

Genetics factors contribute significantly to the etiology of febrile seizures. Risk factors associated with increase recurrence risk were, age of 12 months or less, birth weight of 2 kgs or less, and initial temperature of 38^0C or less ,positive family history of febrile seizure and complex features.

A recent study suggested that zinc supplementation may be able to help febrile seizures. Zinc is known to play a control role in immune system and zinc deficient persons experience increased susceptibility to a variety of pathogens. Zinc also functions as an anti oxidant and can stabilize membranes.

Zinc modulates the activity of glutamic acid decarboxylase,a rate limiting step in the synthesis of gamma amino butyric acid(GABA) ,and affinity of neuro transmitters such as glutamate to their receptors and facilitates the inhibitory effect of calcium on N-methy-D-aspartate receptors and thus prevents the excitatory neuronal discharge.Thus in hypozincemia n methyl d aspartate receptors get activated inducing an epileptic discharge in febrile children.

As per many studies conducted previously has shown that serum zinc levels in febrile seizures are low, we want to study this relation in our population group.

AIMS AND OBJECTIVES OF THE STUDY

1) To study the association between Serum Zinc level and febrile seizure in childhood.

REVIEW OF LITERATURE

Zinc A Trace Element:

Zinc(Zn) is a trace element (with an abundance of .0076%) in Earth's crust. Zinc is found predominantly as a sulphide compound. Pure zinc is silver white solid at room temperature. Like other metals zinc conducts electricity and can be formed into wires or sheets. Zinc is the fourth most used metal (after iron, aluminum and copper).[(1)]

Chemistry:

Zinc (atomic number 30, relative atomic mass 65.39) is a particularly stable ion. Zinc has fast ligand exchange kinetics and flexible coordination geometry, and is a good electron acceptor (strong lewis acid), with no redox reactions. There is a hypothesis that zinc ions present in cytoplasm at 10^{-11}mol/l in equilibrium with numerous zinc metalloenzymes and transcription factors, act as a "master harmone", particularly in relation to cell division and growth.[(2)]

Health Effects:

Zinc is second only to iron in importance as an essential trace element. The main biochemical role of zinc is its influence on the activity of more than 300 enzymes (from the class of oxireductases, transferases, hydrolases, lyases, isomerases, and ligases). Zinc can be essential for the structure, regulation, and catalytic action of an enzyme. Zinc occurs in enzymes that realize the synthesis and metabolism of DNA and RNA. Zinc influences the synthesis and metabolism of proteins, participates in

glycolysis and cholesterol metabolism, maintains membrane structures, affects function of insulin, and affects growth factors. Zinc has a crucial role in the conformation of the "Zinc Fingers" that allows them to bind with DNA to initiate the transcription process. [2,3,4]

Dietary Sources:

Zinc is widely distributed in food mainly bound to proteins. The bioavailability of dietary zinc is dependent upon the digestion of these proteins to release zinc and allow it to bind to peptides, amino acids, phosphates, and other ligands within the intestinal tract. The most available dietary sources of zinc are red meat, fish, wheat germ and whole bran are good sources, but their zinc content is reduced by milling and food processing.[1-3,5-7]

Requirements:

Infants 5 mg / day

Children and Adolescents - 10 mg / day

Adults (males) – 15 mg / day

Adults (Females) – 12mg/ day

In pregnant and lactating females, the daily requirement increases to 15 mg/day and 19 mg / day respectively.

Sea food, red meat, fish, egg and milk are good sources of zinc. Although vegetable contain appreciable amounts of zinc, the fiber and phytate in them bind zinc and

hence diminishes its bioavailability. Hence, vegetarians are at greater risk for zinc deficiency.

Absorption, Transport, Metabolism, and Excretion:

Regulation of the net intestinal uptake of zinc is by control of absorption efficiency and usually ranges from 20% to 50% of the dietary content. At an intake of 12.2 mg zinc per day, the fractional absorption is 26%, but at the very low intake of 0.23 mg zinc per day this has been shown to increase to 100%. Interaction with other dietary constituents, such as phytates, fiber, calcium, and iron reduce the net absorption of zinc. Iron at supplemental dosages (upto 65 mg/day) may decrease zinc absorption so that pregnant and lactating women taking iron may require zinc supplementation.

Absorbed zinc is transported to the liver where active incorporation into metalloenzymes and plasma proteins occur. About 80% of plasma zinc is associated with albumin and most of the rest tightly bound in the high molecular protein alpha 2 macroglobulin. The zinc on albumin is in equilibrium with plasma amino acid mostly histidine and cysteine and this small (<1%), ultrafilterable fraction may be important in cellular uptake mechanism. [(2)]

Total body content of zinc is about 2 to 2.5 g and the metal is present in the cells of all metabolically active tissue and organs. About 55% of the total is found in muscle and approximately 30% in the bone. Red cell zinc concentration is about 10 times higher than in plasma due to large amounts of carbonic anhydrase. Zinc binding to the metal regulatory transcription factor 1 (MTF1) activates metallothionein (Mt) expression. This multifunctional, low molecular weight proteins (9000 to 10000 Da) has a high content of cysteine and reversibly bind zinc.

Metallothionein (Mt) is important in intracellular zinc trafficking and helps to maintain intracellular zinc concentrations. Hepatic synthesis of Metallothionein (Mt) is induced by interleukin-1, interleukin-6 and glucocorticoids in response to trauma, infection and other stressors.[2,3]

Fecal excretion includes both unabsorbed dietary zinc and zinc secreted into the gut. Urine output of zinc is normally only about 0.5 mg / day, but increases greatly during catabolic illness and ketosis. The release of intracellular contents from skeletal muscle has been established as the source of the excess urinary zinc.[2, 3]

Functions:

More than 300 zinc metalloenzymes occur in all six categories of enzyme system. Important examples in human tissue include 1) Carbonic anhydrase (2) Alkaline phosphatase (3) RNA and DNA polymerases (4) thymidine kinase, carboxy peptidases, and (5) Alcohal dehydrogenase. The key role of zinc in protein and nucleic acid synthesis explain the failure of growth and impaired wound healing observed in individuals with zinc deficiency.[1-3, 5-7]

Proteins form domains able to bind tetrahedral zinc atoms by coordination with histidine and cysteine to form folded structures that are known as “zinc fingers”. These have a important role in gene expression by acting as DNA binding transcription factors and play a key role in developmental biology and also in regulation of steroid, thyroid and other harmone synthesis.

Clinical Deficiency:

As might be expected from multiple biochemical functions of zinc, the clinical presentation of deficiency disease is varied, nonspecific and related to degree and

duration of the depletion. Signs and symptoms include (1) Depressed growth with stunting (2) Increased incidence of infection, possibly related to alterations in immune functions (3) Diarrhea (4) Skin lesion (5) Alopecia.[2]

Effect on growth: Dietary zinc deficiency is prevalent in countries world wide where a cereal – based diet high in phytates,any fiber, but low in animal proteins is common. In children, reduced growth and other developmental abnormalities are reversible by zinc supplementation.

Acrodermatitis Enteropathica: Rare Autosomal recessive disorder caused by inability to absorb sufficient zinc from the diet. The genetic defect is in the intestinal zinc specific transporter gene SLC 39 A4. It is characterized by acrodermatitis (inflammation around mouth, nose fingers etc), diarrhea, alopecia (loss of hair in discrete areas), ophthalmoplegia, and hypogonadism.[2-3, 8-10]

Parenteral Nutrition: Some patients requiring intravenous feeding after surgery are likely to be significantly zinc depleted because of poor oral intake before and after surgery. They may also have increased zinc losses from the intestinal tract via diarrhea and in urine from catabolism of muscle during periods of negative nitrogen balance. Other problems include (1) Diarrhea (2) Mental depression (3) Dermatitis (4) Delayed wound healing (5) Alopecia: Provision of adequate zinc intravenously to achieve a positive zinc balance is associated with improvement in nitrogen balance.[2]

Infectious Disease: Zinc depletion impairs immunity and has a direct effect on the gastrointestinal tract, which increases the severity of enteric infections. A review of zinc supplementation of children in low income countries found significant clinic benefits in cases of persistant diarrhea and respiratory diseases.

Subclinical Effects of deficiency

When zinc deficiency is not severe enough to cause clinical signs and symptoms, it may still have a subclinical effect on (1) immune function (2) the synthesis and action of hormones (3) neurological functions.

Immune Functions: In zinc deficiency, there is reduction in the activity of serum thymulin the thymus specific hormone that is involved in T cell function, and an imbalance develop between Th 1 and Th 2 helper cells. The lytic activity of natural killer cells also decreases. These complex changes result in impairement of cell mediated immunity.[2]

Hormones: Zinc has a role in the synthesis and actions of many hormones, via zinc transcription factors. Zinc depletion is associated with low circulating concentrations of (1) testosterone (2) free T4 (3) Insulin like growth factor 1 and (4) thymulin. Both plasma insulin like growth factor-I and growth velocity increases in zinc supplemented children.[2, 3]

Neurological Effects: Severe zinc deficiency is known to affect mental well being, with varying degree of confusion and depression being consistent with zinc enzymes having important activity in brain development and function..

Hypozincaemia in Febrile Convulsions:

Zinc is the most abundant trace element in the human body and is essential for normal development of central nervous system. [3] The highest concentration of zinc in the human brain is found in hippocampus (approximately 30 µg /g dry weight).[4]

- Zinc modulates the activity of glutamic acid decarboxylase, a rate-limiting enzyme in the synthesis of gamma – aminobutyric acid (GABA), and the affinity of Neurotransmitters such as glutamate to their receptors and

facilitates the inhibitory effect of calcium on N-methyl-b-aspartate receptors, thus preventing the excitatory neuronal discharge. [11] Thus in hypozincaemia these N methyl-D-asparatate receptors get activated, inducing an epileptic discharge in febrile children [11-13]

Toxicity: Clinical effects of ingestion of a zinc contaminated diet are (1) Abdominal pain (2) Diarrhea (3) Nausea (4) Vomiting. More than 60 mg zinc per day has been known to result in copper depletion by causing blocakade of intestinal absorption.[1-3,5]

Treatment of Deficiency:

Acquired zinc deficiency states can be treated with 0.5 to 1.0 mg elemental zinc / kg/day for several weeks or months.

- Oral zinc can be administered as the sulfate or acetate.
- 1 mg of elemental zinc is equivalent to 4.5 mg zinc sulphate or 3 mg zinc acetate.
- Intravenous requirements for patients maintained on prolonged intravenous feeding approximate 50 µgm of elemental zinc/kg body weight/day.[2, 8-9]

Laboratory Evaluation of zinc status:

Plasma zinc concentration is measured by atomic absorption spectrophotometry, as well as colorimetric method

- Low urine zinc levels in presence of low serum zinc levels, usually confirms zinc deficiency. [1] Low serum zinc in an apparently healthy patient who has normal serum albumin levels can be used as evidence of zinc deficiency, especially if urine zinc levels are also low.

Reference Interval for Zinc:

- Zinc in serum 60-120 µgm/day .
- Zinc in urine of normal subjects: 140-800 µgm/24 hours.
- Zinc in urine of patient on oral zinc therapy for wilson disease >2000 µgm/24 hours. [1,5]

FEBRILE CONVULSIONS

Febrile convulsions are the most common seizures disorders in childhood with a uniformly excellent prognosis.

There has been three large population based studies:

1) The National Collaborative Perinatal Project (NCPP) which enrolled approximately 54,000 pregnant American women between 1959 and 1966 followed up their children until 7 years of age.
2) The system of medical records linkage of Rochester Epidemiology Project which was used to identify residents of Rochester, Minnesota ,USA, who had seizures.
3) The Child Health and Education Study (CHES), a birth cohort study, which enrolled over 16,000 neonatal survivors born in United Kingdom in one week in April, 1970 and followed them for 10 years .[22]

Historical Review:

"Lastly we may observe, to the great comfort and satisfaction of the parents of those children subject to convulsions, or the epilepsia infantilis, that they need not be apprehensive of its changing into the true epilepsy, for it generally disappears or decreases, as they grow older and acquire more strength"

Hippocrates noted that "convulsions occur to children if acute fever be present… most readily upto their seventh year. Older children and adults are not equally liable to be seized with convulsions in fevers, unless some of the strongest and worst symptoms precede. [15]

Von Rosenstein (1776), Disease of Children and their Remedies. (British Edition)

The great Swedish proto-paediatrician, Von Rosenstein, in his rather optimistic prognosis for early convulsions, showed remarkable insight, not only into the concerns of parents, but also into the tendency towards spontaneous improvement. He clearly recognized the distinction to be made between these young children who are subject to seizures for a limited period and those who, showing a tendency to recurrent attack some what later, justify the use of the word 'epilepsy'[14]

Hughlings Jackson (1888) 'Epilepsy is the expression of occasional, sudden, excessive, rapid, local discharge in the grey matter.[14]

Definitions:

The most widely accepted definition is the one by the National Institutes of Health (NIH) consensus panel (USA, 1980) which defines febrile convulsions as an event in infancy and childhood usually occurring between 6 months and 5 years of age associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous non febrile seizures are excluded. A rectal temperature of 38^0C or more is usually accepted in this definition [16-20]

- All seizures with fever are not benign febrile seizures. "Febrile Convulsions" should be distinguished from "convulsions with fever" which include any seizure in a child of any age with fever of any cause-like those with pyogenic meningitis, encephalitis, hypernatremic dehydration or other metabolic disease. These may carry a more ominous prognosis than that of febrile seizures owing to the effects of associated illness.

- The joint working group of the research unit of the Royal College of Physicians and the British Pediatric Association defines febrile convulsions as "an epileptic seizure occurring in a child aged from six months to five years, precipitated by fever arising from infection outside nervous system in a child who is otherwise neurologically normal. "The working group considered that it was proper to use the term "epileptic" in so far as the neurophysiological substrate of a febrile convulsion is a paroxysmal neuronal discharge, as in an epileptic seizure (3 July, 1990). [21]

The commission on Epidemiology and Prognosis of the International League Against Epilepsy (1993) agreed on the following definition:

"an epileptic seizure… occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizure, and not meeting criteria for other acute symptomatic seizures" [22]

Seizure (convulsion) is defined as a paroxysmal involuntary disturbance of brain function that may manifest as an impairment or loss of consciousness, abnormal motor activity, behavioural abnormalities, sensory disturbances, or autonomic dysfunction. Some seizures are characterized by abnormal movements without loss or impairment of consciousness.

- Epilepsy is defined as recurrent seizures unrelated to fever or to an acute cerebral insult.
- Children with pre-existing neuro-developmental abnormalities may also have febrile convulsions, and such children are included in the definition of the consensus panel. However there is some difference of opinion and type of underlying abnormality.
- The joint working group of British Physicians and Pediatricians have, therefore, limited their definition of febrile convulsions to include only neurologically normal children [19,21]

Status Epilepticus:

The minimum length of time required for a seizure to be regarded as an episode of status epilepticus has become shorter with time. Aicardi, chevrie, oxbury and whitty regarded one hour as minimum. Now 30 minutes is more generally required.

The guidelines published by the International League Against Epilepsy defined status epilepticus as:

"a single epileptic seizure > 30 minutes duration or a series of epileptic seizures during which conciousness is not regained between ictal events in a > 30 minute period".[22]

General Consequence of Infection

- Exogenous pyrogens released during viral and bacterial infections cause an upward setting of the thermoregulatory centers in hypothalamic / preoptic areas. It has been suggested that the associated release of acetylcholine in the caudal hypothalamus with subsequent activation of nicotinic receptors concerned in thermogenesis might be directly related to the precipitation of febrile convulsion.[23]

- Febrile seizure manifest in the first hour of acute infectious illness, eighty percent of febrile seizures occur during the first day of fever before the parent is aware of the fever.[24]

- Whether the most important factor in the induction of the convulsions is the level of the temperature, the rapidity of its rise, or both remains the subject of debate.[16,25]

- The height of the body temperature is the major determinant of seizures with hyperthermia, rather than the rapidity of the rise of temperature.[14]

- The suddenness of the rise of temperature appears to be more important than the actual temperature reached for febrile convulsion to occur.[26-27]

- The notion that the rate of rise of temperature is important has been attributed to Welch in 1888 but was first carefully investigated by Berg and reported in 1939. Berg conducted experiments in Kittens.[28]

- Millichap in his animal studies reported no association between rate of temperature rise and occurrence of convulsions and he noted that animals have seizure once they reached a certain temperature, regardless of the rate of rise of the temperature.[28]

- Millichap followed 51 children with febrile seizures and collected data on the height of fever during all subsequent illnesses. The mean temperature was higher during episodes associated with febrile seizures compared with the maximum temperature observed in episodes in which no seizure occurred (40^0C vs 39.6^0C P<.001). Based on both his animal experiments and clinical observations Millichap concluded that "the height of body temperature was the important determinant in the induction of occurrence of seizures" and postulated that each individual has his or her own threshold above which a seizure may occur.

- The height of temperature at the time of the initial febrile seizure has also been correlated with the risk of recurrent febrile seizures.

- Lennox-Buchthal has reviewed examples of children who, once having had a seizure at a particular temperature did not have another seizure when that same temperature was reached or exceeded days to weeks later.

- Minchom and Wallace studied the occurrence of electroencephalographic abnormalities with height of temperature in nine children. They did not find a

correlation between the two. Although neither of these two reports is definitive, they do underscore, as did the authors, the point that is unclear is what the exact role of fever is in eliciting a convulsion, and they raise the possibility that some other aspect of infection may also be responsible. [28]

Incidence: Febrile seizure have an incidence of 6% among children under 6 years of age.[29-30] Various studies have been conducted and these studies also show a figure ranging from a minimum of 1% to a maximum of 9%. [28] The incidences in various studies are as follows:

A study conducted by Vanden Berg and Yerushalmy in 1969, Annegers et al in 1979 and Variety et al in 1985, shows an incidence of 19 to 36 per 1000 children.[31]

- Another study by Lennox gives a figure of 29 per 1000 under 5 years of age.[32]
- Barucha et al (1991) in their pioneer prevalence study reported a prevalence rate of 17.7 per 1000 population among Indian Children and this indicates that the frequency of febrile seizures may be no different in the developing and developed countries[32]

Author	Year of Study	Per 1000 Hospital Admission	Percentage
Lennox[32]	**1949**	**50**	**5.0%**
Bandari[34] et al	**1959**	**67**	**6.7%**
Millichap [35]	**1968**	**35**	**3.5%**
Vandenbug[31]	**1699**	**23**	**2.3%**
Yerushalmy[31]	**1969**	**19**	**1.9%**
Nelson [36](USA)	**1976**	**42**	**4.2%**
Sehgal[37](India)	**1979**	**17**	**1.7%**

There is not much change in the incidence observed in a developing country like India when compared to figures of developed countries . [37]

Houser (1994) [28] suggests that the commutative incidence of febrile seizures among children in Asia ranges from about 1% in China to maximum of 8% in Japan. Febrile seizures are rather uncommon in malnourished children and this could be related to their inability to manifest marked systemic reactions such as high fever in response to infection or due to some chemical or histological alteration in malnourished brain.[39]

Factors Determining Febrile Convulsion

Age: Age is an important factor in production of febrile convulsion.

Febrile convulsion is age specific and unique for it occurs mainly between the age group of 6 months to 6 years. Various studies conducted also show similar figures [40].

The oldest study dates back to 1968 done by Millichap with a review of 7000 children. In this study 4% of the cases had seizures during 6 months to 3 years and 95% had seizures by 5 years. [35]

In another study by Wallace in 1976[41, 42] 50% of the 303 children had their first seizures during the second year of life. Wallace observed that 60% of the affected children had their first attack under 2years of age 20% each between 2 to 3 years and after 3 years of age. Shegal and Bala (1979) have stated that 81.4% of children had their first febrile seizure between 6 months and 3year.[37,49]

Hauser in 1994 has reported that all children in Europe and United States of America had at least one convulsion as associated with Febrile illness before the age of 5years. Peak incidence of febrile convulsion is around 24 months of age..[28]

The strong relationship between age and incidence of febrile convulsions is of great interest but is imperfectly understood. The relative lack of myelination in the immature brain, its changing chemical composition, difference in water and electrolyte balance increased oxygen consumption, diminished dendritic connections and electro physiologic differences from adult brain have all been implicated as possible reasons for the remarkable correlation between febrile convulsions and a restricted age group. [32, 35]

Sex: More common in boys than girls. Millichap in 1968 gave a ratio of 1.4 to 1 (boys to girl's ratio) .An Indian study by Shegal and Bala (1979) showed a figure of 1.68 to 1 (boys to girl's ratio). [39,43] A study conducted by Hauser et al (1985) [28] had a figure of 1.68 to 1 (boys to girls). Yachcha[44] also had a preponderance of male ratio being 1.8:1.

The increased susceptibility of the males has been explained because of their great liability to suffer from congenital cerebral defects.[43]

It is also observed that girls tended to have their first febrile seizures at a younger age than boys.

It has been postulated that a rapid cerebral maturation in girls accounts for the rapid rate of decline of febrile convulsion after the second year .[26]

Genetics:- Plays an important role. There is a definitive clustering of cases of febrile convulsion in relatives of affected children. Most studies indicate dominant mode of inheritance with reduced penetrance and variable expression. 30% of the children on careful enquiry gave a positive history of febrile seizures.

Lennox[32] figures showed that family history of convulsion is more frequent in febrile convulsion than in any other seizure disorder .10% of the parents of the febrile convulsion children had febrile convulsion during their childhood.[32]

In a study by Acardi, 31% of the relatives of febrile convulsions children had history of febrile convulsion and 9% of the siblings had history of febrile convulsion.[45]

But factors involved in inheritance are still controversial, whether the tendency to seizure or the general lowering of the convulsion threshold is not known.[46]

Analysis of twin and family data at Tokyo health centre showed increased risk among twins also. They are follows:

Parent risk factor	-	17%
Sibling risk	-	27%
II degree relative	-	6.1%
III degree relative	-	4.6%

The difference was found more in siblings than parents, uncles greater than aunts, male cousins greater than female cousins. Segregation analysis showed maternal preponderance.

Characteristic findings in febrile convulsion patients with a febrile convulsion parent or sibling, compared with those with no family history, were early onset of febrile convulsion, lower degree of fever, longer duration of seizure, many recurrences, febrile convulsion recurring after 3 years of age, and background EEG abnormality. Hence, a polygenic mode of inheritance for febrile convulsions receives some support from this study and the inheritability was estimated as 75%.[47]

Linkage studies, in several large families, published in 2007,have mapped febrile seizures gene to chromosome number 19p and 8q 13-21.[38]

Etiology Of Febrile Convulsions:

Conceptual / preconceptual and other-factors involved in the induction of Febrile seizures, the mechanisms, the reason why only infants and young children convulse is still unknown.

Developmental immaturity of the neurons and hereditary predisposition have both been blamed for increased susceptibility of the young.

- Maternal ill health before conception was found in significant figures in cases with febrile convulsion.[48]

- Maternal medication during pregnancy in particular diuretics, antiepileptics drugs, antibiotics, antiemetics, antidepressants, and vaginal bleeding have adverse effects on the foetal developing brain and these actually doubled the risk of febrile convulsion.[48,49]

- Studies have proved that children with history of breech presentations, foetal distress during labour/delivery by cesarean section, had an increased risk for febrile convulsion. [41,50]

Fever:

Fever by definition is always present and is usually high. There is no alteration of the normal mechanism for controlling body temperature during febrile episode.[32] Regulatory mechanisms continue to function but at a higher level of temperature. Control of body heat depends on the integrity of the anterior hypothalamus and preoptic area which contains clusters of temperature sensitive neurons. Few neuron - transmitters like, acetylcholine, dopamine, 5

hydroxytryptamine, norepinephrine, epinephrine and gamma aminobutric acid have important roles in the regulation of body temperature[51,52].

It can be seen that rise in temperature of several degrees will necessitate a very large increase of cerebral blood flow if the oxygen and glucose requirements of the brain are to remain satisfied. If this increase in blood flow does not occur a relative anoxia may result. In children with lower seizure threshold, this may well reach the point where a convulsion is produced.

The mean temperature range associated as recorded in various studies has been around 38^0C to 42^0C [53]. The duration of the fever is not important neither is the rapidity in the raise of temperature. [35]

It is postulated that most children with febrile convulsions have a convulsions threshold of temperature beyond which a seizure is precipitated.[35]

Infectious Agents:

Infectious agents are indirectly responsible for febrile episode, as fever is the direct causative factor here. Infectious agents may be bacteria or virus or following immunization. Most common infections producing fever are upper and lower respiratory tract infections (tonsillitis and otitismedia) forming about two third of the cases, alimentary infections due to shigella and salmonella in a tenth of the cases, infectious exanthemata roughly 5% of the cases.[37, 39]

- Viral infections were predominant in studies conducted.[39]
- Gastro intestinal infections, particularly shigella and salmonella have been recorded in 4% to 13% of the cases [39]

- Shegal and Bala [25] reported that upper respiratory tract infections was the commonest cause (60.6%) associated with febrile convulsion.

- Yachcha[44] et al 1981 also reported that upper respiratory tract infection as the commonest cause of fever in cases of febrile seizures. According to an Indian study viral infection was the causative factor in 71 cases out of 100 cases. There were few cases of seizures secondary to vaccination induced fever.

- The prevalence after primary immunization by Aarker (1977) in an unselected population in oxford in the years 1972-1975 was found to be 0.09 per DPT ,0.6 per polio /0.93 for measles [56-58]

- Genetics – Genetics plays an important factor .There is definative clustering of cases of febrile seizure in relatives of a affected children.

- Most studies indicate dominant mode of inheritance with reduced penetrance and variable expression. 30% of the children. on care full enquiry have a positive family history of febrile convulsions But polygenetic mechanism may also be involved [47]

- Vandenberg observed that 9% of younger siblings of children with febrile seizures, later have at least one convulsion. [59] A British National cohort study (Verity et al 1985) observed that children with a positive family history were more likely to have a complex first febrile seizure than those with a negative history.[41] When siblings have febrile convulsions the risk is 3.5 times than in general population [28]

An incidence of 10% family history of febrile convulsion was observed in a study conducted by Sehgal and Bala 1979 [60]. Family history of febrile convulsions in the first or second degree relatives is a risk factor to develop febrile seizures.[61]

Patho physiology:

Neither experimental nor clinical experience has revealed a definitive mechanism for febrile seizures. Immaturity of thermoregulatory mechanism and limited capacity of young animals to increase cellular energy metabolism at elevated temperatures have been implicated. Animal studies suggest that arginine vasopressin may be an important mediator in the pathogenesis of hyperthermia induced seizures.[16,62]

During infancy there is a lowered threshold to convulse in the presence of fever. The brain in children being immature is unstable, hence it reacts to fever by sudden outburst of abnormal activity resulting in a convulsive episode.[60]

The pathophysiology of febrile convulsion can be examined on the basis of:

- Cerebral development prior to and at the critical age.
- Cerebral damage at the time of the convulsion.

Cerebral development at the age critical for febrile convulsion:

Pregnancy may predispose to febrile convulsion, it is possible that abnormal neuronal proliferation and migration might be contributory events, but there is no pathological evidence to confirm this possibility. There is, however evidence from single photon emission computed tomography (SPECT) that focal areas of hypoperfusion can be found in a proportion of children with febrile convulsion.[23]

Cerebral damage in association with febrile convulsion:

There is a reasonable amount of circumstantial evidence to suggest that single brief (fewer than 15 minutes) generalized convulsions with fever do not cause recognizable cerebral damage.

Biochemical evidence of cerebral hypoxia is lacking when the cerebrospinal fluid pyruvate and lactate levels are measured after brief convulsion with fever. Hypoxanthine, xanthine and uridine levels were comparable in patients and in febrile controls, both of whom had significantly higher levels, than afebrile controls ,findings consistent with increased cerebral metabolism during fever. Either prolongation of the seizure for more than 30 minutes or repetition within a 24 hour period is associated with raised cerebrospinal fluid lactate levels and lactate: pyruvate ratios suggesting that cerebral hypoxia had occurred.[23]

In children who died during illness in which febrile convulsion occurred, neuronal necrosis had been described throughout the cerebral cortex but particularly in the frontal and temporal areas with variable changes in the basal ganglia and selective loss of purkinje cells in the cerebellum.[23]

Clinical Features:

The disease is characterized by sudden onset of seizures preceded by a brief febrile illness. Sometimes the initial manifestation is only seizure, the fever goes unnoticed by the parents initially. The seizure generally is simple, occasionally complex. The termination of the seizure is spontaneous and abrupt. In the majority of cases there is hardly any postictal phase except a few where there can be drowsiness to deep sleep for varying duration. After the attack is over, the child appears well.[25]

Although generalized convulsions are the rule, focal features or a Todd paresis are seen in about 10% of the patients.[17,63]

History may reveal features related to the cause of the fever like cold, cough, infection, skin rash and diarrhea.

Type and duration of seizure:

Febrile seizures are usually generalized and tonic-clonic in nature. Sometimes it may be only tonic, the child become stiff and rigid with up rolling of the eyeball. In some cases it may be only clonic from the beginning. Occasionally the child becomes limp. Pallor is a frequent accompaniment. Focal seizures is seen in about 4% of cases.

Febrile seizures are generally brief lasting for a minute or two. Prolonged seizures lasting for more than 15 minutes are seen in about 6.6% of cases. Majority of the children have only one seizure during one episode of febrile illness, in about 16.2% of cases, more than one seizure occur with in 24 hours.[15,25]

Classification:

Commonly febrile convulsions are classified into simple (benign/typical and complex (atypical)[18-19,24,62,64]

Simple Febrile Convulsion	Complex Febrile Convulsion
• About 85% FC • Generalised • Lasts< 15 minute • Do not recur during same illness • No postictal deficit	• About 15% of FC • Associated with one or more of the following- • Focal features • Duration> 15 minutes • Multiple i.e. more than one convulsion within 24 hours • Postictal transient todds paresis

The classification is helpful in determining the risk of recurrence and epilepsy.

Risk of Recurrence:

While relatively few children who experience febrile convulsions develop epilepsy, many children experience recurrences of febrile convulsions.[16]

The overall recurrence rate is only 25-30%.[19] In the NCPP study about 1/3 of children had atleast one recurrence and ½ of those who had one recurrence had further convulsions, 9% had three or more attacks. 50% of the second attacks occurred with in six months of the first convulsion, 75% with in a year and 90% with in 2 years. [65]

Recurrence risk is not uniform for all children with febrile convulsions. The most important factor appear to be age of onset of the first febrile convulsion. The younger the child at the first attack, the more likely are other febrile convulsions.[16-17,65-66]

In the NCPP study males and females and whites and blacks did not differ significantly in their vulnerability to recurrence.[65]

Risk of Recurrence after Febrile Convulsions[19]	
Risk of another febrile convulsion	
After 1 convulsion	30%
After 2 convulsions	40%
After 3 convulsions	40%
3 or more recurrences seen in	4-9% of cases

Various factors are found to be associated with increase risk of recurrence of febrile convulsions. These are,

1) Younger age of onset.
2) Family history of febrile convulsions
3) Lower temperature at the time of febrile convulsions.
4) Shorter duration of temperature before febrile convulsions.

Complex features have not been strongly or consistently associated with an increased risk of recurrence.

The presence of pre-existing or subsequent neurological abnormality may increase the risk of recurrence, but the magnitude cannot be estimated.

It is now being recognized that none of the risk factors alone identify children at risk or low risk of recurrent seizures. The risk is better predicted by a combination of risk factors which act in a cumulative way and can identify groups of various risk categories with such subgrouping, most children (65-75%) fall into a low recurrence risk of <30% with only a minority (3-10%) having a high risk (>75%) and others intermediate (40-50%) recurrence risk.

In a Nigerian study, Airede has shown the younger the age at first febrile convulsion the more likely the recurrence rate. Those with moderate degree of pyrexia were found to be 10 times more likely to have subsequent recurring convulsions compared to those with high degree of pyrexia. Further the recurrence rate was 5 times more higher in first born compared to second borne or more. A male preponderance was observed.[66]

In a retrospective study in Germany, by Plochl and Laubichler. W, of 411 children with cerebral convulsions over a period of 4 years, 160 patients with febrile convulsions were found. This group consisted of 94 boys and 66 girls. Febrile convulsions started in the first half year, increased in second half year and culminated in the second year of life. This age dependent appearance was explained with passive immunization by maternal antibodies so that febrile convulsion appear when these antibodies decrease. The first occurrence of febrile convulsion appeared on an average of 22.9 months, in children with recurrent febrile convulsion a little earlier with 18.2 months.

The interesting fact was that children with a family history of febrile convulsions should an even earlier occurrence of the first convulsion with 14.5 months.[67]

Risk of Epilepsy:

Population based studies have shown that the overall risk of epilepsy after febrile convulsion is only 2-2.5%. The factor increasing the risk of subsequent epilepsy are

1) Complex febrile seizures.
2) Family history of a febrile seizures
3) Presence of neuro developmental abnormality[17,19,25]

Risk of epilepsy after febrile convulsions	
Overall risk after febrile convulsions	2.0-2.5%
Risk of epilepsy after 1 febrile convulsion	
0 Risk factor	1.0%
1 Risk factor	2.5%
3 Risk factor	5-10%

Note: Risk Factors: Seizures prolonged>15 minutes, one sided or 2 or more seizures during the same day, parent or brother or sister with epilepsy ; neurologic disorder or developmental delay.

In neurologically normal children the number of febrile convulsion is only weakly associated with the risk of later epilepsy.

- Different types of seizures (including absence, complex partial and generalized tonic clonic) may occur in those children who develop epilepsy after previous febrile convulsion.

Intellectual and Motor Function:

There is no evidence that febrile convulsion cause a decrease in intellectual functions, or increase the risk of mental retardation, hypoxic CNS damage, injury or death.[17,19,68]

In the British National Child Development Study, children with febrile convulsions did not show deficits in school performance at 7 and 11 year. In the NCPP report of intellectual performance there was no difference between children with febrile convulsions and their convulsion free siblings on IQ testing at 7 years. There were deficits in children in whom non febrile convulsions developed, but many

of these children were suspect or abnormal prior to first febrile convulsion. Neither recurrent convulsions nor those lasting less than 30 minute's were associated with IQ deficit.[17,22]

Factors related to sub optimal cognitive ability in children are:

a) Low social class and perinatal abnormalities.

b) Prior or continuing neurological abnormalities.

c) Recurrence of febrile convulsions.

d) Progression to epilepsy.

Prior treatment with phenobarbitone has no effect on later cognitive or reading abilities.[23]

Differential Diagnosis:

Other causes of acute loss of consciousness or rhythmic involuntary movements in early childhood are: breath holding attacks, reflex anoxic seizures, syncope, rigors and tetany.

In both breath-holding attacks and reflex anoxic seizures, the episodes are acute reactions to noxious stimuli, which are usually unexpected. Syncope is associated with limpness and bradycardia rather than tonic-clonic movements and a tachycardia. Consciousness is usually not lost during rigors or tetany. Benign paroxysmal vertigo, in which sudden acute episodes of unsteadiness occur, is not associated with loss of awareness.[23,62,69-70]

Investigations:

Recommendations for an appropriate work up after febrile convulsion should be done keeping in mind, the costs benefits and indications.

If the convulsions are brief, non repetitive and non focal and if the child awakens alert and fresh with no neurological findings after seizures then a simple work up and further observation is all that is needed. [71]

Investigations are focused on finding a cause of fever, rather than finding a cause for the seizure.

Blood routine, blood sugar, sr. calcium, serum zinc levels by colorimetric method and CSF study relevant to underlying illness are performed in my study.

Examination of the cerebrospinal fluid:

The routine performance of lumbar puncture in all children with febrile seizures, does not seem to be warranted.[62,71-72]

CSF examination should be done in all children with febrile convulsion who are younger than 12 to 18 months.[71-72] This recommendation is mainly based on the experience that nuchal rigidity and meningial signs are difficult to appreciate in infants. In a study of 314 children with CSF examination, 310 had normal CSF.[71] Lober and Sunderland 1980 confirmed the safety of selective policy of performing the lumbar puncture only when clinical signs of meningitis were present or in the absence of these when a senior member advised it.

Indications for lumbar puncture in febrile seizures are:

1) Children below 18 months
2) Complex febrile seizures

The fluid should be examined for cells, protein, sugar. Cultures should be obtained even if CSF is normal otherwise.

Imaging-

Routine performance of skull x-ray is useless.

Cranial computed tomography(CTscan)or magnetic resonance imaging(MRI) may be considered in special circumstances like, abnormal neurological examination, evidence of trauma, focal seizures, persistent seizures despite anticonvulsant therapy, deteriorating clinical conditions.[31,71]

EEG-(Electroencephalography)

It is not a guide to treatment or prognosis .It is not considered as a part of the evaluation for routine.

EEG recorded during acute stages of febrile convulsions reflect changes related more to the underlying infection than the seizures.[73]During the first week after afebrile seizures, between 50% to 70% of the children had normal EEG.[74] Earlier reports shows marked slowing in association with young age and long duration of fever.

But there is no evidence to prove that EEG changes were related to changes in temperature over a 24 hour period of continuous recording, and there was no

relationship between the frequency of the background rhythm and the height of the pyrexia.[75]

Febrile seizures have been linked with "spike and wave EEG patterns".[76]

Thus although EEG might be expected to give some indication of the likelyhood of recurrence of febrile convulsions or the later development of epilepsy; all studies have suggested that when recorded in acute phase they do not provide any useful information for prognosis.[77]

Abnormal EEG results do not identify those children in whom epilepsy subsequently will develop and should not be used as a basis for deciding which children need long term anticonvulsant therapy.[73]

Serum Zinc levels-in all children with febrile convulsion is measured by colorimetric method(zinc kit by Coral Biosystems).For measurement of serum zinc levels 3ml blood in plain bulb is required. **Colorimetric method is as good as atomic absorption spectrophotometry.[78-80]**

Principle-Zinc in an alkaline medium reacts with Nitro-PAPS[78-80] to form a purple coloured complex.Intensity of the complex formed is directly proportional to the amount of zinc present in the sample.

ZINC + NITRO PAPS+ALK MEDIUM-Purple coloured complex.

Normal Reference Values-

Serum-60-120 µgm/dl[78-80]

Management of febrile convulsions-

The management of febrile convulsions can be considered under the following headings:

- Attention to the effects of the seizure
- Antiepileptic drugs in acute stage
- Identification and treatment of the underlying infection
- Recognition of and allaying of parental anxieties

Attention to the effects of the seizure-

In addition to the maintenance of a clear airway, a semiprone position to minimize the risk of aspiration and monitoring of vital signs it is particularly important in febrile convulsions actively to normalize the body temperature .Lowering the body temperature is achieved by removal of excess clothes, fanning, tepid sponging and antipyretic drugs.

Sponging with ice water may cause cutaneous vasoconstriction and actually increase core body temperature. Sponging with tepid water slowly brings down body temperature but may induce shivering which is a potent mechanism of thermogenesis and is uncomfortable. Since sponging does not reset the hypothalamic thermal set point, fever may return once sponging has stopped.[81]

The commonly used antipyretic medications are Paracetamol and the NSAIDS. The antipyretics inhibit the enzyme cyclo-oxygenase which catalyses the conversion of arachidonic acid to PGE2. Reduced levels of PGE2 causes reverse elevations in the hypothalamic set point induced by interleukin1. Heat production diminishes, heat loss increases and temperature drops.

Paracetamol-40-60mg/kg body weight / day per oral in 3 to 4 divided doses

Injections-Deep IM route 10-15 mg/kg body weight/dose.Intra rectal suppositories also available. NSAIDS like Brufen-10 mg/kg/dose in 3 to 4 divided doses per oral, Mefenamic acid -5 to 8 mg/kg/dose in 3 to 4 divided doses per oral.

The rate of decrease in fever is much more faster with NSAID <1 hour as compared to paracetamol.[82-83]

Antiepileptic drugs in the acute stage-

Most febrile convulsion are brief and would be over by the time a child is brought to the doctor. If the child is still having a convulsion, it needs to be managed just like any other convulsion, with

- Maintenance of clear airway
- A semi prone position to minimize the risk of aspiration
- Monitoring of vital signs

The seizures can be terminated by intravenous diazepam or midazolam. Diazepam is injected intravenously in a dose of 0.2-0.3 mg/kg /body weight. It is injected slowly at a rate of 1mg per minute. An alternative formula for use when exact weight is unknown is,1mg per year of age plus additional 1 mg (so that a 2 year old child would require 2+1=3mg).Respiratory depression, respiratory and cardiac arrest may occur and resuscitation may sometimes be needed. The risks are higher when the child has already received barbiturates or paraldehyde, and when convulsing children are sent to hospital, full details of their regular emergency medications should accompany them. It is much less effective by the intramuscular route.Alternatively injection midazolam can be given in a dose of 0.1-0.2 mg/kg/dose intravenously.

Rectal diazepam 0.5mg/kg is safe and effective. It is completely absorbed and plasma concentration is obtained within 5-10 minutes, almost as rapidly as when it is given in to a vein. Suppositories are unsatisfactory, giving therapeutic blood levels only after 20-30 minutes. The undiluted intravenous preparation is sucked in a small syringe and given through a polythene tube which is gently inserted 4-5 cm into the anus, after lubricating with vaseline.

Should the seizure fail to respond to the first dose of either intravenous or rectal diazepam after 15 minutes, a further comparable does can be given. If this fails to control the convulsion, the child should be nursed in a unit where intubation and ventilation can be carried out. Such cases usually respond to loading doses of phenytoin 15mg/kg/dose I.V or phenobarbitone 15mg/kg/dose I.V which is followed by maintenance dose of 5-6 mg/kg /day for short term. Febrile convulsion is an important cause of status epilepticus in children and it should be managed with right earnestness.[11,14,23-25,62,84]

Identification and Treatment of the underlying infection-

Since a febrile convulsion is always a symptom of a generalized illness, it is clearly important that a good physical examination is performed and that treatment for any remediable condition is instituted. Almost 90% of febrile convulsions are related to viral infections and for these children symptomatic therapy will be appropriate. Of the 10% with bacterial infections it is particularly important to consider and in most cases exclude by lumbar puncture. Bacteria and urinary tract infections are present in small percentages of children with febrile convulsions, are often unsuspected and should be excluded.[23]

Recognition of and allaying parental anxieties-

Counselling the often extremely anxious parent is an important aspect of acute management. Once they have calmed down they need instructions on management of possible recurrences that may occur during the same illness or a later one. They should be told in the event of another convulsion to stay calm and place the child on his side or stomach on protected surface to observe carefully and to bring the child to medical care if the seizure last longer than 10 minutes. It seems reasonable to provide parents with instruction on management of fever, dosage, timing of antipyretics, and tepid sponging.

Rectal diazepam administration has also been advocated for home based management of convulsion by the parents. They have to be taught the technique and informed about exact dose needed for their children. They are advised to keep one dose available at home so as to give it soon after the onset of convulsion and not to give it if the convulsion has stopped. Now more convenient disposable plastic tubes (stesolid) containing 5 or 10 mg of diazepam are available [14,17,19]

Many parents have feeling that their child may die during a febrile convulsion but are apprehensive to vocalize this anxiety. Clear simple worded re-assurance between febrile convulsion and epilepsy should be explained to parents. Most of them are also apprehensive that their child may become epileptic or develop mental retardation as a sequele. Careful and tactful questioning and re-assurance helps to allay this fear near totally.[85]

Prophylaxis

Patients with febrile convulsion have a good outcome. Several studies have found benign outcome with simple and complex febrile convulsion. The long term prognosis in terms of subsequent epilepsy, neurological ,cognitive and scholastic ability was not influenced by the type of treatment given. There is no evidence that the treatment to prevent recurrence can prevent the subsequent development of epilepsy

Diazepam ,sodium valproate, phenobarbital and clobazam have been used to prevent the recurrence of febrile convulsion. Prescription of prophylaxis should be resevered for rare cases in which

1) Multiple seizure have occurred in a child below one year
2) Abnormal neurological development
3) Had focal paralysis following a seizure
4) Parents anxiety will remain high even after reassurance.

Prophylaxis is of two types-

Long-term- Phenobarbital and Sodium Valproate are used

Intermittent –Diazepam therapy consists of giving diazepam orally or rectally when child is feverish in 3 divided doses to total 1mg/kg/day or oral clobazam in a dose of 0.5 to 1mg/kg/day when child is feverish for d 0-3 days.

Phenobarbital is not at all useful for intermittent prophylaxis. Phenobarbital 5mg/kg/day has been used continuously in a daily or twice daily dosage. But it can cause behavioral problems and affect intellectual performance adversely.

Finally a meta analytical review of the preventive treatment of recurrence of febrile convulsion has been done. Continuous phenobarbital prophylaxis versus intermittent diazepam prophylaxis has been compared and found to have adverse effects and long term prophylaxis of febrile convulsion cannot be recommended. Intermittent prophylaxis can be given.[17,19,23,64,84]

MATERIALS AND METHODS

SOURCE OF DATA:

All the Pediatric cases admitted in the Pediatric ward at B.L.D.E University Shri B.M. Patil Medical College, Hospital & Research centre, Bijapur-586103.

DURATION OF STUDY ; From 1st Nov 2009 to 31st OCT 2010

TYPE OF STUDY-PROSPECTIVE CASE CONTROL STUDY

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

- All children with febrile seizures between 6 months and 5 years from the pediatric wards of BLDE University Shri B. M. Patil Medical College and Research centre, Bijapur will be taken as cases.
- Age and wt (nutrition) matched 15 children with and 15 children without fever will be taken as controls.

Exclusion criteria:

- Children on zinc supplementation since past 1 week
- All Afebrile seizures
- Compromised nutritional status
- Fever with convulsion due to CNS pathology
- Children with delayed developmental milestones

After taking written informed consent, address and fulfilling inclusion criteria, children in the age group of 6 months and 5 years will be included in the study.

METHOD OF STUDY:

As per proforma, detailed clinical history comprising of age, sex, birth order, birth weight, and present weight, developmental milestones, body temperature at admission, cause of fever, history of recent zinc supplementation, family history of febrile seizure, as well as details of seizure history, duration, frequency, type of seizure (simple or complex) and duration between initiation of fever and convulsion. Detailed physical and routine systemic examination will be recorded.

Blood samples will be collected only once within 24 hours of febrile convulsion. Children will be included in the study only once. Routine hematological investigations after collection of blood samples will be performed for all patients. Routine investigations like blood routine and peripheral smear will be done. Serum zinc levels by colorimetric method will be done. Other relevant investigations will be done to find out the cause of fever E.g. CSF Examination.

Laboratory Evaluation:

1) **Blood investigations :** Blood routine and Peripheral smear
   Serum Zinc levels by Colorimetric method
   Other relevant investigations to find out
   cause of fever e.g. CSF Examination.

OBSERVATIONS

Age Distribution

30 children with febrile seizures were studied in the group (6 months – 5 years). Maximum numbers of cases were seen in 1-2 years age group. As the age increases the incidence of febrile convulsions were less.

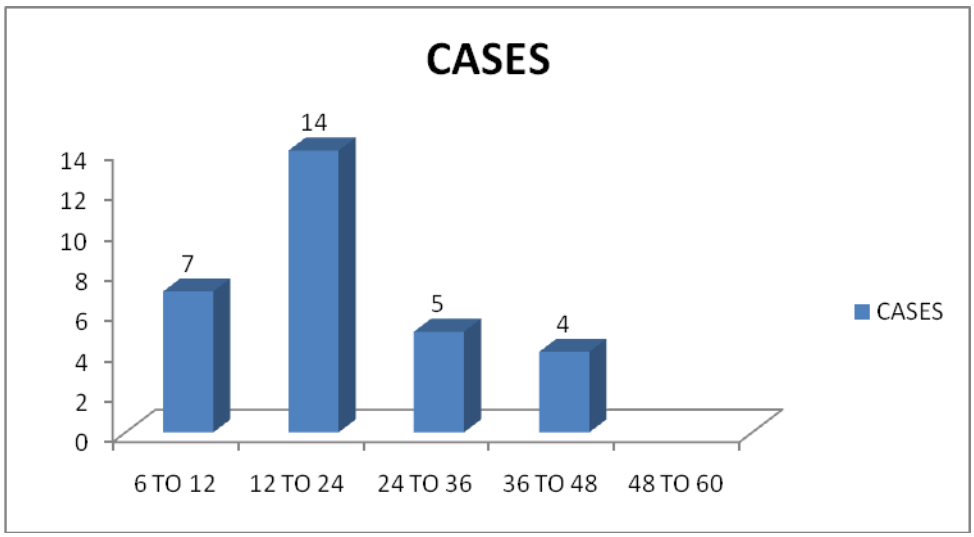
Table – 1

Age Distribution

Age in Months	No of cases	Percentage
6-12	7	23.33
12-24	14	46.66
24-36	5	16.66
36-48	4	13.33
48-60	-	-

Graph – 1

Age Distribution



Sex Distribution

In the age group between 6-36 months the incidence of febrile convulsions was significantly more in male children as compared to female children.

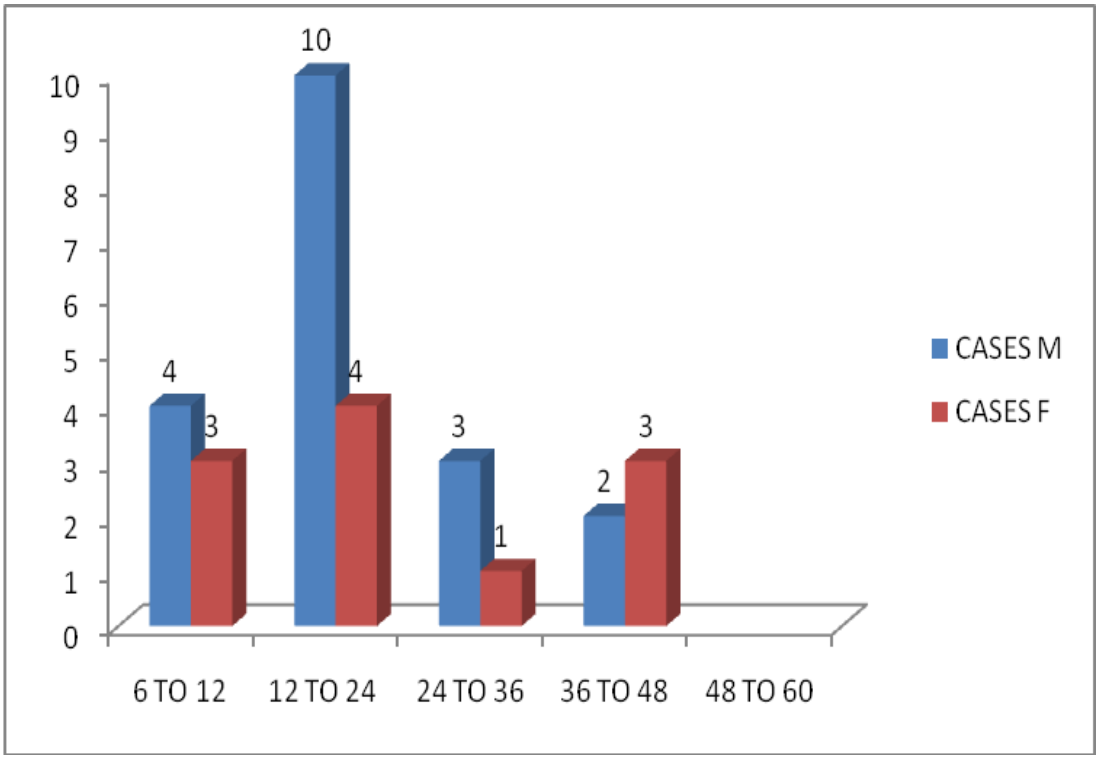
Table – 2

Sex Distribution

Age in Months	No of cases	
	Male	Female
6-12	4	3
12-24	10	4
24-36	3	1
36-48	2	3
48-60	-	-

Graph – 2

Sex Distribution



PRESENTING SYMPTOMS-

Major symptoms noticed were:

- Upper Respiratory Tract Infection in 23 children
- Lower Respiratory Tract Infection in 2 children
- Acute Gastroenteritis in 4 children
- Chronic Suppurative Otitis Media in 1 child

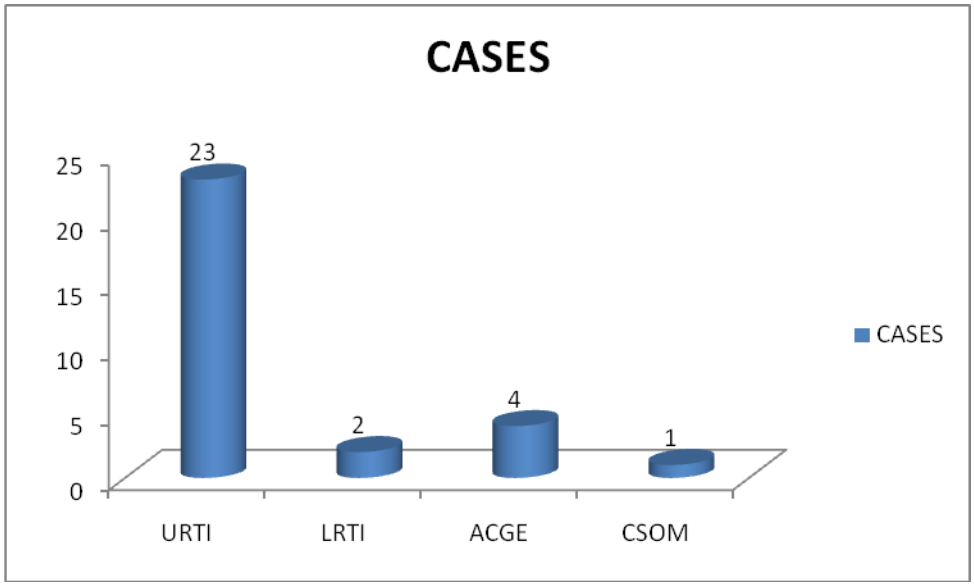
Table – 3

Presenting Symptom

Causes of Pyrexia	No of cases	Percentage
URTI	23	76.66
LRTI	2	6.66
AcGE	4	13.33
CSOM	1	3.33
Total	**30**	

Graph – 3

Presenting Symptom



Type of Seizures

Most of the seizures associated with a febrile illness were generalized. In the present study 26 cases had generalized seizures. Focal seizures were present in 4 cases and all were clonic seizures. Tonic clonic seizures were most common.

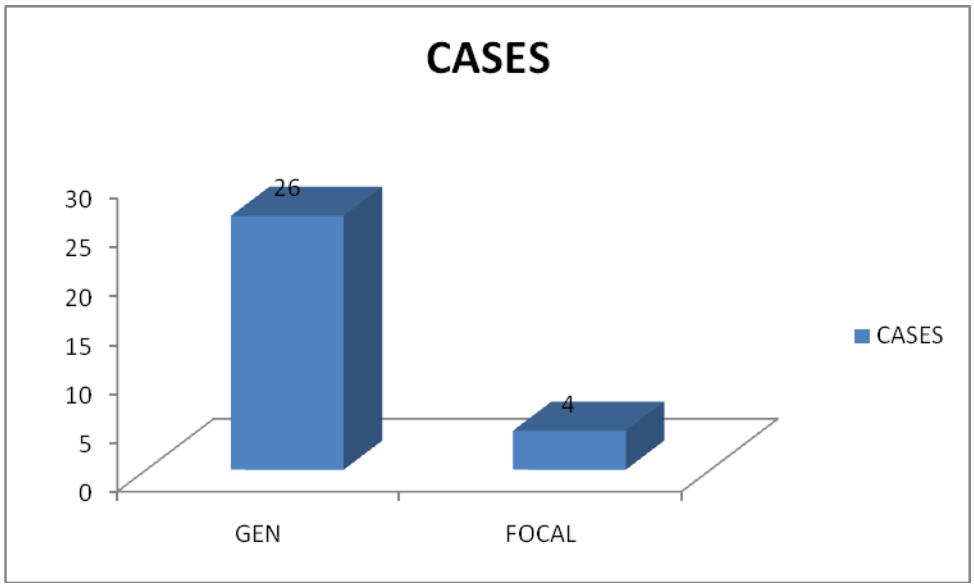
Table – 4

Type of Seizures

Types	No of cases	Percentage
Generalized	26	86.6
Focal	4	13.3
Total	**30**	

Graph:4

Type of seizure



Duration of Seizures

In the present study febrile seizures lasted for less than 15 mins in 30 cases. Majority of the cases had seizure lasting less than 10 mins (15 cases), 11 cases had seizure lasting for 10-15 mins and 4 cases had seizure lasting for less than 5 mins.

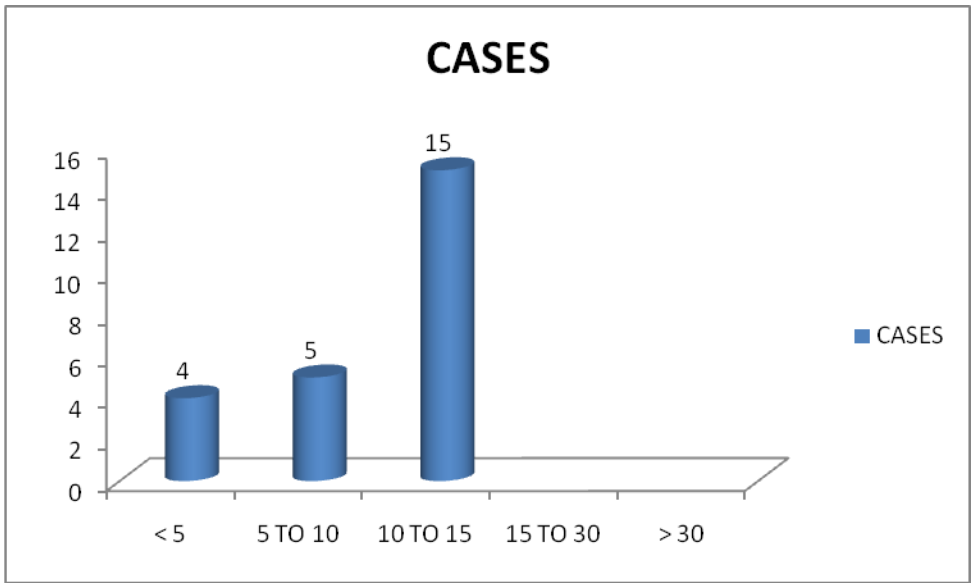
Table – 5

Duration of Seizures

Duration (min)	No of cases	Percentage
5 min	4	13.3
5-10 min	15	50
10-15 min	11	36.6
15-30 min	-	-
> 30 min	-	-
Total	**30**	

Graph – 5

Duration of Seizures



Frequency of seizure in one febrile episode:

Out of 30 children 26 had single episode of febrile seizure, 4 had more than 1 episode.

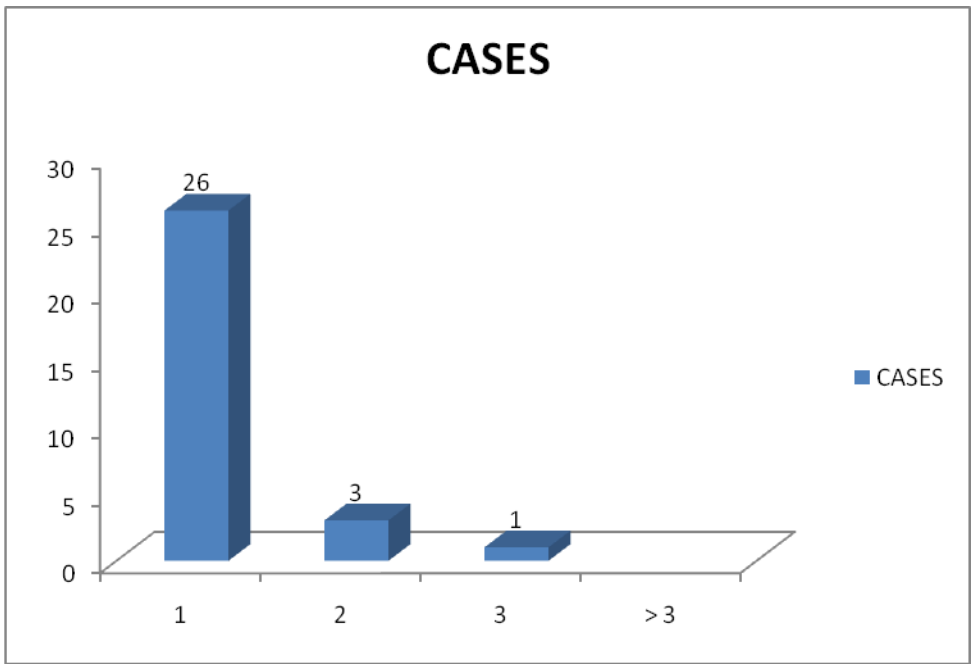
Table – 6

Frequency of seizure in one febrile episode

No of seizures	No of cases	Percentage
One episode	26	86.6
Two episode	3	13.3
Three episode	1	
> Than three episode	-	-
Total	**30**	

Graph– 6

Frequency of seizure in one febrile episode



Family History of Febrile Convulsion:

Family history of febrile convulsion was positive in 4 out of 30 cases

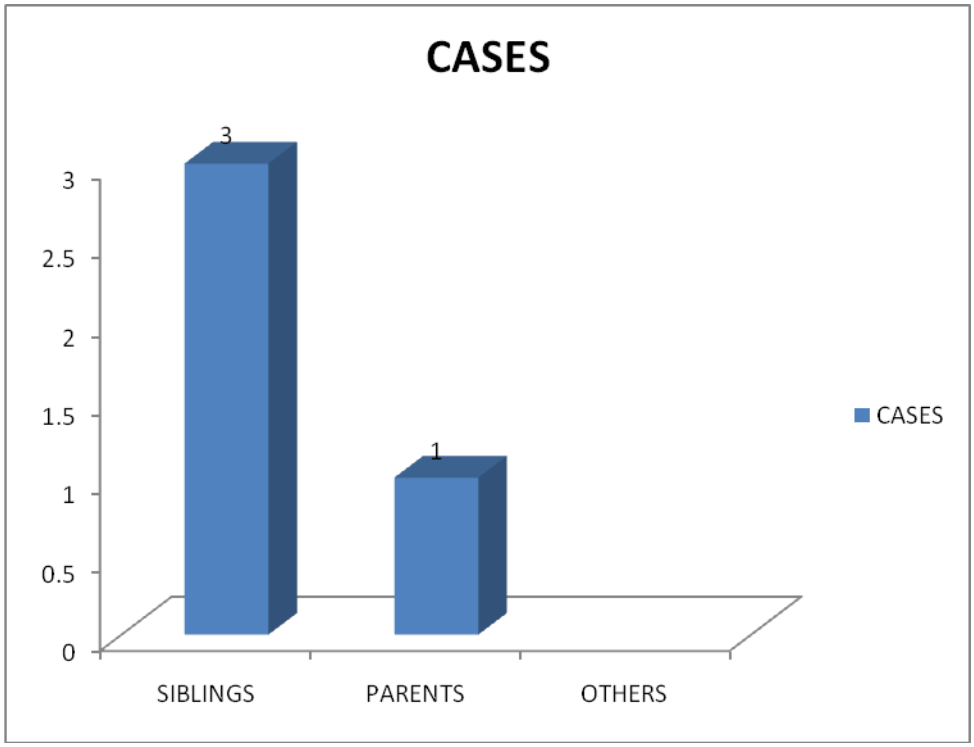
Table – 7

Family History of Febrile Convulsion

No of seizures	No of cases
Siblings	3
Parents	1
Other Relatives	-
Total	**4**

Graph– 7

Family History of Febrile Convulsion



RELIGION:

Out of 30 cases studied majority of the children were from Hindu community (29 cases 96.66%)

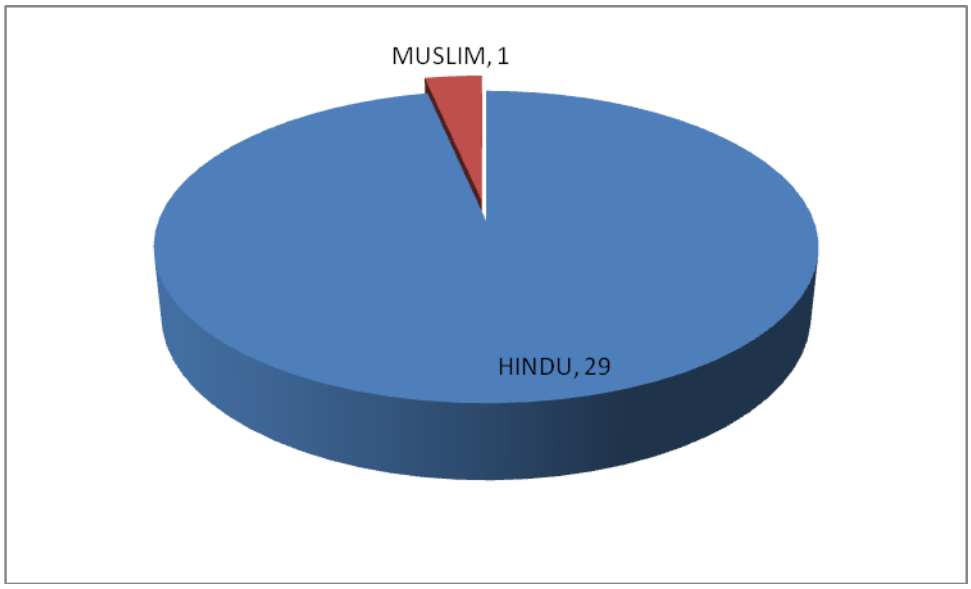
Table – 8

Religion

Religion	No of cases	Percentage
Hindu	29	96.66
Muslim	1	3.33
Christians	-	-

Graph– 8

Religion



Month Wise Distribution of Cases:

In the chart showing month wise break up cases. Two peaks were seen one during month of April and other during month of October.

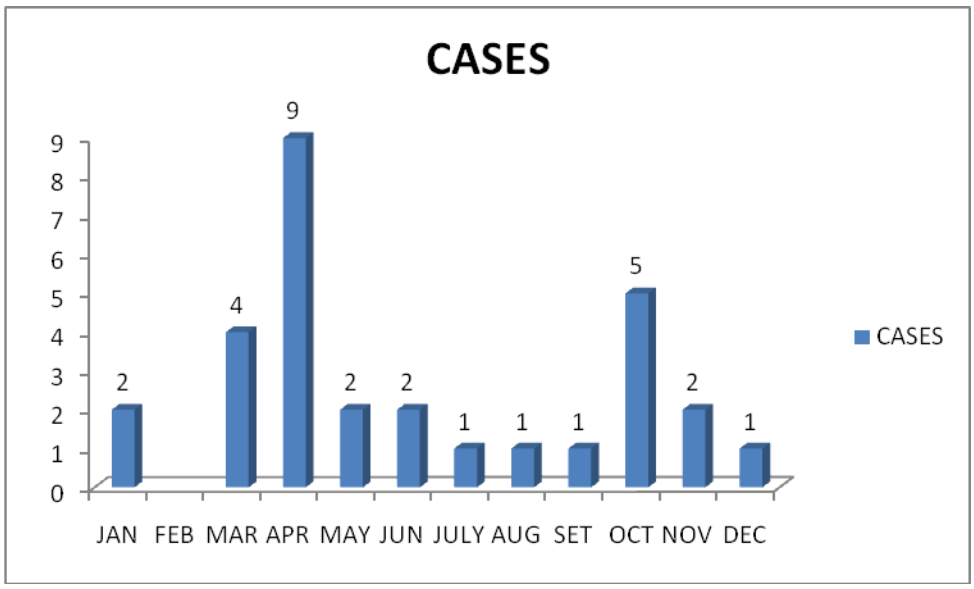
Table – 9

Months wise Distribution of cases

Month	No of cases	Percentage
January	2	6.66
February	-	-
March	4	13.33
April	9	30
May	2	6.66
June	2	6.66
July	1	3.33
August	1	3.33
September	1	3.33
October	5	16.66
November	2	6.66
December	1	3.33

Graph – 9

Months wise Distribution of cases



Biochemical studies:

Serum Zinc levels in cases:

Normal values of Serum Zinc level are 60-120µgm/dl. Out of 30 cases serum zinc levels were low in 20 cases (66.66%) and normal values in 10 cases (33.33%), P value <.0098

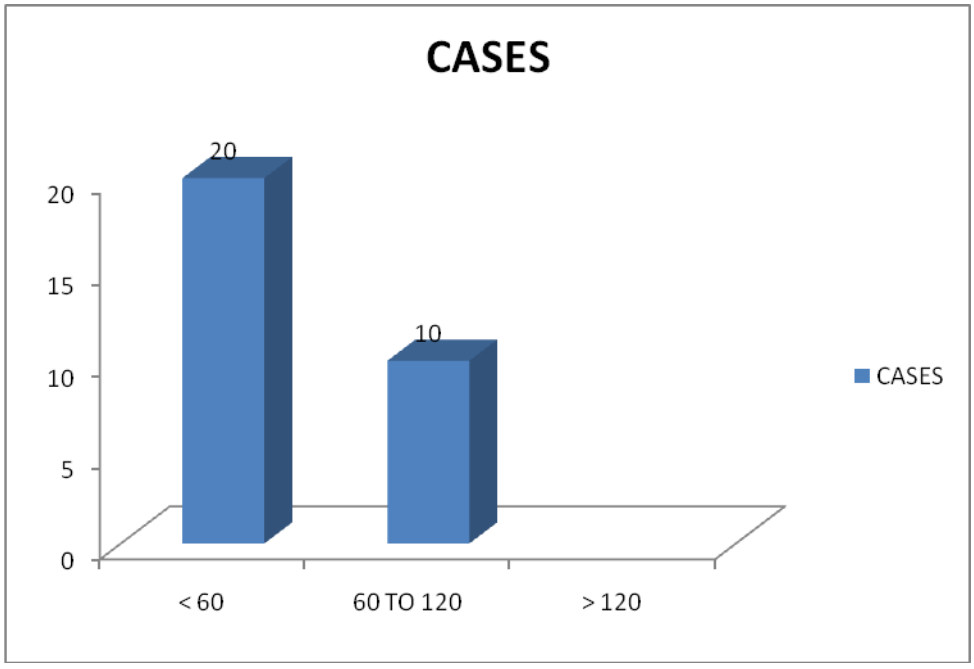
Table – 10

Serum Zinc Levels in Cases

Serum Zinc Levels (µgm/dl)	Cases (febrile convulsion)	Percentage
< 60	20	66.66
60-120	10	33.33
> 120	-	-
Total	**30**	

Graph– 10

Serum Zinc Levels in Cases



Serum Zinc Levels in Controls with Fever V/S without Fever

30 controls- Out of 15controls with fever 10 had normal Zinc levels, 3 had low values and 2 had high values, whereas in 15 controls without fever, 13 had normal Zinc levels and 2 had low Zinc levels.

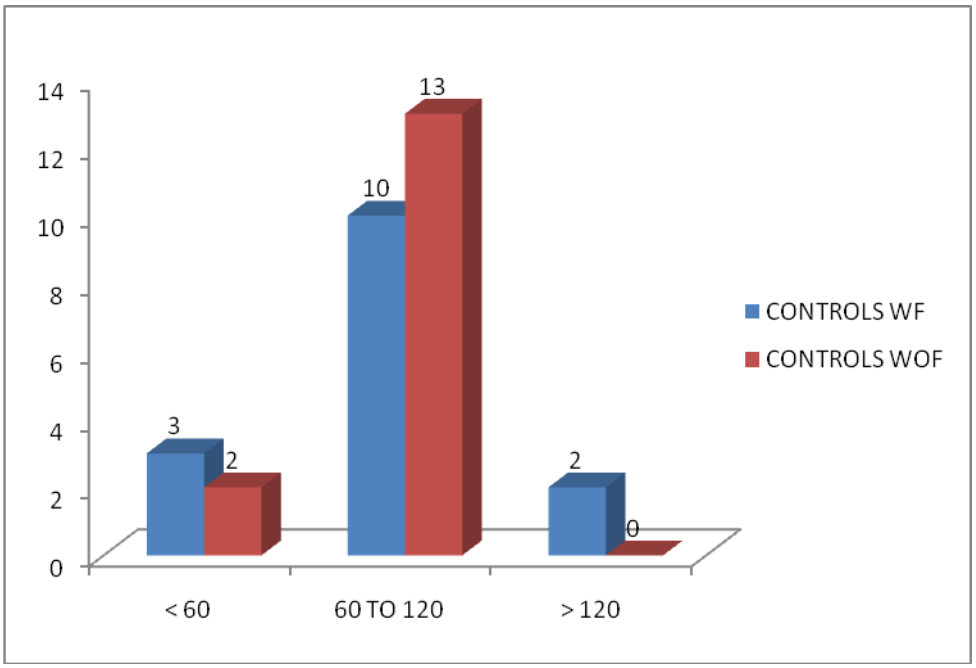
Table – 11

Serum Zinc levels in controls with Fever V/S without Fever

Serum zinc levels (µg/dl)	Controls with fever	Controls without fever	P – value
< 60	3	2	>.06
60-120	10	13	>0.19
> 120	2	0	>0.14

Graph – 11

Serum Zinc levels in controls with Fever V/S without Fever



Comparison of Serum Zinc levels in Cases vs Controls (with fever and without fever)

Out of 30 cases with febrile seizure, 10 had low serum Zinc levels. Out of 30 controls with fever and without fever, 5 had low serum zinc levels, 23 had normal values and 2 had high values.

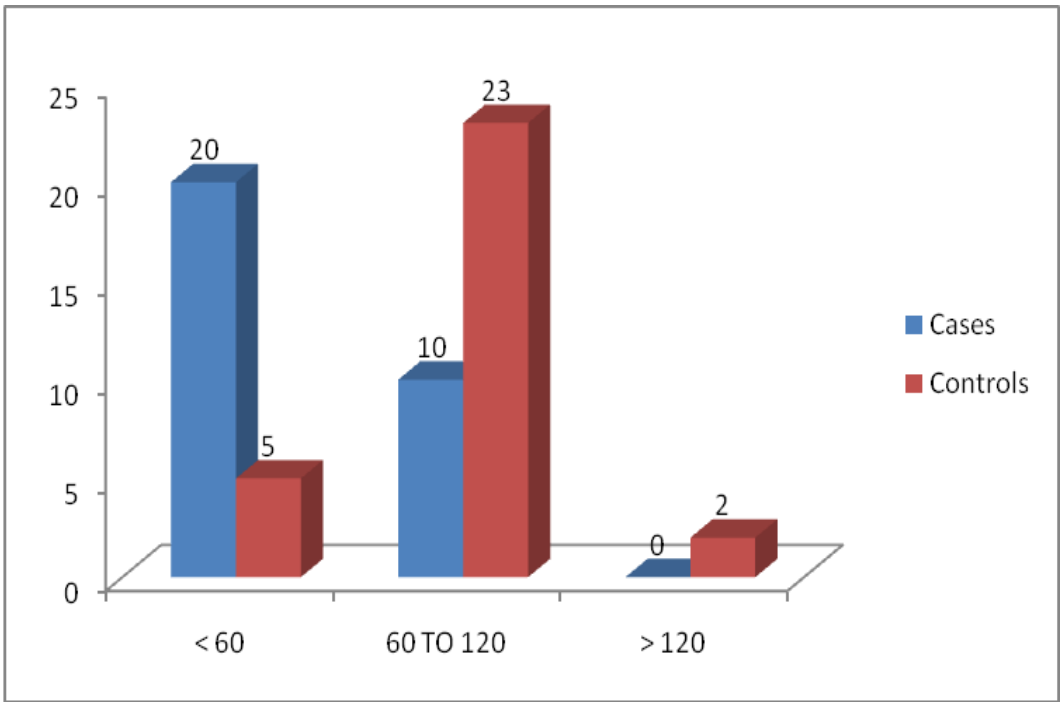
TABLE: 12

Comparison of Serum Zinc levels in Cases vs Controls

(with fever and without fever)

SERUM ZINC LEVELS	CASES	CONTROLS
< 60	20	5
60 - 120	10	23
> 120	0	2
Total	30	30

GRAPH: 12



DISCUSSION

My observations are compared with those of others who have undertaken similar studies.

Age Incidence:

In the present study the majority of cases were seen in the age group of 12-24 months. As the age increases the incidence of febrile convulsions were less which can be explained by the fact that maturity and myelination of brain progressively increases.

Table – 1

Age Incidence

Nelson K.B. and Ellenberg J.H. (NCPP study) [65]	On set in majority were before 3 years. Average age of onset 23.3 months for 760 girls and 23.3 months for 933 boys
Hirtz D.G. [56]	Average age of onset 18-22 months
Verity and Butler[41]	Onset in majority before 3 years
Present study	Onset in majority in 12-24 months

Sex Incidence:

In the present study febrile convulsions were noticed in 19 male children (63.33%) and 11 female children (36.6).Male to female ratio being 1.72:1.

The incidence among male children compared to female children in less than 1 year (4 V/S 3), 1-2 years (10 V/S 4), 2-3 years (3 V/S 1), 3 to 4 years (2 V/S 3) and 4-5 years (nil)

Table – 2

Sex Incidence Comparison

Study	Ratio (Boys : Girls)
Millichap[35]	1.4:1
Sehgal and Bala[37]	1.68:1
Hauser et al[28]	1.68:1
Yachcha et al[14]	1.78:1
Present study	1.72:1

While comparing with other studies the figures in the present study also shows boys outnumber the girls (1.72:1).

Symptoms:

The causes of fever in the present study comprised of respiratory tract infection in the majority. 76.6% with upper respiratory tract infection, 6.66% with lower respiratory tract infection, 13.33% with acute gastroenteritis and one child developed seizures with chronic Suppurative Otitis media without any neurological signs but only with fever.

Table – 3

Symptoms

Type of infection	NCCP study[65]	Millichap[35]	Sehgal[37]	Yachcha et al [14]	Present study
Upper respiratory tract infection (pharyngitis ,tonsillitis)	38%	62%	60.6%	50%	76.6%
Lower respiratory tract infection	15%	13%	10.6%	2%	6.6%
Acute Gastroenteritis	7%	7%	11.5%	8%	13.3%
Otitis media	23%	4%	11.3%	4%	3.33%
Mumps	-	-	-	-	-
Measles	-	2%	-	-	-
UTI	-	-	-	-	-

The causes of fever analyzed according to various studies have shown that upper respiratory tract infections constitute around 61% to 70%, lower respiratory tract infections ranged around 2% to 13%, acute gastroenteritis ranged around 3% to 11% and otitismedia ranged around 4 to 11%. All these figure shows that viral respiratory illness is main cause of fever.

Types of Seizure:

Seizure associated with febrile episodes is mostly generalized. In the present study majority of cases i.e. 86.6% presented with generalized seizures, only 13.3% had focal seizures.

Table – 4

Types of Seizure

Type of seizure	Shegal and bala[37]	Fishman[31]	Present study
Generalized	95.4%	95%	86.6%
Focal	4.6%	5%	13.3%

Other studies also show similar results .According to an Indian study by Sehgal and Bala maximum number of cases had generalized seizures i.e. 95.4% and 4.6% had focal seizures. Fishman observed that 95% of cases presented with generalized seizures and only 5% presented with focal seizures.

Duration of Seizures:

Table – 5

Duration of Seizures

Duration	No of cases		
	Sehgal and Bala [37]	**Fishman[31]**	**Present study**
< 5 min	40%	40%	13.3%
5-10 min	28%	90%	50%
10-15 min			36.6%
15-20 min	26.7	10%	-
>20 mins	5.3%		

In the present study 13.3% of cases had seizures lasting for less than 5 minutes. Totally 86.6% of the cases had seizures lasting for less than 15 minutes.. According to Sehgal & Bala 68% of the cases had seizures lasting less than 15 minutes ,26.7% of the cases had seizures lasting for less than 20 minutes and on only 4% of had cases seizures lasting for more than 20 minutes. Fishman on 1994 had noted that prolonged seizures occur in less than 10% of cases of febrile convulsion.

In our study there were no cases of seizures lasting for more than 15 mins.

Frequency of seizure per episode of fever:

Most of the cases had single episode of convulsion per episode of febrile illness.

Table – 6

Frequency of seizure per episode of fever

Duration	No of cases		
	Sehgal and Bala[37]	**Yachcha et al [14]**	**Present study**
One episode	65.4%	86%	86.6%
1-4 episodes	28.4%	14%	13.3%
More than 4 episodes	6.6%	Nil	Nil

In our study 86.6% of the cases had single seizures with each febrile episode, 13.3% of the cases had more than one convulsion per febrile episode. Sehgal and Bala(1979) has observed that 65.4% of the cases had one episode of seizures ,28.4% had more than one episode of seizures and 6.6% of the cases presented with more than 4 episodes.

According to a study by Yachcha et al (1981) 86% had a single episode of convulsion, 14% had more than one episode and none had more than 4 episodes.

Family History of Febrile Convulsions:

In the present study 13.3% of the cases had family history of febrile seizures out of which 10% have occurred in the siblings, 3.3% had occurred in the parents.

Table No 7

Family History of Febrile Convulsion

Family history of febrile convulsions	Tsuboi et al[47]	Sehgal et al [37]	Present study
Siblings	27%	6%	10%
Parents- father, mother	17%	2%	3.33%
Close Relatives	6.4%	2%	-
Negative	50.4%	90%	86.6%

According to study by Tsuboi et al 50% of cases had family history of febrile seizure out of which 27% occurred in siblings 17% in parents and 6.4% in close relatives.

According to study by Sehgal and Bala 10% of cases had family history of febrile seizures out of which 6% had occurred in the siblings 2% in the parents and 2% in the close relations.

Hence history of febrile seizures in the family has to be enquired carefully in all cases.

Religion:

In the present study 29 children (96.6%) were from Hindu community and 1 children from Muslim community (3.3%).

The higher incidence febrile convulsion seen in Hindu population in this study could be a attributed to the fact that majority of the children attending the hospital are from that community.

Seasonal variation :

In the present study two peaks were seen for the occurrence of febrile convulsions one during the month of March and April and the other during the month of October. This can be explained most probably by the fact that diarrheal disorders are noticed more commonly during months of March and April and respiratory infections are noticed during the months of October.

Nelson K.B and Hirtz D.G[24]. have observed some seasonal variation in the occurrence of febrile seizures, peaks occur in November and January perhaps related to respiratory infections and peak also occur from June to August when gastrointestinal illness are prevalent.

The difference in the observations can be attributed to the differences in the disease patterns in different places.

Comparison of Serum Zinc Levels In Cases And Controls:

Table – 8

Cases 30 cases with febrile convulsion

Controls 15 cases with fever, 15 cases without fever

Mean Serum zinc levels(µgm/dl) ± Std deviation	No of cases		
	R. Ganesh et al [11]	Fahimeh Ehsanipour et al[86]	Present study
Cases	32.17±15.05	76.82±24.36	59.4±16.78
Controls with Fever	87.6±17.6	90.12±14.63	82.36±24.72
Controls without Fever	----------	94.53±17.39	84 ±28.47

In the present study mean serum zinc levels in the cases were 59±16.78, in controls with fever was 82.36 ± 24.77 and controls without fever was 84 ± 28.47 (P value .000106), which is statistically significant. In another study conducted by R. Ganesh et al (2008) mean serum zinc level in cases with febrile convulsion was 32.17 ± 15.05 and that of controls with fever was 87.6 ± 17.6, (P value <.001). In another study conducted by Fahimeh Ehsamipour et al (2009) mean serum zinc level in cases was 76.82 ± 24.36 and that of controls with fever was90.12 ± 14.6 and afebrile seizure was 94.53 ± 17.39,(P value <0.006).

SUMMARY

30 children in age group of 6 months to 5 years admitted to Pediatric ward of B.L.D.E. University Shri B.M. Patil Medical College with febrile convulsion were matched with 30 controls i.e. 15 with fever and 15 without fever to find out the association between serum zinc levels and febrile seizures in childhood. Other observations were also made like age incidence, sex ratio, duration, type of convulsion, family history and religion etc.

This study showed an increased incidence in children in age group of 6 months to 3 years. 6 months- 1 year- 7 cases (23.3%),1-2 years -14 cases (46.6%), 2-3 years- 5 cases (16.66%). Male children out numbered the female children in the incidence of febrile seizures. Males formed 63.3% and the females 36.6% of the cases. Male to Female ratio was 1.72:1.

Peak incidence of febrile convulsion noticed in the months of April and October .The commonest cause of fever in febrile convulsion cases was upper respiratory tract infection?? Viral i.e 76.6%, followed by acute gastroenteritis 13.3% and lower respiratory tract infection 6.6%.

In this study 86.6% of the cases had generalized seizures and 13.3% had focal seizures. Of the 30 cases studied 86% of the cases had single seizure during febrile episode,13.3% of the cases had more than one seizure per febrile episode. History of febrile seizures either in siblings, parents or close relatives accounted for 13.3% of the cases.

Majority of children were from Hindu community 96.6% followed by Muslim community 3.3%.

In the present study mean serum zinc levels in cases was 59.4±16.78 µgm/dl and in controls with fever was 82.36±24.72 and in cases without fever was 84±28.47 (p value .000106).

Whether zinc supplementation in febrile seizures reduces the recurrence rate is to be studied and if proved will be a evidence based prophylactic supplementation.

CONCLUSION

The observations made both in clinical and biochemical parameters in the present study was in conformity with other studies that serum zinc levels are low in children with febrile convulsions.

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ANNEXURE – I

CASE PROFORMA:

NAME	**:**	**CASE NO**	**:**
AGE	**:**	**IP/OP NO**	**:**
SEX	**:**	**DOA**	**:**
RELIGION	**:**	**DOD**	**:**
ADDRESS	**:**		

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

H/O FEVER

DURATION:

RISE OF TEMP: GRADUAL/ ABRUPT

GRADE OF FEVER

H/O CONVULSIONS

TYPE OF CONVULSIONS:

DURATION

FREQUENCY OF CONVULSIONS DURING EPISODE OF FEVER.

STATE OF CONSCIOUSNESS:

POST CONVULSION DEFICITS

PAST HISTORY:

H/O PREVIOUS CONVULSIONS IF YES IN DETAIL

H/0 INFECTIONS

H/O IMMUNIZATION

H/O TRAUMA

H/O DRUG INTAKE

FAMILY HISTORY:

H/O CONVULSIONS IN FAMILY IF YES FEBRILE CONVULSION OR EPILEPSY.

H/O CONVULSION IN SIBLINGS

H/O CONGENITAL ABNORMALITY

H/O MENTAL DEFICIENCY

BIRTH HISTORY:

ANTENATAL:

1) MULTIPARA/PRIMI
2) ANY INFECTION
3) H/O DIABETES
4) EXPOSURE TO RADIATION
5) ANY IMMUNIZATION
6) HAEMORRHAGE
7) DRUG INTAKE
8) TRAUMA .
9) QUICKENING

NATAL:

1) HOME/HOSPITAL
2) RUPTURE OF MEMBRANES
3) PERIOD OF GESTATION
4) MODE OF DELIVERY
5) INSTRUMENTATION
6) ANY DIFFICULTY IN 2ND STAGE OF LABOUR
7) CONDITION OF NEW BORN AT BIRTH

NEONATAL HISTORY:

1) RESPIRATORY DISTRESS
2) INFECTIONS
3) CONVULSIONS
4) JAUNDICE
5) ANY CONGENITAL DEFORMITY
6) PREMATURITY

MILE STONES:

GROSS MOTOR

FINE MOTOR

PERSONAL AND SOCIAL

LANGUAGE

DIETARY HISTORY : ESP ZINC CONTAINING DIET

IMMUNIZATION HISTORY:

BCG :

OPV :

DPT :

MEASELS :

MMR :

HEPATITIS B :

ANTHROPOMETRY : AS PER IAP CLASSIFICATION

1) WEIGHT
2) HEIGHT
3) HEAD CIRCUMFERENCE
4) CHEST CIRCIMFERENCE
5) MID ARM CIRCUMFERENCE
6) UPPER TO LOWER SEGMENT RATIO

GENERAL EXAMINATION:

BUILT : **NOURISHMENT :**

PULSE : **RESP RATE :**

BP :

PALLOR : **PRESENT/ ABSENT**

EDEMA : **PRESENT/ ABSENT**

CLUBBING : **PRESENT/ ABSENT**

CYANOSIS : **PRESENT/ ABSENT**

ICTERUS : **PRESENT/ ABSENT**

LYMPHADENOPATHY : **PRESENT/ ABSENT**

SYSTEMIC EXAMINATION

CVS:

RS:

P/A:

CNS:

HIGHER FUNCTIONS : LEVEL OF CONCIOUSNESS
MENTAL DEVELOPMENT
CRANIAL NERVES
MOTOR SYSTEM
SENSORY SYSTEM
REFLEXES
CEREBELLAR OR MENINGIAL SIGNS

DIAGNOSIS:

INVESTIGATIONS:

BLOOD : BLOOD ROUTINE AND PERIPHERAL SMEAR

SERUM ZINC LEVELS BY COLORIMETRIC METHOD

OTHER RELEVANT INVESTIGATIONS TO FIND THE CAUSE OF FEVER, eg. CSF STUDY

ANNEXURE – II

BLDEU'S SHRI B.M.PATIL MEDICAL COLLEGE, HOSPITAL &

RESEARCH CENTRE, BIJAPUR-586103.

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT :		ASSOCIATION BETWEEN SERUM ZINC LEVEL AND FEBRILE SEIZURES IN CHILDHOOD
GUIDE	**:**	DR.R.H.GOBBUR PROFESSOR AND CHIEF C UNIT
P G STUDENT	**:**	DR. VARUN MUNJAL

PURPOSE OF RESEARCH:

I have been informed that the present study will help in assessing clinical association between zinc deficiency and febrile seizures in childhood.

PROCEDURE:

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations, a final work up for the etiological identification and appropriate management is planned.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomforts during the examination or during my treatment. This is mainly the result of my condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study will have no direct benefit to me other than the potential benefit of the treatment.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime; Dr. Varun Munjal at the department of pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Varun Munjal may terminate my participation in the study after he has explained the reasons for doing so.

ANNEXURE – III

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me. But, no further compensation would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

Dr. Varun Munjal Date
(Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. Varun Munjal has explained to me the purpose of research, the study procedure, that I will undergo and the possible discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to signature) Date

ANNEXURE – V

KEY TO MASTER CHART

Mo : Moderate degree

Hi : High degree

G/F : Generalized or Focal

T : Tonic

C : Clonic

T-C : TONIC/CLONIC

DUR : Duration of seizures expressed by the informant in minutes.

LC : Loss of consciousness during or after seizures

TEM : Temperature at time of convulsions expressed by the informant.

NO : Number of seizures in one episode of fever.

PH : Past history of febrile seizures

BH : Birth History

A : Birth asphyxia

S : Neonatal seizures.

DH : Development History

P : Physical development

M : Mental development

FH : Family history of Febrile Convulsions.S-Siblings, P – Parents,

O : Others

Wt : Weight of the patient

HC : Head circumference of the patient

Temp : Temperature recorded at the time of admission to hospital

Sys : Systems includes all the systems

RS : Respiratory system.

AFC : Atypical Febrile convulsions

TFC : Typical Febrile convulsions

LRTI : Lower respiratory tract infection

AGE : Acute gastroenteritis

URTI : Upper respiratory tract infection

CSOM : Chronic suppurative otitis media

VR : Viral Fever

CL : Cellulitis

AG : Acute gastritis

VOMI : Vomiting

An : Anemia

TC : Total Leukocyte count > 11000 / mm^3

Lym : Lymphocytosis

Neu : Neutrophilia

WNL : With in Normal Limits

CASES
LABORATORY EVALUATION

Sl. No	Blood Sugar	CSF Cells	CSF Sugar	CSF Protein	CSF C/S	EEG	Sr.Ca	Serum Zinc levels (µg/dl)	CBC
1	125	-	-	-	-	-	11	50	AN, LYM
2	80	10	39	12	S	-	8.7	46	LYM
3	80	5	41	10	S	-	10	63	WNL
4	100	-	-	-	-	-	12	55	AN, LYM
5	86	-	-	-	-	-	8.9	58	AN, LYM
6	76	-	-	-	-	-	10.6	49	LYM
7	118	-	-	-	-	-	8	46	NEU,AN
8	121	-	-	-	-	-	10.3	84	AM,LYM
9	96	-	-	-	-	-	8.5	72	WNL
10	82	-	-	-	-	-	8.5	64	WNL
11	66	-	-	-	-	-	8.8	50	AN,NEU
12	94	-	-	-	-	-	9.2	53	AN,LYM
13	68	-	-	-	-	-	8.6	35	AN
14	58	-	-	-	-	-	8.9	81	WNL
15	58	-	-	-	-	-	8.5	97	WNL
16	96	-	-	-	-	-	8.5	52	WNL
17	90	-	-	-	-	-	10.2	110	WNL
18	80	-	-	-	-	-	8.7	80	NEU,TC
19	98	5	64	12	S	-	9.6	52	WNL
20	100	-	-	-	-	-	10.5	72	AN
21	115	-	-	-	-	-	10.8	61	TC, AN
22	106	-	-	-	-	-	8.9	54	WNL
23	68	10	62	15	S	-	9.6	52	WNL
24	96	-	-	-	-	-	10.4	48	WNL
25	69	-	-	-	-	-	9.5	55	WNL
26	63	-	-	-	-	-	10.8	42	NEU,TC
27	125	-	-	-	-	-	8.6	48	WNL
28	72	-	-	-	-	-	8.9	53	AN,TC
29	96	-	-	-	-	-	10.8	55	WNL
30	64	-	-	-	-	-	8.9	45	WNL

CONTROLS WITHOUT FEVER

Sl. No	Blood Sugar	Chest X-ray	Stool R	Urine R	Sr.Ca	Serum Zinc levels (µg/dl)	CBC
1	-	-	N	-	-	68	WNL
2	-	-	N	-	-	73	WNL
3	-	-	-	-	-	92	TC, NEU
4	-	-	-	N	9.9	72	WNL
5	-	-	-	-	10.3	48	WNL
6	-	-	-	-	-	108	TC, NEU
7	-	-	-	-	9.3	92	WNL
8	-	-	-	-	-	68	WNL
9	-	-	-	-	-	42	WNL
10	-	-	-	-	-	102	AN, LYM
11	-	-	-	-	-	88	WNL
12	-	-	-	-	-	68	AN, LYM
13	-	-	-	-	-	72	WNL
14	-	-	-	-	-	108	AN, LYM
15	-	-	-	-	-	110	TC, NEU