STUDY OF SERUM VITAMIN B 12, POLIC ACID LEVELS AND PLATELET INDICES IN CHILDREN WITH FEBRILE CONVULSIONs

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MD PEDIATRICS

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ABBREVATIONS :

NCPP : National Collaborative Perinatal Project

CHES : Child health and education study

NIH : National Institute Of Health

FS : Febrile Seizure

IL : Interleukin

DPT : Diphtheria , Pertussis, Tetanus

MMR : Measles , Mumps , Rubella

SPECT : Single Photon Emission Computed Tomography

CSF : cerebrospinal fluid

HHV : Human Herpes Virus

CMV : Cytomegalovirus

LP : Lumbar Puncture

EEG : Electroencephalogram

CT : computerized tomography

MRI : Magnetic Resonance Imaging

AAP : American Academy of Pediatrics

FS : Febrile Seizure

Ca : Calcium

Mg : Magnesium

URTI : Upper respiratory tract infections

GE : Gastroenteritis

INTRODUCTION

One of the most frequent issues in pediatric practice is febrile seizure (FS).

FS is defined as convulsion that

i) occurred in more than a month aged children ,generally between 3 months to 60 months.

ii) linked to a febrile episode not related to a CNS infection,

iii) aren't linked to a past neonatal or unproved seizure, and

iv) don't meet the requirements for other acute symptoms of seizures[133].

The most frequent brain condition affecting children is febrile seizures, but its exact etiopathogenesis is unknown. Environmental and genetic factors, including immunologic responses and micronutrient deficiencies, are thought to involved[133] .

According to some studies, patients with FS had significantly lower serum zinc levels than febrile kids who weren't having seizures. Other authors have found that children with FS have significantly higher rates of iron deficiency anemia than febrile children without seizures. It is still unknown whether folic acid and vitamin B12 play a similar role in FS, despite some small studies suggesting that low vitamin B12 levels may be a factor in triggering seizures. This study's objective is to evaluate the relation between vitamin B12 and folic acid levels in febrile seizure children.[133]

The relationship between platelet volume and platelet activation and function has been discovered. The MPV is investigated as an inflammatory marker in numerous diseases. Myocardial infarction and cerebrovascular diseases showed increased MPV.Ozaydin[133], reported lower MPV value in CFC patients than SFC and Abuhandan[114], showed significantly higher MPV value in SFC than the control group.

AIMS AND OBJECTIVES :

- To assess vitaminB12 and folic acid levels in children with febrile seizures.
- To see the correlation between vitamin B12 and folic acid levels and recurrence of febrile seizures.
- To evaluate CBC in febrile convulsion patients and correlate platelet indices with febrile convulsion patients.

REVIEW OF LITERATURE

Seizures are unusual electrical activity of neurons located in brain which result in gradual stereotypical signs and symptoms where involuntary movements and altered consciousness are noted .[4]

Definitions:

Seizures which occur due to a known etiology are known as **symptomatic seizures**[4].

Provoked seizure – which occur due to acute conditions like fever, decreased glucose levels, consumption of any toxic substance, intracranial infection, injury, or any other factors precipitating to this condition . [4,5]

Unprovoked seizure – seizure which do not occur due to any acute condition, which consists of 3 types[5]:

1. Caused by pre – existing brain abnormality or any insult leading to **remote symptomatic seizure**
2. Seizure due to genetic cause leading to idiopathic seizure
3. Cryptogenic seizure – where the cause is not known

- **Febrile seizure** – seizure which occur in children aged between 6 months to 5 years having a temperature $\geq 38^0$C (100.4^0F) and without CNS infection, disturbances in metabolic, or previous history of afebrile seizure .

- **Infantile spasms** – they are a type of myoclonic-tonic seizure where there is flexor, extensor, or mixed flexor-extensor spasms where it occurs in infants, and unlikely in children who are very young .

  - **Epilepsy** : It is the disease of the brain where two or more unprovoked or reflex seizure which occur in less than 24 hours apart in duration (or) 1 unprovoked seizure and with a high risk (≥ 60%) of reappearing of seizures over the next ten years .
  - Diagnosis of an epilepsy syndrome

- **Status epilepticus** – it's a condition which results due to either from lack of mechanisms which are responsible for seizure cessation or due to mechanisms which initiate the seizure, this leads to seizures which prolong , and which can lead to long-term complications, which includes death of neuron, injury to neuron , neuron networks alteration, or depend on seizure type and duration.

FEBRILE SEIZURES

Febrile seizures are the most common seizures in children with an uniformly excellent prognosis and the prevalence is between 3-4%.[6]

There has been 3 studies based on population :

- NCPP had includedapproximately 54,000 American women in the years between 1959 & 1966 and h a v e b e e n their children were followed until the age of seven years.
- Rochester epidemiology project was used to identify the residents of Rochester , Minnesota ,USA who have had seizures for which system of medical records were linked to this project .
- CHES it's a birth cohort study where sixteen thousand neonates live born were enrolled in UK from first week of April 1971 and were followed for 10 years[7].

Prevalence:

Febrile seizures prevalence reported was ranging from 0.1 percent to 15.1 percent with an average prevalence of 5.3%.[8] The wide variation is attributable to different ways of finding the case and definitions of FS.

Figures which were most accurate were probably those attained from population containing children longitudinally. Ross and his colleagues have used the 1958 British cohort and found 2.5 perecent of children had FS and Verity & associates reported a prevalence rate of 2.3% in a longitudinal study conducted in US ,w h e r e Nelson & Ellenberg noticed prevalence of FS of 3.5 perecent at 7 years of age in white children and in black children was 4.2 percent. Prevalence of febrile convulsions in tropics range from 2.4/1000 and in Eucador is also high i.e., 14% in Mariana Island[9-12].

In Parsi community in Mumbai, India, Bharucha et al.[9] demonstrated the prevalence of febrile seizures to be 5.4/1000. Upto 10 percent of children experience FS which was suggested by Indian studies. Incidence rate is similar to that of western countries was suggested by recent data collection.[9,13,14]

Waruiru C et al.[15](2004) carried out a clinical review on Febrile Seizure and their main focus of the review was on the recent information and knowing of FS & outlined the very useful information of the management of children who come with an apparent "**Febrile seizure**". However, they did haven't discussed detailed FS management. According to their review, a cumulative incidence of 2 percent to 5 percent of FS were reported in the population studies in Western Europe and the USA. Incidence in India is 5-10% , 8.8 percent in Japan and 14 % in Guam and noted that incidence of FS varies .[15]

Incidence rate is 3-4% worldwide according to Michael V. Johnston.[16]

Definitions:

By definition according to AAP criteria, the child to have fever, and who was neurologically well between six months to five years of age where the episode of seizure is of short duration i.e less than fifteen minutes, generalized tonic clonic type of seizure which occurs once only i . e . simple FS or multiple times i.e complex FS within a period of 24-hour following a fever.[9]The most widely accepted definition is by the National Institute of Health(NIH) Consensus panel (USA 1980) which defines febrile Convulsions, as an event in infancy or childhood occurring between 3 months and 5 years of age, associated with fever but without evidence of intra cranial infection.[17]

FS was defined by The International league against epilepsy as seizure activity which occurs during the age of 3 month to five yrs , which is followed by fever but not in association with any CNS infection ,where the child was seizure free since birth.[18]

A temperature checked axillary of either > 38 degree Celsius or more than 37.8 degree Celsius as a simple cut off level has been proposed to diagnose a febrile seizure, but there are still no consensus.[19]

The Joint Working Group of the research unit of Royal College of Physicians and the British Paediatric Association defines Febrile Convulsions as an Epileptic Seizure occurring in a child aged from 6 months to 5 years precipitated by fever arising from infection outside the nervous system in a child who is otherwise neurologically normal.[19]

A Seizure is defined as a “paroxysmal involuntary brain function that may manifest as an impairment or loss of consciousness, abnormal motor activity, behavioural abnormalities, sensory disturbance, or autonomic dysfunction.”

Epilepsy is defined as a disorder of brain characterized by an endurating predisposition to generate seizures and by the neurobiological, cognitive, psychosocial, and social consequences of this condition.[16]

Status Epilepticus:

The guidelines published by the International League Of Epileptic Society defines Status Epilepticus as, "A single seizure lasting for more than 30 minute duration or a series of epileptic seizure during which function is not regained between ictal events in a >30 minute period".[7]

Age:

Febrile convulsions occur mainly in the age group of 6 months to five years. These are not seen in a child aged >5 years which indicates a particular possibility of young children where fever is precipitant. Although there are some exceptions, children outside this age range are less likely to have febrile convulsions. The onset of febrile convulsions in the majority of children occurs before 3 years with the average age of onset between 18 and 22 months. The reported prevalence of febrile convulsions in the United States is about 3-4%.[20]

The incidence of FS and its relation with age is not understood clearly where it is said that due to lack of myelination of underdeveloped brain, where chemical composition changes and there are water and electrolyte balance differences, consumption of oxygen is increased , decreased dendritic connections and there's a difference between adult brains electrophysiologic to that of younger children where all of this are shown as probable reasons for correlation between FS and a targeted age group.

Girls have more rapid cerebral maturation which accounts fro rapid decline rate of FS after the second year of life.[20]

Gender :

In most of the studies, it is seen that simple febrile convulsions have occurred more frequently in males, with a male to female ratio ranging from 1.1: 1 to 4:1.[17]

Aetiological aspects:

A) Preconceptual factors:

- Chronic maternal health predating the conceptions of children with febrile convulsions have

been found significantly frequently.[21]

- Parental sub fertility is common in families where children particularly males, have seizures when pyrexial. Maternal smoking, maternal motor deficits and mental retardation in an older half sibling are also reported to increase the risk for febrile convulsions.
- Thus, in some affected children the prenatal environment may not be conducive to optimal cerebral development.[22]

B) Prenatal factors:

- Vaginal bleeding either in early or late pregnancy, maternal medications during pregnancy in particular anti-epileptic drugs, anti-emetics, antibiotics, and anti-depressants might have adverse effects on the developing nervous system.[23]
- In a case control study in Western Washington, mothers smoking cigarette and alcohol consumption at the time of during pregnancy were identified as risk factors for FS in their children. Maternal smoking Prenatally has shown to have a two fold risk of developing a simple FS.
- These results says that stoppage of alcohol and smoking during pregnancy, was routinely advised at the time of pregnancy will be useful in preventing FS .[23] Vestergaard M et al.[24] also confirms the association between prenatal exposure to cigarettes and the risk of febrile seizures in his 2 population based cohorts study.[24]

C) Perinatal factors:

Some studies have shown febrile convulsions are more common in breech deliveries and small for gestational age babies.[7] But in the analysis of the information gathered during the National Collaborative Perinatal Project (NCPP), Nelson and Ellenberg (1990) did not find any of a large number of factors related to pregnancy, labour, and delivery that increase the risk for febrile convulsions.[22,25]

D)Family history of seizures**:**

- Twenty five to forty percent of children may present with FS who has a family history positive for FS and reported frequency of febrile seizures in their siblings ranges from 9-22%. FS occurring in families with genetic susceptibility where it could be transmitted from both the parents[11].
- If the child's sibling also has FS then its 1 in 5 risk of getting FS & its 1 in 3 risk of getting FS if both the parents are effected with FS.[26]
- The first degree family history of febrile seizures is important in assessing the recurrence risk of FS , whereas 2nd & 3rd degree family history are given as minor risk factor . if the 1st degree relative is affected with FS it gives the highest recurrence risk for FS.[27]
- A family history of non febrile seizures has been reported in several studies as a risk factor for the development of non febrile seizures following febrile seizures. In one large study by Nelson et el.[11] in 1978, it was seen that the risk of epilepsy was increased among children who had a family with a history of non febrile convulsions . A increase in risk of epilepsy associated with a positive family history was not marked unless there was a previous neurological abnormality or a lengthy focal or multiple first seizure in the proband.[25]

A British National cohort study observed that children with a positive family history were more likely to have a complex first febrile seizure than those with a negative history. In both American and British studies, if onset is in the early age and if family history is positive & these were considered as predictors of FS.[25]

NCPP conducted studies where it has shown that a if family history is positive for seizure disorder and this makes it an important contribution for risk of getting FS & if mother has FS then that will have the highest influence .[11,25]

Febrile convulsions are 2-3 times more likely in family members of affected children than in general population, whereas no clear association exists between febrile convulsions and family history of afebrile seizures.[8,25]

If family history positive for FS then it could show twenty five to forty percent of patients with FS . If more than one family member has a history of febrile convulsions, the risk of febrile convulsions in siblings of probands with febrile convulsions significantly rises.. Rosenberg found that if two or more members of a family had a history of febrile convulsions, their incidence in the siblings of probands with febrile convulsions was 45%, compared with incidence of 0.8% if no family member had febrile convulsion. The NCPP data indicate a positive family history of convulsions in approximately 7% of individuals with febrile convulsions.[28]

In a prospective study, Van Esch A, from Netherlands studied 115 children to determine the value of a detailed family history for the assessment ofthe risk of recurrence of febrile seizures. A positive first-degree family history of febrile seizures elevated the chance of recurrence to 27–52%. Children with second degree relatives who had febrile seizures did not significantly enhance their likelihood of having febrile seizures again.. [27]

Genetic factors in febrile convulsions:

The Febrile seizure susceptibility genes have recently been linked to FEB1 (chromosome 8q13-q21) and FEB2 (chromosome 19p13.3) in multiple large Japanese families, demonstrating an autosomal dominant pattern with reduced penetrance..[29,30]

Furthermore, a family with the clinical subtype known as generalised epilepsy with febrile seizures plus syndrome (GE FS (+)) was found to have a mutation in the voltage-gated sodium (Na+) channel beta subunit gene (SCN1B) at chromosome 19q13.1. One affected sibling increases the likelihood of another kid developing febrile seizures by 1 in 5, and two parents and a previous child increase the risk by 1 in 3.[31]

The mode of genetic inheritance is generally believed to be autosomal dominant with incomplete penetrance but polygenic mechanisms may also be involved and the mode of inheritance may vary from family to family.[12,32,33]

Twin studies:

It has been acknowledged that a sizable hereditary component contributes to the risk of febrile seizures.[32] According to studies, monozygous twins have a greater concordance rate of febrile convulsions than dizygotic twins.[23] In a study done by Marianne J K , he reported that a significantly higher proband wise concordance rates for monozygotic twins compared to dizygotics.[34] Monozygotic twins matched for similar neurological development showed a concordance rate of 80% for febrile convulsions, according to Lennox-Buchthal. They have found monozygotic twins had a lower concordance rate of febrile convulsions (46%), despite the fact that the rate was significantly larger than that of dizygotic twins (13%). Bower discovered 31% in monozygotics as opposed to 14% dizygotes, nevertheless..[35]

Risk of Afebrile convulsions:

While it appears clear that siblings of patients with epilepsy have an increased risk for febrile convulsions, it is not clear whether the siblings are also at increased risk for epilepsy. 3.4% of parents and 4.7% of siblings of febrile convulsion probands have afebrile convulsions. However other investigators have not found an increased risk of epilepsy among siblings of febrile convulsion probands.[35]

Lesions resulting from febrile illness of childhood:

During the age of susceptibility to febrile convulsions, the brain is in a phase of active growth and maturation. On general grounds therefore, it could be due to excess neuronal discharge and hypoxia, occurring during prolonged and / or recurrent convulsions might be particularly likely to cause brain damage. Immerman described cortical neuronal necrosis, sometimes widespread, occasionally laminar, and often most evident in the walls and depths of sulci in 11 children who died within 1 to 13 days of onset of severe febrile convulsions. The distribution of lesions included cerebral cortex, hippocampus, amygdaloid nucleus, thalamus and basal ganglia. On viewing retrospectively, patients with temporal lobe epilepsy have a greater than normal probability of having had febrile convulsion

in early life. Furthermore patients with temporal lobe epilepsy and a preceding history of febrile convulsion are more likely to have siblings who have also had febrile convulsions.[12,25]

Iron deficiency and Febrile Seizures

Iron deficiency anemia is one of the most prevalent micronutrient deficiencies in young children in India and other parts of the world, and it is strongly associated with persistent cognitive and motor delays even after the anemia and Iron deficit have been repaired.[36]

Iron deficiency though commonest micronutrient deficiency worldwide is a preventable and treatable condition.[37]

Fevers can increase low serum ferritin's detrimental effects on the brain and lead to seizures.[20] For the metabolism of many neurotransmitters, monoamine, and aldehyde oxidase in the brain, iron is used as a co-factor.[38,30] Thus, iron deficiency may affect a child's seizure threshold. Iron insufficiency is a disorder that is easily treatable and is posited as a risk factor for febrile seizures in children.. [40,41]

In order to determine the association between iron deficiency and febrile seizures, Pisacane A conducted a case-control study in 156 infants younger than 2 years in 1996. It was found that fever can exacerbate the negative effects of anaemia and iron deficiency on the brain, and that seizures can result as a result..[42]

Another study by Azhar in 2002 used a prospective case-control design to examine the relationship between iron stores and the first febrile seizure. They came to the conclusion that there may be a role for iron deficiency in the occurrence of first febrile seizures since ferritin levels are low in children who had their 1st FS than in the reference group..[30]

A study in Karachi was done in 2005 to see whether there is a connection between iron deficiency anaemia and FS. They came to the conclusion that FS are more common in kids with iron deficient anaemia...[43]

Hartfield studied in children with febrile seizures were almost twice as likely to be iron deficient as those with febrile illness alone suggesting that screening for iron deficiency should be considered in children presenting with febrile seizures.[44]P Leela Kumari in their study have shown that iron

deficiency is a significant risk factor for simple febrile seizures in children of age group between 6 months to 3 years.[45]

Fever and Febrile Seizures:

Fever provokes seizures in case of a child with febrile convulsions and hence termed febrile seizures.[46]Temperature influences numerous cellular processes, including the electrical activity of neurons.[47]The functions of several neuronal ion channels are dependent markedly on temperature in the physiological and fever ranges, approximately 36– 42^0C .[48]

The temperature also modulates the amplitude and kinetics of major ionic currents.[46]Thus these facts suggests that an increase in the temperature of neuronal tissue could enhance the rate, magnitude or synchrony of neuronal firing, leading to seizures; this notion is supported by the fact that, in children hyperthermia induced by hot bath or anticholinergic medications might also provoke seizures .[29]

Fever mediators also may contribute to the generation of febrile seizures.[46]Fever mediators like cytokines and specifically interleukin IL_1b, enhance neuronal excitability in part by augmenting glutamate – receptor function .[49]

Brain hyperthermia also elicits rapid release of endogenous IL_1b. [50]Which in turn contributes to the generation of Seizures [51.] Mutations in the IL_1b gene promotes, that result in increased production of cytokine, have been reported in individuals with febrile seizures .[52]Thus the available data support a significant role of fever in case of febrile seizures.

Exogenous pyrogens released during viral and bacterial infections cause an upward setting of the thermoregulatory centers in the hypothalamic/ pre optic 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 febrileconvulsions.[53]

Eighty percent of febrile seizures take place during the first day of a fever before the parent is aware of the fever, beginning within the first few hours of an acute infectious illness.[25]Whether the most important factor in the induction of convulsions is the level of temperature or the rapidity of its

rise but both remains the subject of de bate.[35,54]

When seizure begins temperature is at its peak at 39 to 40^0celsius.[54]Although some studies indicate that the height of body temperature is a primary predictor of seizures associated with hyperthermia, the rapidity with which the temperature rose appears to be more significant than the temperature at which febrile convulsions started.[33,55]

Welch is credited with the idea that the pace of temperature increase is significant in 1888, but Wegman conducted the first thorough investigation in cats and published his findings in 1939.[56]In his investigations on animals, Millichap noted that there was no correlation between the rate at which the temperature rose and the occurrence of convulsions and that animals would seize once the temperature reached a particular point, regardless of the rate at which the temperature rose.[56]

The likelihood of subsequent febrile seizures has also been linked to the peak body temperature at the time of the initial febrile seizure.[33]

Hence with above data it appears that the suddenness in rise in temperature maybe the triggering aspect of seizure than the height of fever.[55]

Precipitating Event:

Only when a fever illness occurs during the key age range do febrile convulsions occur in kids with risk characteristics.[22]It has been hypothesised that the convulsion is influenced by the type of bacteria causing the infection, as well as fever, age, and genetic predisposition. According to epidemiological research conducted in western Europe and the USA, upper respiratory tract infections and other viral disorders are linked to febrile convulsions.[31]

Children who are hospitalised after their first febrile convulsion are most frequently unwell due to viruses. Upper respiratory tract infections, otitis media, gastro-intestinal infections, and roseola infantum are some of the conditions that are frequently linked to one another.[10] Febrile convulsions are less usually linked to measles.. Lewis and Colleagues using Elaborate and Extensive testing implicated a viral etiology in 86% of children admitted to the hospital for first febrile convulsion.[35]Amarendra has noticed 86% children had predisposing URI, 8% had Acute

Gastroenteritis.[57]

Some seasonal variations has been observed in the occurence of febrile seizures. Peaks occur in November and January, perhaps related to common respiratory infections. Peaks also occur from June through August when gastrointestinal infections are prevalent.[25]Helen M Lewis studied 73 children (37 boys, 36 girls) with febrile convulsions. A viral illness was demonstrated by isolating a virus from the CSF, blood or urine in 27% of 73 children who were admitted to the hospital after a first episode of febrile convulsion.

Interferon tests and complement fixation tests

However, just 4% of children had the pathogen isolated from the CSF, blood, or urine, according to parallel bacterial cultures that detected a potential infection in 29% of the children. There was no connection between the type of pathogen and the intensity of the convulsion, the level of fever, the CSF protein, or the CSF white cells. The findings imply that a febrile convulsion may be a reaction to a virus or other microorganism invading the bloodstream. Because successful separation of the virus from the blood is not more frequently performed, invasion may be of a short duration.[31]

Human herpes virus 6 had been suggested that HHV-6 may have neurotropic properties and can be involved in the pathogenesis of febrile seizures in infants. Hukin et al, in their study in British Columbia have concluded the occurrence of HHV-6 infection was same in patients with febrile seizures and same age controls..[57]Recurrences of febrile seizures in the respiratory seasons has been associated with Influenza Type A virus.[58]

In a study conducted by Akpede.G.O in Nigeria in children less than 5 years with convulsions associated with fever of acute onset, 74% had no localising signs of infection. Of these 68% had malaria, 4% bacteremia and 7% malaria with bacteremia. All the malarial parasites were Plasmodium falciparum. Among children with bacteremia (11%), Staphylococcus Aureus was the commonest single isolate (33%), 56% of the bacteremic children had simple febrile convulsions while 44% had complex convulsions[59].

In a retrospective study (1980-82) conducted at Liverpool by McIntyre All blood sample cultures'

results were examined. 2919 blood samples were cultured during the course of the two years. Out of them, 205 (7%), an organism grew, and 110 (4%), were thought to be harmful to the patient. The most prevalent group of microbes was Enterobacteriaceae (28%) with Ecoli accounting for 2/3 of these.[60]

Children who reported with fever and convulsions were routinely given blood and urine cultures as part of a 12-month prospective trial at the Children's Hospital in Brisbane. Of the 282 patients, 12 (4.3%) had bacteraemia. In half of these cases, there was no clinical suspicion. Of the 272 patients, 7 (2.6%) had UTIs, and clinical suspicion for it was present in 6 of these cases. Nine of the 12 individuals who had undetected bacteremia or UTIs experienced simple febrile convulsions. All 12 patients had a prolonged fever. Patients under the age of 2 years had a considerably higher prevalence of bacteremia. It was determined that routine culture testing increases the likelihood of finding bacteremia and UTI in children who are admitted to the hospital with febrile convulsions.[61]

Febrile seizures and Immunization:

There has been a wide range of studies with respect to relationships between vaccination and febrile seizures. There are lot of evidence showing that vaccination does trigger the onset of febrile seizures in certain genetically susceptibility children.[62]

A study was done by Center for Disease Control and prevention vaccine safety data link working group in regard to association of certain vaccines and febrileconvulsions. They discovered that receiving the DPT vaccine was only connected with a higher risk of febrile seizures on the day of vaccination, whereas receiving the MMR vaccine was linked to a higher risk of febrile seizures 8 to 14 days later. A higher incidence of non-febrile seizures was not linked to any immunisation. However, they discovered that there was no evidence linking the aforementioned risks to any long-term negative effects.[63]

Seizures occurring after immunization are likely to be febrile occurring in response to temperature elevation especially those occurring within 48 hours of DPT and 7-10 days after measles

immunizations.[10]

Farrington et al found a higher incidence of convulsions within the first three days following DPT vaccination. The third dose of the vaccination, for which the attributable risk (across all ages), was 1 in 12,500 doses, had the only effect. After the UK switched to an accelerated immunisation schedule, there may have been a 4-fold drop in febrile convulsions linked to the DPT vaccine if the vaccination was completed by 4 months rather than 10 months. The measles component of the MMR vaccine was to blame for 67% of admissions for convulsions that appeared 6–11 days after receiving the immunisation. Only vaccines containing the Urabe mumps strain were reported to have an increase of hospitalizations for convulsions 15–35 days following MMR immunisation (1 in 2600 Urabe doses).[64]

The prevalence of febrile seizures after primary immunization was found by Harker (1977) in oxford to be 0.09 per 1000 doses for DPT and 0.93 for measles. With newer measles vaccine the prevalence is lower.[33]

Pathophysiology:

Neither experimental nor clinical experience has revealed a definitive mechanism for febrile seizures. Immaturity of the thermoregulatory mechanism and limited capacity of young animals to increase cellular energy metabolism at elevated temperatures have been

implicated. Animal studies

fever. The parents sometimes may only complain of seizures but on examination the child appears febrile. They are usually generalized tonic clonic seizure which lasts for a brief period (<15minutes) but however in some children the seizure duration can exceed 15 minutes and may have focal seizures and in rarest of the cases the child may also have febrile status epilepticus. After the seizure episode the child usually has a small duration of postictal drowsiness for a very brief period but still certain children appear drowsy for a longer duration. A detailed history has to be taken and a complete clinical examination has to be done.

Simple febrile seizure:

A simple febrile seizure is a generalised seizure in a neurologically healthy child that lasts less than 15 minutes and only happens once in 24 hours.[5]

Complex FS:

A complex febrile seizure is one that has one or more of the following characteristics:

• The seizure has a focal onset, displays focal features while occurring, or is followed by a neurological impairment.

• Lengthy time (more than 15 minutes).

• Recurring in the same febrile episode or within 24 hours.

Numerous studies have revealed that between 9 and 35% of people experience complicated febrile seizures..

Differential Diagnosis:

Other causes of acute loss of consciousness or rhythmic involuntary movements in early childhood are:

- Breath holding spells
- Reflex anoxic seizures.
- Syncope
- Rigors and Tetany.
- In breath holding spells & reflux anoxic seizures, the episodes are acute reactions to noxious stimuli, which are usually unexpected.
- Syncope is associated with limpness & bradycardia rather than tonicclonic movements & tachycardia.
- Consciousness is usually not lost during rigors & tetany.
- Benign paroxysmal vertigo, in which sudden acute episodes ofunsteadiness occur, is not associated with loss of awareness.[65,66]

Investigations:

No investigations are routinely necessary in all children after febrile convulsion. It is prudent to measure the blood glucose concentration with a glucose oxidase strip in any child who is still convulsing or not arousable when seen with or without fever.[14]

The 2 important aims o f sending investigations in a child with FS are to evaluate any CNS infection or fever of unknown cause .Child who is admitted for the first time due to FS is most commonly due to virus.[67]

However, Hb, MCV, MCH, and MCHC along with serum Ferritin can be done so as to evaluate for Iron deficiency anaemia which has a strong association withfebrile convulsions.[36-39,68]

To pinpoint the source of the fever and determine the cause of the fever, a thorough clinical examination is required. There is no routine requirement for testing electrolytes, sugars, Ca, Mg, or total counts unless clinically necessary.[11] Urine analysis is recommended in children with no obvious focus of infection to rule out urinary tract infection.[71]

Although neutropenia usually related to viral illness occurs commonly, blood counts are not helpful in management.

Viral studies are seldom of value in the management and prognosis of febrile convulsion. Though detailed studies will often give evidence of viral infection of the CNS the outcome does not seem to be influenced by this, though it is suggested CMV infection may play a part in the evolution from febrile convulsion to epilepsy.[3]

In a study from United Kingdom by Mcintyre P, Kennedy R and Harris showed an incidence of 2.3% for occult bacteraemia in children admitted with febrile convulsion. The probability of a serious bacterial infection rose to 80% when the segmented

neutrophil count was greater than 10 x 109 or the band neutrophil count was greater than 5 x 109/L[60]

Bacteraemia is much more prevalent in individuals under the age of 2 years old, according to studies done in Australia in 1984 by Mcintyre Leucocytosis (>15,000) was a sensitive (75%) but unreliable (57%) diagnostic tool for bacteremia.[61]

Studies by Gombos M M et al, USA, showed occult bacteremia to affect approximately 5% of febrile children aged 2 to 36 months.[70]

Since different studies have proved the occurrence of occult bacteraemia in febrile convulsions, the following investigations are done in all cases of febrile convulsions taken up for the study.

- TLC & DLC
- PBS
- BC / sensitivity
- Urine microscopy
- Stool microscopy

In selected cases, Ear swab for culture & sensitivity in presence of ear discharge, Throat swab for culture & sensitivity in presence of acute pharyngitis or tonsillitis, CSF analysis, EEG , Neuro Imaging are done.

CSF analysis:

Because meningitis signals may be weak or non existent in patients under the age of 12 months who appear with fever and seizures, the AAP strongly advises LP in these cases. Children between the ages of 12 and 18 months should be evaluated for LP because meningitis symptoms and signs might be modest. Children who have gotten antibiotics and are experiencing febrile seizures may also have meningitis symptoms and indications that are concealed, thus LP is also necessary in these situations.[73]In case of older children LP is indicated whenever a doubt of meningitis exists.[72]

It is not routinely recommended to do CSF analysis in all cases of febrile convulsions.[15] CSF analysis is indicated when:

• Young children (under 18 months)

• Excessive or inexplicable sleepiness or agitation.

• if sings of Meningitis are seen .[15]

Electro-encephalogram (EEG):

Since the EEG is of questionable value following febrile convulsions, routine EEGs are not necessary . EEG does not predict which children progress to a seizure disorder. Epileptiform abnormalities are relatively common in children with benign febrileseizures.[73]Further EEG has a low sensitivity in children under 3 years of age following an unprovoked seizure.[74]

Hence for all these above reasons EEG is not recommended in case of febrile seizures. There is no evidence so far that EEG abnormalities if present also help predict either recurrence of febrile seizures or the development of subsequent epilepsy. [71]

If an EEG is performed soon after a convulsion, it typically reveals a considerable generalised slowing that can last for a week or longer and may be asymmetrical. Specific abnormalities are more frequently observed in older kids, those who have had several prior febrile convulsions, minor abnormalities that were present before, or those who have had focal seizures. However, these abnormalities are not predictive of recurrent epilepsy nor of recurrences. When febrile convulsions are followed by focal neurological abnormalities, an EEG may occasionally be required to help rule out an underlying structural lesion. In spite of this, neuroimaging is more helpful.[15]

Neuro Imaging in Febrile Seizures :

A young child with simple febrile seizures should not be handled with a CT scan or an MRI head.[11]

On the basis of the available evidence and consensus, the AAP recommends that neuroimaging not be performed in the routine evaluation of the child with a first simple febrile seizure.[71]

Even though laboratory tests, taking cultures, and imaging are performed in daily practices when approaching febrile seizures, the association with serious infections is rare and usually overestimated. The diagnostic approach should be individualized to each case.[75]

Management of febrile convulsions

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

- Attention to the effect of the seizure

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

It is crucial to actively normalise body temperature in febrile convulsions in addition to maintaining a clear airway, risk of aspiration will be less in semi prone position , and vitals should be monitored. Lowering the body temperature is achieved by removal of excess clothes, tepid sponging and use of antipyretic drugs.

Sponging with ice water will cause cutaneous vasoconstriction and actually increase core body temperature. Sponging with tepid water slowly brings down the 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 is stopped.[76]The commonly used antipyretic is Paracetamol. Dose: 15 mg/kg/dose q 6 to 8th hrly orally . Rectal suppositories are also available and given when child not able to take orally.

Antiepileptic drugs in the acute stage:

.If the infant is still convulsing, it must be treated like any other convulsion, with medication if necessary.

• Preservation of an open airway

• The semiprone position, which reduces the aspiration risk

• Vital signs observation.

Diazepam or Lorazepam administered intravenously can stop seizures. 0.1 mg/kg/dose of lorazepam is intravenously given at a rate of 1 mg per minute.

It is secure and efficient to use rectal diazepam at 0.5 mg/kg. Within 5 to 10 minutes, it is totally absorbed and plasma concentration is attained, virtually as quickly as when it is administered intravenously.

After rubbing the anus with Vaseline, a tiny syringe is used to draw in the undiluted intravenous

anticonvulsant mixture. The polythene tube is then carefully pushed 4-5 cm into the anus.

In a pilot research, children with epilepsy who received midazolam by nasal inhalation showed effective seizure control. Recent research has demonstrated that intranasal administration of midazolam is effective just like intravenous diazepam for treating febrile seizures .

If seizure fails in responding to the first dose of diazepam after 15 mins, a further comparable dose can be given. If still there is no response, child should be managed with phenobarbitone/phenytoin loading followed by maintenance dose Intravenously. Febrile convulsions is an important cause of status epilepticus in children & should be managed intensely.[22,65]

Identification & treatment of the underlying infection:

Since febrile convulsion is always a symptom of a generalized illness, it is clearly important that a good physical examination is performed & 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's particularly important to consider and in most cases to remove bacterial meningitis. Children with febrile convulsions may have modest amounts of bacteraemia and urinary tract infections, which are frequently undiagnosed and should be ruled out.[22]

Risk of recurrence:

While relatively a few children who had experienced febrile convulsion develop epilepsy, many children develop recurrence of febrile convulsions.[35]

The recurrence rate is 25-30%. In the NCPP study about 1/3 rd of children had at least one recurrence, 9% had three or more attacks. 50% ofthe second attacks occurred within 6 months of first convulsion, 75% in a span of 1 year and 90% in span of 2 yrs.[6] Recurrence of febrile seizures can be divided into major and minor risk factor.

Major factor :

- Age < 2 yr

- Duration of fever < 24hours
- Fever 38 – 39^0C

Major factors :

- Family history of febrile seizures
- Family history of epilepsy
- Complex febrile seizures
- Male Gender
- Low serum sodium

Having no risk factors carries a risk of about 12%, 1 risk factor (25 – 50%), 2risk factors (50 – 59%), 3 or more (73 – 100%).[7]

suggest that Arginine Vasopressin may be an important mediator in the pathogenesis of hypothermia induced seizures.[9,35]

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 convulsive episode.

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

1)Cerebral development prior to and at the critical age.

2) Cerebral damage at the time of the convulsion.

Cerebral development at the age excitical for febrile convulsion:

Between the ages of 6 months and 3 years, when febrile convulsions are more common, both organization and myelination are occurring in the child's brain. Since prenatal factors and adverse events in early pregnancy may predispose to febrile convulsions, 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 convulsions.[22]

Cerebral damage in association with febrile convulsion:

There is a reasonable amount of circumstantial evidence that single brief (less than 15 minutes) generalised convulsions with fever do not cause recognisable cerebral damage. Biochemical evidence of cerebral hypoxia is lacking when the CSF pyruvate and Lactate levels are measured after brief convulsions with fever. Either prolongation of seizure for more than 30 minutes or repetition within a 24hour period is associated with raised lactate levels and lactate:Pyruvate ratios suggesting that cerebral hypoxia has occurred.[22]

Clinical features:

The disease is characterised by sudden onset of seizures within 24 hours of the child developing/

In the NCPP study, males & females and white & blacks did not differ significantly in their vulnerability to recurrence.[6]

Numerous factors have been discovered to be linked to a higher chance of febrile convulsions returning. These are:

- Younger age of onset (< 15 months)
- Family history of febrile convulsions.
- Epilepsy in first degree relative.

The likelihood of recurrence has not been strongly linked to complex traits.

In a study done by S.G.Ling in Singapore the following factors were attributed to as the risk factors for complex first febrile seizures and subsequent development of recurrence. They are age of 15months or less, birth weight of 2 kg or less and an initial temperature of less than 38 degree Celsius. [78]

A study by Anne Berg , it was seen a shorter duration of fever before the initial febrile seizure and a lower temperature at the onset of febrile seizure were associated with an increased risk of recurrence in children who have febrile seizures.[77]

A neurological anomaly that develops later on may raise the risk, however it is impossible to determine how much.

It is currently understood that none of the risk variables by themselves can classify kids as having a high or low risk of recurrent seizures. A combination of risk indicators that function cumulatively and can identify groups of different risk categories can more accurately estimate the risk. According to this subgrouping, the majority of kids (65–75%) have a low recurrence risk of less than 30%, while a small group (3–10%) have a more risk than others who have an low risk.

In a Nigerian study, Aierde has shown that the younger the age at first febrile convulsion the more likely the recurrence rate. Those with moderate degree of pyrexia were 10 times more likely to have subsequent recurrent convulsions compared to those with high degree of

pyrexia. Further, the recurrence rate was 5 times higher in first borns compared second born or more. A male preponderance was observed.[31]

Risk of epilepsy:

Although febrile convulsions are benign in nature but a low proportion ofchildren (2 to 4%) may go ahead and develop epilepsy later in life.[79]

Vestergaard M and his follow investigators investigated into the long term risk of epilepsy after febrile seizures in susceptible subgroups in Denmark. They concluded that children with a history of febrile seizures had a higher rate of epilepsy that lasted into adult life, but less than 7% of children with febrile seizures developed epilepsy during 23 years of follow up. The risk was high for those who had a family history of epilepsy, cerebral palsy, or low APGAR scores at 5 minutes at birth.[80]

C M Verity, and Jean Golding in their study which was done in U.K. to know the risk of epilepsy after febrile convulsions concluded that the risk of epilepsy after FS is very less than reported in many hospital based studies.[81]

Mikati M A and Rahi A have reported that 15% of children with epilepsy have had febrile seizures and only 2% to 7% of children who experience febrile seizures proceed to develop epilepsy later in life. They have reported several predictors of epilepsy after febrile seizure.[77]

The risk factors for epilepsy are:

- Complex febrile seizures.
- Family history of febrile convulsions.
- Presence of neurodevelopmental abnormality

Overall risk after febrile convulsions – 2% to 2.5 percent. Epilepsy risk after one febrile convulsion is ,

- 1% have no risk factors.
- 2.5% for 1 risk factor
- Three risk factors: 5% to 10%

Children who experience epilepsy following prior febrile seizures may experience absence, complex partial, and generalised tonic-clonic seizures.

Intellectual & motor function:

There is no proof that febrile convulsions promote intellectual decline or raise the risk of death, cerebral palsy, or mental impairment.[67,82]

In the British National Child Development study, children with febrile convulsions did not show deficits in school performance at 7 and 11 years of age.

In the NCPP report of intellectual performance in children with febrile convulsions, there was no difference between children with febrile convulsions and their convulsion free siblings on IQ testing at 7 yrs. Neither recurrent convulsions nor those lasting > 30 minutes were associated with IQ deficit.[70]

Prophylaxis :

Patients with febrile convulsion have good outcome. Several studies have found benign outcome. The long term prognosis in terms of subsequent epilepsy, neurological, cognitive & 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, phenobarbitone & clobazam have been used to prevent recurrence of febrile convulsion. Prescription of prophylaxis should be reserved for the rare cases in which:

Multiple seizures have occurred in a child below 1 year.

- Abnormal neurological development
- Had focal paralysis following a seizure
- Parents anxiety will remain very high even after reassurance.

Prophylaxis are of 2 types :

a) Long term – Phenobarbital and Sodium Valproate are used.

b) Intermittent – Diazepam orally or rectally when the child has got fever in 3 divided doses

to total of 1 mg/kg/day in three divided doses. If side effects like lethargy or ataxia occurs, the dosage is halved. Clobazam 0.1 to 1mg/kg/day is also used in intermittent prophylaxis.

A potential drawback of intermittent medication is that seizure could occur before fever is noticed

In children with febrile seizures, this treatment does not reduce the likelihood of developing epilepsy in the future.

Phenobarbital 5mg/kg/day has been used as continuous prophylaxis in one or two divided doses. Valproate is as effective as phenobarbitone in preventing recurrence.In controlled trials, just 4% of children receiving valproate experienced a second febrile seizure, compared to 35% of control individuals. Adverse effects include fatal hepatotoxicity, thrombocytopenia, pancreatitis, GI disturbances.

Neither valproate nor phenobarbitone is effective in reducing the risk of epilepsy in children with febrile seizures

Finally, a meta-analytical assessment of the preventive measures against febrile seizure recurrence was conducted. Continuous Phenobarbital prophylaxis versus intermittent diazepam prophylaxis was compared & found to have adverse effects with long term use of phenobarbitone & thus long prophylaxis of febrile convulsion is not recommended.[67]

Vitamin B_{12}:

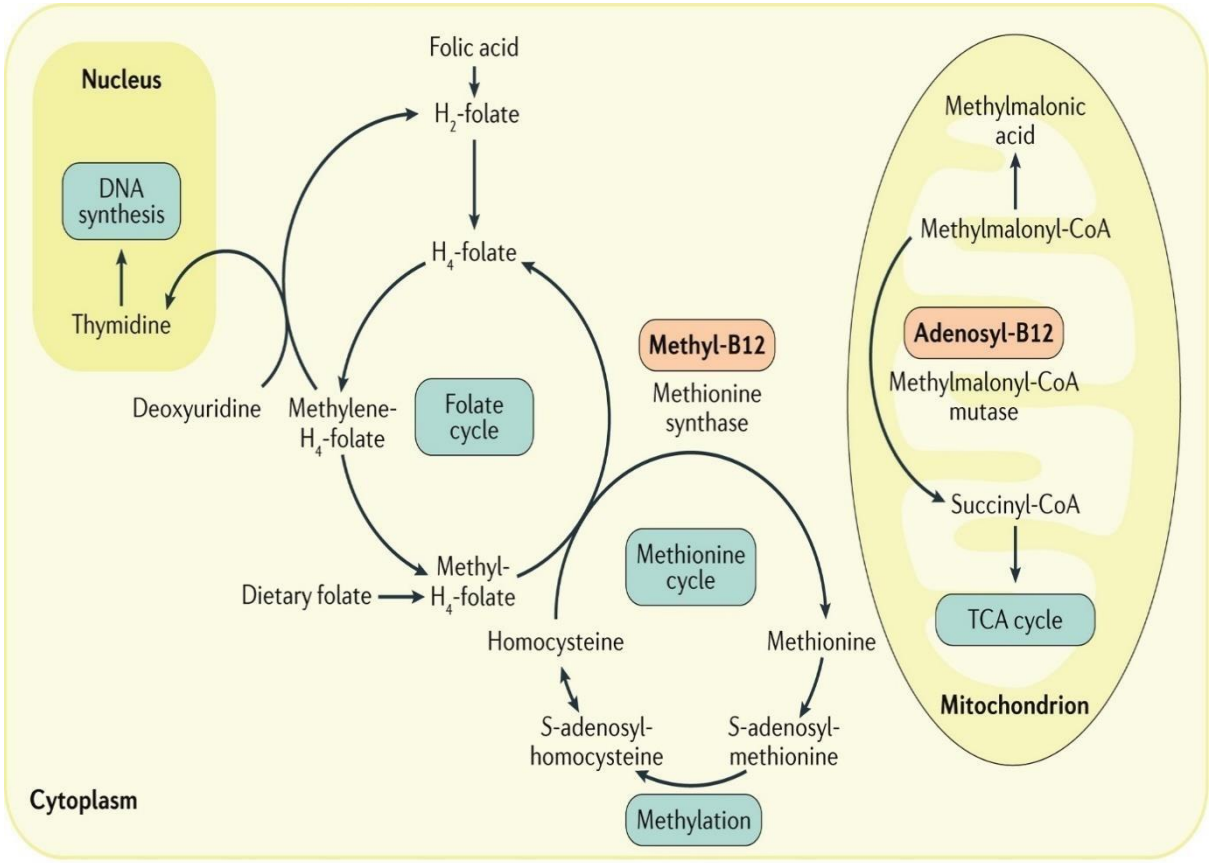
- Vitamin B12 is a water-soluble vitamin, also known as cobalamin found in, milk products, and eggs. It is available as including methyl-, cyano-, ,vanddeoxyadenosyl**.** The cyano form is found in trace amounts in food

Vitamin B_{12} Function

- Methionine synthase is required for purine and pyrimidine synthesis. The reaction is

codependent on methyl cobalamin and folate.

- Megaloblastic anemia is caused by a lack of folate, which is not caused by a lack of vitaminB12 .
- Methylmalonyl CoA mutase is a cofactor-dependent enzyme that converts
    - methylmalonyl CoA to succinyl CoA.
- The neurological effects of vitamin B12 deficiency due to methylmalonyl CoA [2].



- Figure 4 . Vitamin B_{12} function.

Vitamin B_{12} Deficiency :

- Decreased IF production, atrophic gastritis, ileal diseases impair **B_{12}** absorption

- Vegans who do not consume animal products can get their vitamin B12 from supplements.
- Injections or oral doses of vitamin B12 are used to treat pernicious anemia. Because the gastric antrum is the site of IF and acid secretion, vitamin B12 deficiency will also develop.[122]
- Vitamin B12 deficiency is also caused by ileum resection or Crohn's disease or other chronic bowel inflammatory conditions.[122]
- The potential for folate fortification of the food supply to mask vitamin B12 deficiency has also raised some safety concerns.
- Neurological damage has been reported in 20-30% of cases of vitamin B12 deficiency in the absence of anemia .. Patients suffering from pernicious anemia require higher doses of oral supplements (500-1,000 g/d) or intramuscular injections. Fortification may have a greater impact in developing countries because population intake is low.

MATERIALS AND METHODS :

- This study will be carried out in PEDIATRIC WARD AND PICU OF Shri B M Patil medical college hospital and research centre, BLDE(DU), Vijayapura, Karnataka in children with complaints of febrile seizures.

METHODOLOGY :

- After assessing the inclusion criteria, all febrile seizure patients included in the study. After stabilization, A 5ml of blood sample collected from all patients and transferred in cold boxes to the lab. Vitamin B12 level will be detected using chemiluminescent immunoassay, and serum folic acid levels and platelet indices will also be seen.
- STUDY DESIGN: Prospective observational study
- PERIOD OF STUDY: One and a half year, From Jan 2021 to June 2022.

INCLUSION CRITERIA:

- Children aged from 6 months to 60 months with febrile seizures .

EXCLUSION CRITERIA:

Children with epilepsy ,renal ,rickets ,liver ,endocrine disorders.

EXPOSURE:

Sample size

With anticipated Mean±SD of Folic acid among children 12.88±2.72 (ref) the study would require a sample size of 45 children with 98% level of confidence and a precision of 1

Formula used

- $\mathbf{n=\frac{z^2\ S^2}{d^2}}$

Where Z= Z statistic at α level of significance

d 2 = Absolute error

S=Common standard deviation

Statistical Analysis :

- The data obtained will be entered in a Microsoft Excel sheet, and statistical analysis will be

performed using a statistical package for the social sciences (SPSS Version 20).

Results will be present as Mean (Median) ±SD, counts and percentages and diagrams

- For normally distributed continuous variables will be compared using the independent t-test. For not normally distributed variables Mann Whitney U test will be use.
- Categorical variables will be compare using the Chi-square test.
- Correlation between variables will be calculated by Person's/ Spearman's Correlation.
- $P<0.05$ will be considered statistically significant. All statistical tests will perform two-tailed.,…

Type of study

Prospective observation study

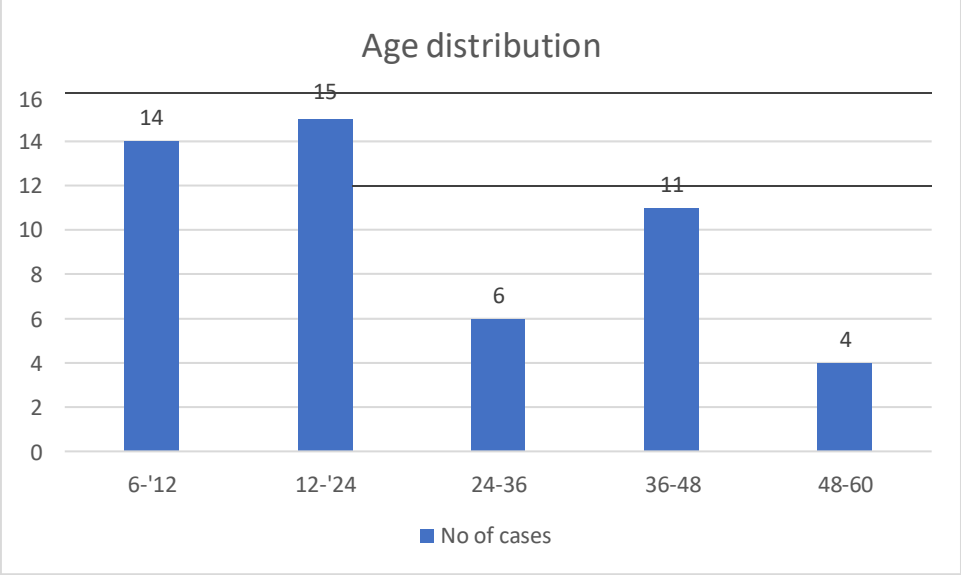
RESULTS

Age distribution :

50 children with febrile seizures were studied in the group (6 months – 60 months).Out of 50 children 14 children (28%) between 6 – 12 months,15 children (30%) between 12 - 24 months, 6 children (12%) between 24 - 36 months ,11 (22%) between 36 – 48 months ,4 children (8%) between 48 – 60 months . As the age increases the incidence of febrile convulsions were less.

Table 7. **Age Distribution**

Age in Months	No of cases	Percentage
6-12	14	28
12-24	15	30
24-36	6	12
36-48	11	22
48-60	4	8



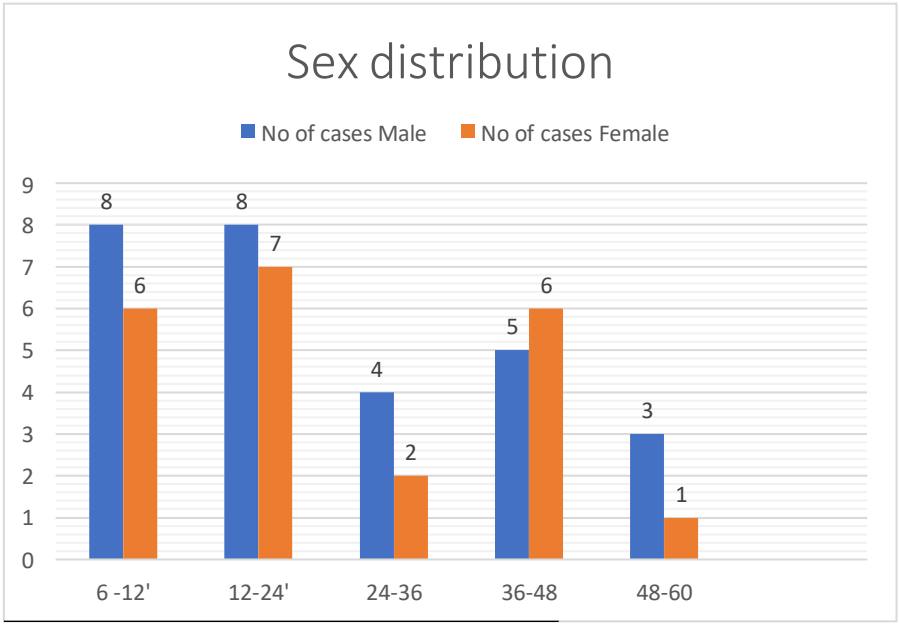
Graph -1. Age distribution

Sex distribution :

In this study out of 50 children ,28(56%) children were male ,22 children (44%) were female. In the age group between 6-36 months the incidence of febrile convulsions was more in male children as compared to female children.

Table 8. Sex Distribution with age

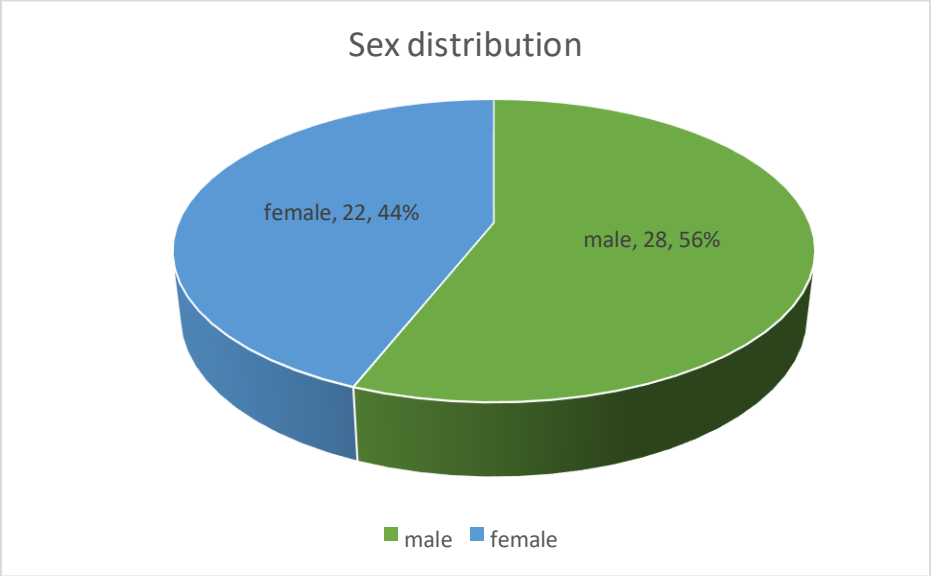
Age in Months	No of cases	
	Male	Female
6-12	8	6
12-24	8	7
24-36	4	2
36-48	5	6
48-60	3	1



Graph 2. Sex distribution with age

Table 9.Sex distribution frequency

Sex distribution	Frequency	Percent
Male	28	56
Female	22	44
Total	50	100



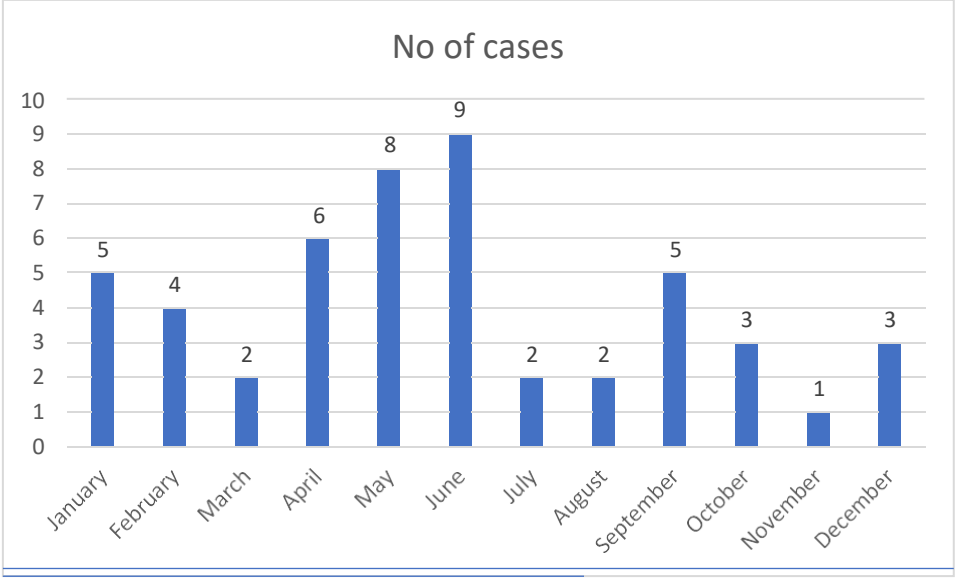
Graph 3. Sex distribution frequency

Month wise distribution of cases :

The chart depicts the month-by-month distribution of cases. Two peaks were observed, one in May and one in June.

Table 10 .Month wise Distribution of cases

Month	No of cases	Percentage
January	5	10
February	4	8
March	2	4
April	6	12
May	8	16
June	9	18
July	2	4
August	2	4
September	5	10
October	3	6
November	1	2
December	3	6



Graph 4. Month wise distribution of cases

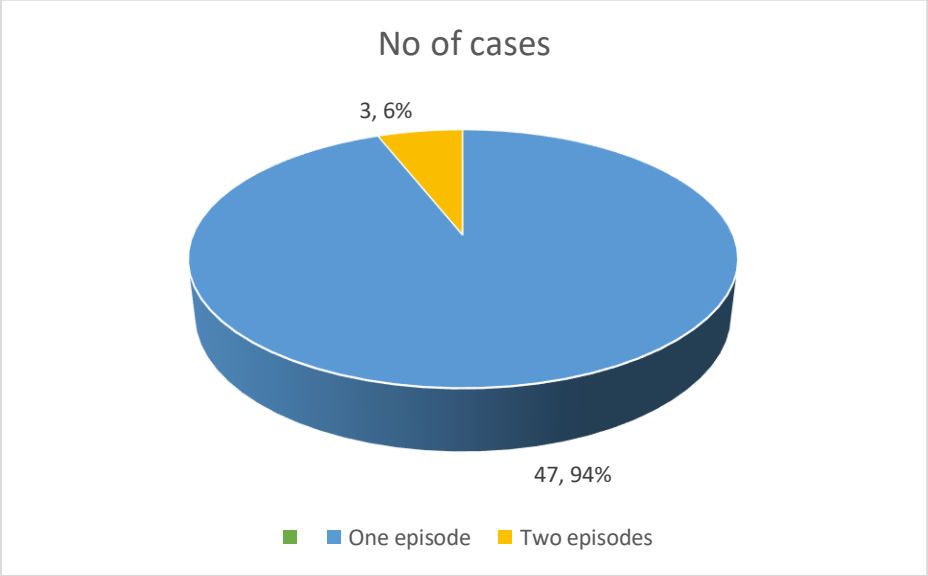
Frequency of seizure in one febrile episode:

Out of 50 children 47 children had single episode of febrile seizure, 3 children had more than

1episode.

Table 11 . Frequency of seizure in one febrile episode

No of seizures	No of cases	Percentage
One episode	47	94
Two episodes	3	6
Three episodes	-	-
>Three episodes	-	-
Total	50	100



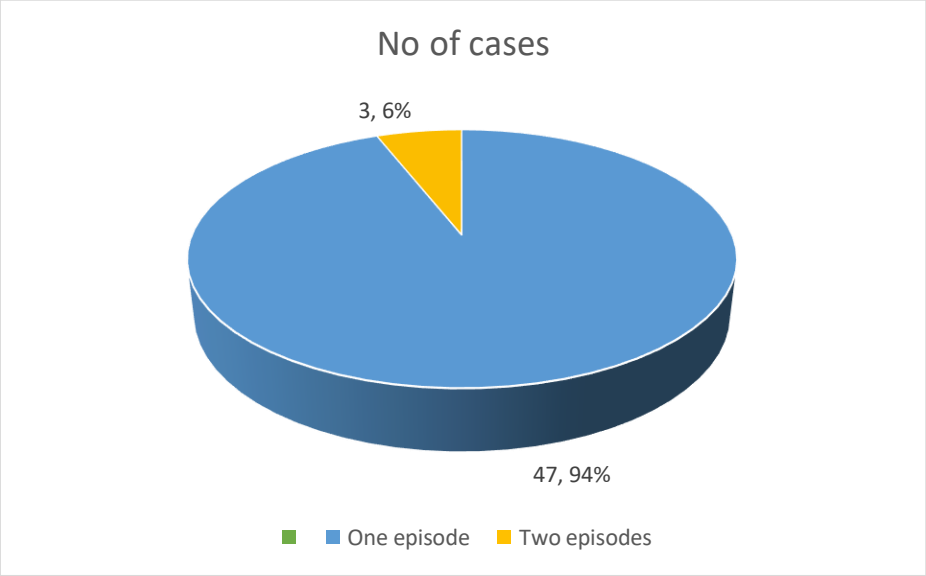
Graph 5. Frequency of seizure in one febrile episode.

Recurrent febrile seizures:

In this current study out of 50 children ,6 children(12%) had recurrent febrile seizures. Remaining 44 children (88%)had no recurrence in following years.

Table 12. Recurrent febrile seizures:

Recurrent FS	Frequency	Percent
NO	44	88
YES	6	12
Total	50	100



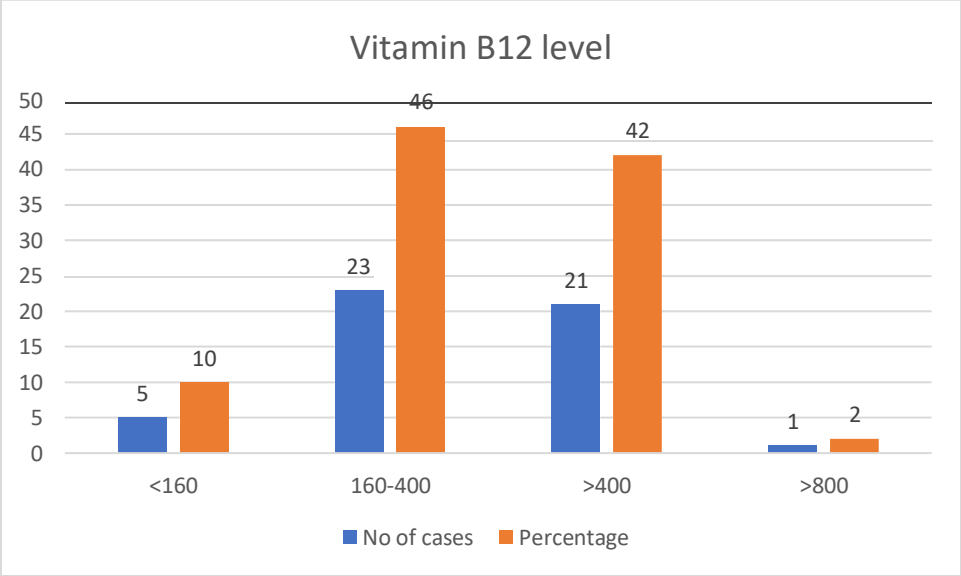
Graph 6. Recurrent febrile seizures:

Vitamin B12 levels in cases :

Among 50 children 5 children(10%) has vitamin B12 < 160 means deficiency. Out of 50 ,23 children has low values between 160 - 400(46%) .Out of 50 ,21 children has normal values >400 (42%).

Table 13. Vitamin B12 levels in cases

Vitamin B12 levels(pg/ml)	No of cases	Percentage
<160	5	10
160-400	23	46
>400	21	42
>800	1	2
Total	50	100



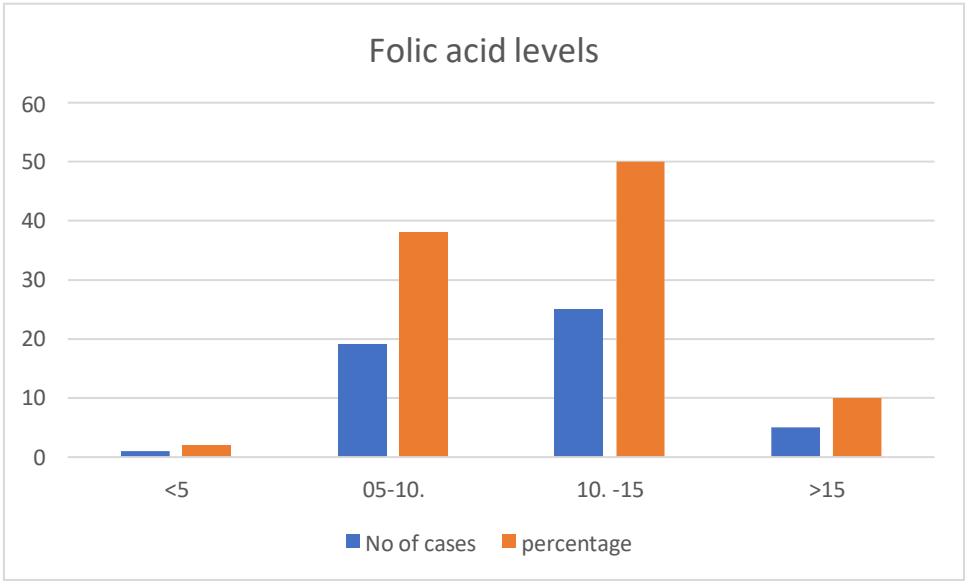
Graph 7. Vitamin B12 levels in cases

Folic acid levels in cases:

Among 50 children, 20 children(40%) have low levels of folic acid .Out of 50 ,30 children(60%) have normal folic acid levels.

Table 14. Folic acid levels in cases

Folic acid levels (ng/ml)	No of cases	percentage
<5	1	2
5-10	19	38
10-15	25	50
>15	5	10



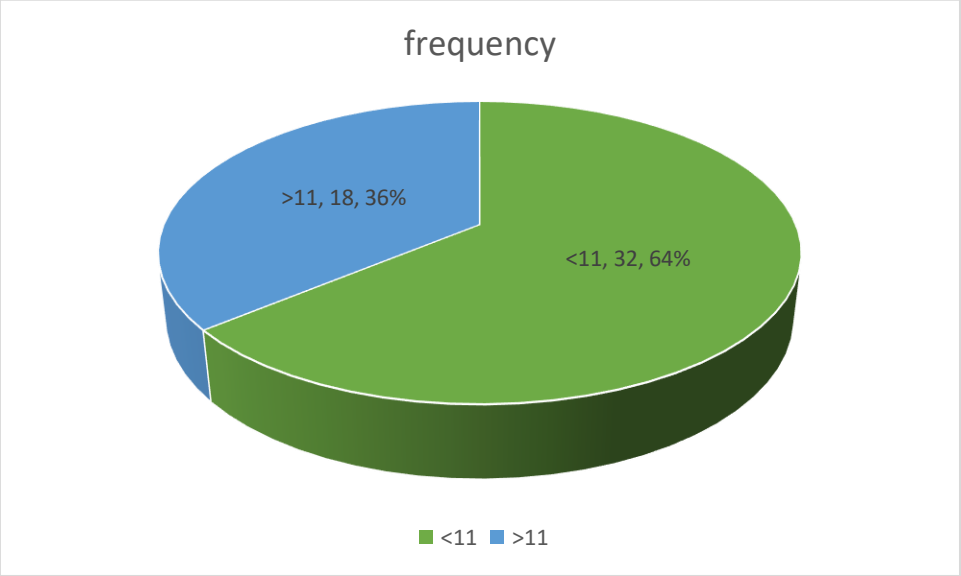
Graph 8 .Folic acid levels in cases

FS association with Anemia :

Anemia is defined by the WHO as a Hb level of < 11 gm/dl. 32 (64%) out of 50 FS children had Hb <11 gm/dl. The Hb level in the remaining 18 children (36%) is >11gm/dl.

Table 15.Hb levels in cases

Hb (g / dl)	Frequency	Percent
<11	32	64
>11	18	36
Total	50	100



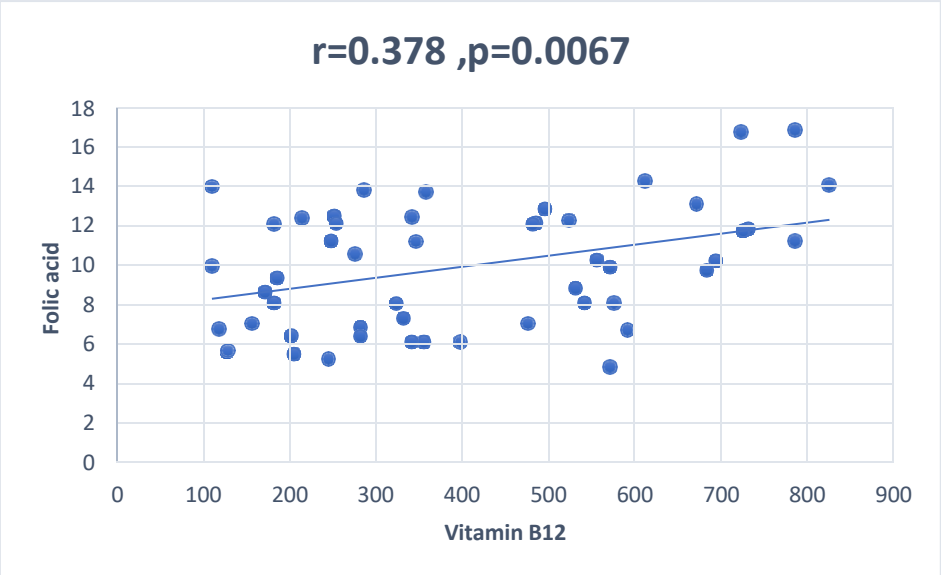
Graph 9. Hb levels in cases

Correlation between vitamin B12 and Folic acid :

The Correlation coefficient between vitamin B12 and folic acid r= 0.378 and

p-value = 0.0067**.** There is a significant positive correlation between vitamin B_{12} and folic acid

If vitamin B_{12} value is increased folic acid also increased, if vitamin B_{12} is decreased folic acid is also decreased,



Graph 10. Correlation between vitamin B12 and Folic acid

Platelet indices :

This table comprises Platelet count ,MPV,PDW,PCT values in cases.

Table 16 . Results for Platelet, MPV and PDW in FS cases

	Minimum value	Maximum value	Mean ± Std Deviation
Platelet count	132000	615000	35104.00 ± 116322.381
MPV	6.9	11.1	8.72 ± 1.027
PDW	8	16.5	11.25 ± 1.824
PCT	0.12	0.60	0.31 ± 0.102

There is a significant positive correlation between MPV and PDW (P value = 0.0023) .The correlation between platelet count and PDW is significant positive correlation (P value = 0.0048).But there is nonsignificant positive correlation between platelet and MPV.

Table 17 . Correlation between mean platelet values, MPV and PDW in FS cases

	Correlation coefficient (r)	P value
MPV – PDW	0.421	0.0023
Platelets - MPV	0.195	0.173
Platelets - PDW	0.392	0.0048

Discussion :

Febrile convulsions are a common pediatric emergency encountered worldwide. Febrile seizures occur between the ages of 6 months and 5 years("Febrile Seizures: Clinical Practice Guideline for the Long-Term Management of the Child With Simple Febrile Seizures," 2008). According to some studies, the incidence in India is nearly 10%. However, recent research indicates that the occurrence is nearly comparable to the Western population(Karande, 2007). Some febrile children will develop febrile convulsions, while others will not. Several mechanisms, including genetic factors, a family history of febrile convulsions+, and vitamin B12 and folic acid deficiency, have been proposed(Waqar Rabbani et al., 2013). Some other studies observed that insufficiency of vitamin B12 and folic acid may cause occurrence of seizures. In this study, we observed that low vitamin B12 and Folic acid levels may cause to develop febrile convulsions.

1) Mean age in months:

The mean age in the current study was 23.26± 14.79 months.

Table 18.Mean age in months.

Study	Mean age in months
Ganesh et al study 's[123]	23.8 months
Mahyar et al. study[125]	27.13 ± 15.72 months
Farah et al.'s study[120]	21.25± 11.53 months
Waqar Rabbani et al. study(Waqar Rabbani et al., 2013)	23.97±14.45 months
Ihsankafadar et [134]	18 months
Current study	23.26± 14.79 months

2. Sex incidence :

In this study population, 56% (28) of the cases were male, while 44% (22) were female. The male to female ratio was 1.27:1. Males had more febrile seizures than females.

Table 19. Sex incidence

Study	**Male %**	**Female %**
Farah et al. study[120]	60 %	40 %
Mahyar et al. study[125]	57.7 %	42.3 5
Ganesh et al, study[123]	50 %	50 %
Waqar Rabbani et al, study[135]	66 %	34 %
Jun-Hwa Lee et al, study[128]	53.6 %	46.4 5
Current study	56 %	44 %

3. Temperature as a risk of seizures:

It is clear that the raise in temperature rise may be a risk factor for the cause of seizures.

In this current study, the mean temperature in cases was 100.5 $\pm$ 0.69^{o}F.

Table 20. **Mean temperature in cases**

Study	Cases	Controls
Ganesh et al, study[123]	102°F	101.4°F
Margareta et al, study[129]	39.01 ± 0.56° C	38.64 ± 0.45°C
Jun-Hwa Lee et al, study[128]	38.3 ± 0.9°C	36.5 ± 0.3°C
Hassan et al, study[116]	39 ± 0.5°C	38.5 ± 0.7° C
Current study	100.5 + 0.69° F	

4.Seasonal Variation :

In this current study, there were two peaks in the occurrence of febrile convulsions, one in May and one in June.This is most likely due to the fact that diarrheal disorders are more common in the months May and June. Nelson K.Band Hirtz D.G24. discovered some seasonal variation in the occurrence of febrile seizures, with peaks occurring inNovember and January, possibly due to respiratory infections, and also from June to August, when gastrointestinal illnessis prevalent. The disparity in observations can be attributed to differences in disease patterns in different locations.

5.Frequency of episodes per one febrile episode :

The majority of the cases experienced a single episode of convulsion per episode of febrile illness.In this current study, 94% of the cases had single seizures with each febrile episode, while 6% had multiple convulsions per febrile episode. According to Sehgal and Bala (1979), 65.4% of the cases had one episode of seizures, 28.4% had more than one episode, and 6.6% had more than four episodes. According to Yachcha et al (1981), 86% of participants had a

single episode of convulsion, 14% had more than one episode, and none had more than four episodes.

Table 21. Frequency of seizure per episode of fever

Duration	No of cases		
	Sehgal and Bala[37]	**Yachcha et al [62]**	**Present study**
One episode	65.4%	86%	94%
1-4 episodes	28.4%	14%	6%
More than 4 episodes	6.6%	Nil	Nil

6.Recurrence of Febrile seizures :

In this current study discovered that 12% of children with FS had recurrence.

Similarly, Anil Raj Ojha et al.

Table 22. .Recurrence of Febrile seizures

Study	Recurrence of FS %
Anil Raj Ojha et al. study[130]	51%
Ausi Indriani et al. study[126]	37.7 %
Jyoti Agrawal et al, study[115]	30.6 %
Z.Habib et al. study[124]	16 %
KK Chan et al. study[119]	22.6 %
Berg AT et al. study[118]	27 %
Current study	12 %

7.Vitamin B12 :

Vitamin B12 is essential in humans, particularly for the central nervous system. Vitamin B12 deficiency in children can develop as a result of inadequate intake, abnormal absorption, dysfunctional vitamin B12 transport, and congenital metabolic defects. Convulsions are caused and exacerbated by a deficiency in vitamin B12[117]. In this current study vitamin B12 levels were low in the cases ,the mean value of vitamin B12 was 410.72 $\pm$ 210.48 .According to Osifo et al[132], individuals with FC had reduced serum vitamin B12 levels relative to the healthy group and the febrile group without seizures. Vitamin B12 levels were lower in the current study group , implying that low vitamin B12 levels may play a role in the etiopathogenesis of FC.

Table 23. Vitamin B_{12} levels in different studies.

Study	**Vitamin B_{12} levels in study**
Ozkale., et al. study[117]	mean vitamin B12 level in the FC group was significantly lower than the control group.
Osifo et al. study[132]	individuals with FC had reduced serum vitamin B12 levels relative to the healthy group and the febrile group without seizures
Current study	vitamin B12 levels were low in the cases

8.Folic acid :

In this current study Folic acid levels were 60 % children had high folic acid values The same study found no statistically significant difference in mean cerebrospinal fluid folic acid levels between the FS and non-seizing febrile children groups.(Osifo et al., 1985) Osifo et al.(Osifo et al., 1983) observed the relationship between serum folic acid levels and the occurrence of convulsions in 32 febrile children aged between 8 months to 5 years. They also discovered that children with FSE had significantly higher red cell folic acid levels than children with less than 30 minute convulsions. Osifo et al(Osifo et al., 1985)proposed that folic acid accumulation in serum and red cells may be causally related to the development of convulsions in febrile children.

9.Anemia :

In this current study 64% of children had low Hb values (Hb< 11 g / dl). Similarly, Mashaer Abidlqader et al discovered that 62.7% of the children had anemia associated with febrile seizures. The mean Hb was 9.98 $\pm$ 1.85 in cases and 11.14 $\pm$ 1.81 in controls . 57.7% of children had recurrent FS with anemia, while 42.3% had a normal hemoglobin levels ($\geq$11 g/dl).

10.Platelet indices :

The importance of platelet indices in the inflammatory response has been demonstrated, and platelet size is correlated with the degree of inflammation. Mean platelet volume represents the volume of circulating platelets on average

(MPV). Conditions that are inflammatory, infectious, or allergic in nature cause the bone marrow to produce more platelets and release larger platelets into the bloodstream. In this instance, an increase in MPV and platelet count was noted. Prior to the increase in platelet count, MPV increases . It has been established through numerous studies investigating the significance of MPV that it more accurately represents platelet functions than platelet count. Platelet activation and function are related to MPV. Increased MPV is a sign of activated platelets. Ozaydin et al proposed that MPVs in complex FS should be lower than in simple FS because epilepsy is an inflammatory disorder of the brain and MPV declines in inflammatory conditions. In order to compare MPVs in children with simple and complex FS retrospectively,. In contrast to Ozaydin et al., Ozkale et al. found that children with complex FS had significantly higher MPVs and PDWs within an hour of seizure than did children with simple FS. One month after the seizure, there was no appreciable distinction between patients in the simple FS and complex FS groups in terms of MPVs and PDWs. This finding suggests that in the complex FS, the acute phase of disease activity is when the brain experiences the most inflammatory changes. There is a significant positive correlation between MPV and PDW in the current study.

Table 24. Platelet indices in various studies

Study	Platelet indices in various studies
Ozaydin et al. study[133]	Children with complex FS had significantly lower MPVs than children with simple FS, according to research done on MPVs in

	children with both types of FS.
Ozkale et al, study[117]	Children with complex FS had significantly higher MPVs and PDWs within an hour of their seizure than children with simple FS. There was no discernible difference in MPVs and PDWs between patients in the simple FS and complex FS groups at one month following the seizure.
Current study	there is significant positive correlation between MPV-PDW .

CONCLUSION

- In this current study we observed that vitamin B_{12} and folic acid levels are low in children with febrile seizures.
- The correlation between vitamin B_{12} and folic acid is positive, significant correlation(P value =0067). In recurrent febrile children both vitamin B_{12} and folic acid levels are low.
- In this study we observe that most of the children has low Hb values in children with febrile seizures.

- In this study MPV values are low in children with febrile seizures. These findings could be attributed to immature hematopoietic systems in children or to active inflammatory states.

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RESEARCH INFORMED CONSENT FORM

BLDE(DU)'s Shri B.M.PATIL Medical College, Hospital & Research Centre,

Vijayapura, Karnataka -586103.

TITLE OF THE PROJECT : "STUDY OF SERUM VITAMIN B 12 ,FOLIC ACID LEVELS AND PLATELET INDICES IN CHILDREN WITH FEBRIL ECONVULSIONS"

GUIDE : DR S S KALYAN SHETTAR,MD

PROFESSOR & HOD

DEPARTMENT OF PEDIATRICS

PG STUDENT : DR. CHINTAM V K KUMAR REDDY

PURPOSE OF RESEARCH:

I understand that, the present study is being carried out , to help , assess clinical profile of all febrile seizures in children and see the association of vitamin B12 and folic acid, to assess the correlation of vitamin B12 and folic acid with recurrence of febrile seizures and its risk factors and source of the fever .

PROCEDURE:

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations, a final work up of the procedure and its outcome 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 any time; Dr. Chintam V K Kumar Reddy , 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 Chintan V K Kumar Reddy may terminate my participation in the study after he/she has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to my child resulting directly from child's participation in this study, if such injury were reported promptly, the appropriate treatment would be available to the child. 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. CHINTAM V K KUMAR REDDY Date 16/12/2022

(Investigator)

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr. Chintam V K Kumar Reddy is doing a study of association of vitamin B12 and folic acid deficiency in febrile seizures childrens admitted In Pediatrics ward and PICU In Shri B. M. Patil Medical College Hospital, Vijayapura, Karnataka. Dr. Chintam V K Kumar Reddy has explained to us the purpose of research and the study procedure. We are willing to allow our child to get treated in Shri B.M. Patil Medical College Hospital, Vijayapura. We have been explained about the study, benefits and possible discomforts in detail in our native language and we understand the same. We are aware that child will get best treatment, and no compensation like financial benefits will be given if our child's condition deteriorates and any untoward complication happens, and we will not sue anyone regarding this. Therefore we agree to give our full consent for child's participation as a subject in this research project.

(Parents / Guardian) (Witness to signature) Date 16/12/2022

Date 16/12/2022

PROFORMA OF CASE TAKING:

NAME :

AGE : WEIGHT:

SEX :

IP NO. :

ADDRESS :

DATE OF BIRTH :

DATE OF ADMISSION :

DATE OF DISCHARGE :

GRBS AT TIME OF ADMISSION :

TEMPARATURE AT TIME OF ADMISSION:

PRESENT C/O :

PREVIOUS H/O FEBRILE SEIZURES :

NO OF EPISODES :

SYSTEMIC EXAMINATION:

CVS:

RS :

ABDOMINAL:

CNS:

INVESTIGATION:

CBC: CRP:

PLATELET INDICES:

VITAMIN B12:

FOLIC ACID:

IEC/No-09/2021
Date-22/01/2021

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Study of serum Vitamin B12, Folic acid levels and platelet indices in children with febrile convulsions.

Name of PG student: Dr Chintam V K Kumar Reddy Department of Paediatrics

Name of Guide/Co-investigator: Dr S S Kalyanashettar, Professor & HOD of Paediatrics

DR .S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

3

	NAME	AGE	SEX	TEMPERATURE AT A	PLATELET COUNT	MPV	PCT	PDW	VITAMIN B12	FOLIC ACID	HB	RBC	TC	FEBRILE SEIZUERS (YES/N	FEBRILE SEIZURES(RECURENCE)
3	AYUSH.S.DODDAMA	48 MONTHS	MALE	100	4,29,000	7.8	0.33	11.1	110	3.95	10.4	5.22	17630	YES	YES
4	LALASAB SURESH BA	36 MONTHS	MALE	101	1,38,000	8.5	0.12	12.7	356	6.08	12	4.65	7,360	YES	NO
5	PREETAM GOUDA	48 MONTHS	MALE	101.2	2,13,000	8.3	0.19	8.6	282	6.82	10.8	4.1	3730	YES	YES
6	MAYURI GAJANAND	9 MONTHS	FEMALE	99.8	4,67,000	7.9	0.37	11.5	342	12.42	10.7	4.35	8,920	YES	NO
7	KASPIYA TORPI	36 MONTHS	FEMALE	101	3,47,000	7.2	0.25	9.6	556	10.24	11.8	4.89	7,170	YES	NO
8	ANIRUDDA R	30 MONTHS	MALE	101.2	1,89,000	10.7	0.19	10.7	252	12.48	9.6	4.59	7180	YES	NO
9	UMERA INAMDAR	12 MONTHS	FEMALE	100.6	5,30,000	9.1	0.48	9.1	186	9.32	8.9	4.93	18,010	YES	YES
10	UDAY SANTOSH RAT	12 MONTHS	MALE	101.4	2,85,000	7.6	0.22	10.6	248	11.22	9.6	3.75	12,910	YES	NO
11	RIDHA RAFIQ JAMAD	7 MONTHS	FEMALE	100.2	3,18,000	8.7	0.28	12.5	156	7.04	10.1	3.66	10,360	YES	YES
12	SAHANA RAJU MAD	16 MONTHS	FEMALE	100.2	4,59,000	8.3	0.38	11.9	245	5.26	8.2	4.03	8,430	YES	NO
13	WAGESH PRAKASH E	48 MONTHS	MALE	100.1	4,24,000	6.3	0.29	8.2	202	6.42	10.6	3.81	21,150	YES	YES
14	SANKET SHRISHAIL	8 MONTHS	MALE	100	4,42,000	7.5	0.33	10.7	118	6.78	10.8	4.68	5810	YES	NO
15	SWARA RAMAKRISH	30 MONTHS	FEMALE	100.4	4,16,000	7.6	0.32	10	182	8.08	12.2	4.52	16,630	YES	NO
16	MASTER VEDANSHA	12 MONTHS	MALE	100.6	1,99,000	9.7	0.19	15.7	172	8.62	9.8	3.81	7880	YES	NO
17	POOJA HANAMANT H	6 MONTHS	FEMALE	102.5	4,42,000	8.6	0.38	12.4	476	7.02	11.5	4.2	14,940	YES	NO
18	ADITYA CHANNAPA	24 MONTHS	MALE	100.4	3,08,000	7.8	0.24	10.8	346	11.18	10.7	4.18	11220	YES	NO
19	SREENIDHI SHIVANA	12 MONTHS	FEMALE	100.6	3,47,000	7.5	0.26	10.3	592	6.72	10.8	4.53	12,280	YES	NO
20	RAMU SATHISH KAR	17 MONTHS	MALE	99.4	3,68,000	8.3	0.31	12.4	486	12.12	10.7	5.22	5,980	YES	NO
21	MASTER AYUSHMAT	10 MONTHS	MALE	99.8	3,09,000	10	0.31	16.5	276	10.56	10.3	4.38	25320	YES	NO
22	ANUSHREE	18 MONTHS	FEMALE	102.2	3,69,000	7.9	0.29	11.4	786	11.2	12.1	4.98	7.07	YES	NO
23	BABY MARIYAN BE(	7 MONTHS	FEMALE	100.1	3,18,000	8.8	0.28	13.2	694	10.2	9.5	4.25	6,100	YES	NO
24	PREMA GANDAR BIF	36 MONTHS	FEMALE	99.8	3,61,000	7.5	0.27	10.3	342	6.08	11.8	4.59	9.56	YES	NO
25	ANJALI VITTAL KALA	12 MONTHS	FEMALE	102	3,35,000	8	0.27	11.7	482	12.04	9.9	4.32	3,320	YES	NO
26	CHRANJEEVI R PARA	12 MONTHS	MALE	101.6	2,06,000	8.7	0.18	9.1	572	9.87	10.5	5.21	6420	YES	NO
27	SAHITYA SACHIN	15 MONTHS	FEMALE	101	2,86,000	9.8	0.28	11.4	358	13.72	11.3	4.5	18,420	YES	NO
28	AMBRESH A HOLASA	17 MONTHS	MALE	100.2	4,23,000	8.4	0.35	8	542	8.08	9	4.68	19,470	YES	NO
29	KRITI PATIL	30 MONTHS	FEMALE	100.2	2,12,000	9.5	0.2	9.7	214	12.38	12.2	4.25	2,680	YES	NO
30	GAGANDEEP J PAYA	36 MONTHS	MALE	101	2,91,000	8.1	0.24	11.7	205	5.48	9	4.75	14,700	YES	NO
31	SHRI HARSHA SANTO	6 MONTHS	MALE	101.5	4,13,000	10.4	0.43	12.9	110	13.95	11.3	5.13	16,620	YES	NO
32	KAVERI NINGAYYA M	30 MONTHS	FEMALE	99.8	4,58,000	7.3	0.34	9.5	576	8.06	9.9	3.51	21,710	YES	NO
33	SHANVI MAHADEVA	38 MONTHS	FEMALE	100.8	3,12,000	7.6	0.24	10.2	612	14.24	10.2	4.58	19,110	YES	NO
34	DEEPAK Y SHINDE	32 MONTHS	MALE	101.2	4,85,000	8	0.39	11.7	524	12.24	11	4.62	22,060	YES	NO
35	AYOSH MAHESH KAL	29 MONTHS	MALE	100.4	3,42,000	8.5	0.29	12.4	786	16.82	11.5	4.71	12,140	YES	NO
36	UTAVIKA SATISH NA	18 MONTHS	FEMALE	100.6	2,27,000	8.4	0.19	12.4	732	11.82	10.7	4.15	11,450	YES	NO
37	SIYANATH N SHEIKH	36 MONTHS	FEMALE	99.8	1,94,000	9	0.17	14.2	684	9.72	11.2	4.59	7,790	YES	NO
38	SHIVANI V RATHOD	36 MONTHS	FEMALE	101.6	3,96,000	7	0.28	8.8	324	8.02	10.1	4.23	6,730	YES	NO
39	AARIZ F INAMDAR	12 MONTHS	MALE	100.2	3,16,000	8.4	0.26	11.8	182	12.04	9.2	5.1	3,730	YES	NO
40	SAMAIRA AMEENSA	11 MONTHS	FEMALE	100.2	3,11,000	10.1	0.31	11.5	532	8.82	8.6	3.8	26,030	YES	NO
41	ARJUN SANTHOSH B	13 MONTHS	MALE	99.9	5,52,000	9	0.5	9.8	254	12.08	7.2	4.1	16,920	YES	NO
42	MUTTU ASHOK DONI	24 MONTHS	MALE	100.1	6,15,000	9.6	0.6	10.7	826	14.02	10.5	5.11	18,570	YES	NO
43	SAMPAT MADIWALA	36 MONTHS	MALE	100	2,26,000	11.1	0.25	14	436	12.82	9.6	4.55	4,330	YES	NO
44	PREETAM POLICE PA	6 MONTHS	MALE	100.2	5,56,000	9.6	0.27	10.8	726	11.72	9.5	4.14	26,900	YES	NO
45	KRISH APPASAHEB Y	24 MONTHS	MALE	100.2	4,52,000	10	0.45	11.4	282	6.38	11.6	5.41	19,730	YES	NO
46	KASHIM M NADAF	11 MONTHS	MALE	100.6	3,97,000	9.6	0.38	10.8	332	7.28	10	3.84	12,640	YES	NO
47	SONU BHIMASHANK	60 MONTHS	FEMALE	101	4,05,000	10.2	0.46	11.4	672	13.08	11.5	5.04	16,100	YES	YES
48	AMAIRA AMEERPAS	45 MONTHS	FEMALE	101	2,12,000	9.8	0.42	12.8	128	5.62	12.3	4.65	9,520	YES	NO
49	SATVIK ANIL RATHOI	14 MONTHS	MALE	99.6	1,75,000	9.4	0.38	10.8	398	6.08	11.1	4.87	10,490	YES	NO
50	KISHOR PARAMAPPA	10 MONTHS	MALE	99.8	4,23,000	8.3	0.37	9.1	724	16.72	11.7	3.51	13,120	YES	NO
51	ANJANAYYA SHIVAI	8 MONTHS	MALE	100.2	5,22,000	9.3	0.48	9.3	572	4.82	9.1	3.62	17,280	YES	NO
52															