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Research Article

Iron Deficiency: A Risk Factor for Simple Febrile Seizures

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Abstract

The most prevalent type of convulsive disorder, occurring in approximately 2 to 5% of children, are febrile seizures. The prognosis for febrile seizures is often very good. A seizure or convulsion is a brief, intermittent alteration in behavior or motor activity brought on by aberrant electrical activity in the brain. In boys, febrile seizures are a little more frequent. In comparison to febrile controls without seizures, the risk variables for a first febrile seizure have been investigated. Higher temperatures, perinatal factors, and low plasma ferritin levels, which indicate poor iron status or iron deficiency, are risk factors. This study's objectives are to ascertain the prevalence of iron deficiency in kids who have simple febrile seizures and the relative risk of iron deficiency as a cause of simple febrile seizures. It was discovered that uncomplicated febrile seizures in children at risk of iron shortage could be avoided with early identification and iron supplementation.

Keywords: Iron deficiency; Febrile seizures; Perinatal; Anaemia; Ferritin; Paediatric.

Abbreviations: CBC-Complete Blood Count; CNS-Central Nervous System; CSF-Cerebro Spinal Fluid; EEG-Electroencephalogram; FS-Febrile Seizures; Hb-Hemoglobin; Hct-Hematocrit; ILAE-International League Against Epilepsy; IQ- Intelligent Quotient; MCV-Mean Corpuscular Volume; MCH-Mean Cell Hemoglobin; TIBC-Total Iron Binding Capacity; WHO-World Health Organization; PBS-Peripheral Blood Smear; MCHC-Microcytic Hypochromic; PR-Pulse Rate; RR-Respiratory Rate.

Introduction

The most prevalent type of convulsive disorder, occurring in 2 to 5% of children, are febrile seizures. The prognosis for febrile seizures is often very good. A febrile seizure is one that occurs in children between the ages of 6 months and 5 years old, is associated with

a fever of more than 38 °C (rectal temperature), is not caused by an infection of the central nervous system, lacks previous neonatal seizures or prior unprovoked seizures, and does not meet the criteria for other acute symptomatic seizures.

About 30% to 40% of the time, an initial febrile seizure is complicated (which lasted more than 15 minutes, partial, or multiple within 24 hours) [1]. The usual age of onset is between 14 and 18 months, with the peak incidence occurring in the subsequent year of life [2]. In boys, febrile seizures are a little more frequent.

In comparison with febrile controls without seizures, the risk variables for an initial febrile seizure have been investigated. Higher temperatures, perinatal variables, and low plasma ferritin levels, which indicate poor iron levels or iron deficiency, are risk factors [1,3-7].

A creche attendance, newborn discharge at 28 days or later, parental reports of sluggish development, and a family history of febrile seizures were additional risk factors [1]. The febrile seizure gene has been located on chromosomes 19p and 8q13–21 by linkage analyses in multiple big families. Some families have an autosomal dominant inheritance pattern.

Aim and objectives

1. To find out how often children suffering with simple febrile seizures are iron deficient.
2. To assess the likelihood that iron shortage may result in uncomplicated febrile seizures.

Review of literature

A seizure or convulsion is a brief, paroxysmal alteration in behavior or motor activity that is caused by aberrant brain electrical activity [1]. About 10% of children in the pediatric age range experience seizures. The following definition of febrile seizures was adopted in 1980 by the National Institutes of Health's consensus development conference [8,9]. A febrile seizure is an incident that happens in infancy or childhood, typically occurring between 3 months and 5 years of age, associated with fever, but without evidence of intracranial infection or defined cause. It is defined as an abnormal, sudden, excessive electrical discharge of neurons that propagates down the neuronal process to affect an end organ in a clinically measurable fashion. They were characterized as follows in 1989 by the ILAE classification, which categorized them as "situation related seizures" (also known as "conditions with epileptic seizures that do not require a diagnosis of epilepsy"). Generalized seizures that happen during a severe fever illness are virtually invariably a defining feature of febrile seizures, an age-related condition. The British Pediatric Association's Research Unit Working Group decided that it was appropriate to use the term "epileptic" in place of "event" and to distinguish between "convulsion with fever" and "febrile convulsion." As a result, the term "febrile convulsion" should only refer to an epileptic seizure that occurs in a kid between the ages of 6 months and 5 years that is triggered by a fever caused by an infection that is external to the nervous system in a child with a neurologically normal overall condition.

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Demographic data

The most prevalent type of pediatric seizure condition, febrile seizures affect 2 to 5% of kids between the ages of 6 and 60 months [10]. It is unacceptable for the pure type of febrile seizures to begin outside of this age range.

Types of febrile seizures

Simple and complicated febrile seizures are subcategorized into febrile seizures due to various prognostic consequences.

Simple febrile seizures

Simple febrile seizures are precisely defined as being experienced by neurologically healthy children between the ages of 6 months and 5 years old, whose seizure is brief (less than 15min), generalized, and occurs only once during a period of 24 hours while a fever, according to the 1999 practice parameter of the American paediatric academy [11,12]. The following characteristics should be present, in accordance with the definition given by American family physicians [13].

1. A time frame of under 15 minutes.
2. Seizures with generalization.
3. No history of neurological issues.
4. Only happens once throughout the first 24 hours.

Complex febrile seizures

Seizures with focal characteristics or those that are chronic or recurrent are what are meant by this. Complex febrile seizures are those that exhibit any of the following characteristics [13].

1. A duration of over 15 minutes.
2. Focal seizures.
3. A repeat within the first 24 hours.

It is simple to diagnose complex febrile seizures that are prolonged or repeated. However, it may be difficult to identify and classify focal aspects, such as lateral eye deviation, staring episodes, and motor asymmetries in the setting of a bilateral convulsion [14].

Onset

At least 380 °C in the rectal temperature is required for the body temperature to be considered feverish. Although a quick rise is thought to be a trigger, the actual temperature may matter more [15]. Twenty-one percent of febrile seizures happen within the first hour after the commencement of the fever, 57% happen between the first and 24th hours, and 22% happen more than 24 hours later [16].

Duration of febrile seizures

92% of the time, seizures last 3–15 minutes and are short. The convulsions last longer than 15 minutes in the remaining 8% of cases, and 2/3 of these prolonged seizures result in febrile status epilepticus.

Long-lasting febrile seizures may be the first step of hemi convulsion-hemiplegia syndrome1, but they are extremely rare (0.06%) [17,18] and only occur in kids with clearly identifiable CNS illnesses. In comparison to age-matched febrile and non-febrile control children, risk variables for a first febrile seizure have been investigated [19,20].

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Having two or more of the independent risk factors listed below increases a child's chance of experiencing their first febrile seizure by about 30%:

1. A close relative suffering from febrile seizures.
2. A delayed neonatal discharge that occurs after more than 28 days.
3. Parenteral report of sluggish growth
4. Participation in nursery.

A parent who is likewise afflicted increases the risk for younger siblings of affected children by about 10-20%. In general, men are more prone than women. After a febrile seizure, 50% of kids will experience recurrences-32% have one, 15% have two, and 7% have three or more.

The following risk variables increase the likelihood of recurrences [21]:

1. In the first year of life, the first febrile seizure happens.
2. The initial febrile seizure takes place during a brief and mild feverish sickness.
3. A first-degree relative has a history of febrile seizures.
4. A complicated initial febrile seizure occurs.
5. Persistent neurological abnormalities are present.

Etiology

Given that febrile seizures are frequently familial [22,23], genetic predisposition is crucial. Children who have siblings or parents who have febrile seizures are at four- to five-times more vulnerable than the average person. Up to 70% of monozygotic twins and 20% of dizygotic twins have reported concordance rates.

Given the high number of parents who are sick and the low risk to siblings, autosomal recessive inheritance is implausible [18]. Large autosomal dominant kindreds with febrile seizures allowed for the identification of at least four distinct loci, ensuring heterogeneity, on chromosomes 8q13-21,38,39; 19p13.3 and 19q13.1,40,41; 5q14-15,42; and 6q22-24,43. Numerous sodium channels, GABA A receptors, and other auxiliary proteins may be involved in the etiology of febrile seizures and even simple febrile seizures, according to the available evidence [22].

The central histaminergic neuronal system may be implicated in the control of childhood febrile illness-related seizures. Children who experience a febrile illness but do not see an increase in CSF fluid histamine may experience febrile seizures [24].

The prevalence of viral diseases is higher; however, this may be due to children being more susceptible to them. It has been suggested that acute human herpesvirus 6 infection and febrile seizures have a specific relationship [24].

Outcome

There are four potential negative outcomes for a child who has had a simple febrile seizure that might possibly be changed by proper therapy:

1. IQ decline.
2. A higher chance of epilepsy.

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3. Possibility of repeated febrile seizures.
4. Death.

Recurrent febrile seizures have not been demonstrated to result in IQ decrease or neurocognitive inattention [25] 431 kids who had simple febrile seizures were investigated by Ellenberg and Nelson [26], who found no discernible difference between their learning and that of their control siblings.

In a related study, 2,72,303 kids suffering from febrile seizures and control children were compared. Except for those kids who had neurological abnormalities prior to their first seizure, no difference in learning was found [26,27].

Children who experience uncomplicated febrile seizures are 1% more likely than the overall population to develop epilepsy by the age of 7 [17]. The probability of getting a generalized afebrile seizure by the age of 25 years increases to 2.4% in children who have had repeated simple febrile seizures, are under the age of twelve at the period of their initial febrile seizure, and have a family record of epilepsy [28].

There is a 50% chance that children who are under 12 months old at the period of their initial febrile seizure may experience additional febrile seizures. Children who are older than 12 months at the period of the initial incident have a 30% risk of experiencing a second febrile seizure, and of those who do, 50% are likely to experience at least one subsequent recurrence [29].

Last but not least, there is a theoretical possibility that a child could pass away during a straightforward febrile seizure due to aspiration, injury, or cardiac arrhythmia, but this has never been documented.

Management

Diagnostic procedures

If the diagnosis is certain, there is no need for further testing in febrile seizures. The difference between a "febrile convulsion" and a "convulsion with fever" is crucial because the latter can occur in cases of meningitis, encephalitis, cerebral palsy with concurrent infection, and metabolic or neurodegenerative diseases. Children who experience a convulsion and fever in the initial year of life may require a lumbar puncture as a matter of course.

Electroencephalography

EEG is not required in simple instances [30]. Between 2 to 86% of children with febrile seizures have EEG abnormalities, according to reports [31]. Such a big disparity is partly explained by how the EEG abnormalities were defined, how long had passed since the febrile seizure, and how old the patient was when the EEG was taken.

According to some writers, 'hypnagogic paroxysmal spike activity' is a unique EEG feature that is frequently observed in children having febrile seizures. As the child slips off to sleep, this wave consists of brief (1-2s) bursts of sluggish waves intermingled with small larval spikes. But this lacks specificity and has no predictive power. According to research by other authors, 20-50% of kids who get repeated EEGs beginning at least two years after their first febrile seizure exhibit spikes or spike and wave abnormalities as well

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as photosensitivity [32]. Additionally, it appears that infants with febrile seizures frequently experience rolandic spikes [33,34].

Treatment

Advantages and disadvantages of ongoing anticonvulsant therapy.

Phenobarbitone

Simple febrile seizures can be prevented from recurring with phenobarbitone [35]. For instance, in research by Farewell, et al., children whose Phenobarbital levels were within therapeutic range experienced a decrease in recurrent seizures; but, because Phenobarbital medication had such a high noncompliance rate, an overall effect was not seen.

Primidone

Primidone has also been demonstrated to lower the frequency of recurrence of febrile seizures when administered at levels of 15-20mg/kg/day [36,37]. The fact that 29 out of 32 children in a Minigawa and Miura study had derived Phenobarbital levels below therapeutic limits is interesting and suggests that primidone alone may be effective in avoiding seizure recurrence.

Valproic acid

In randomized, controlled investigations, just 4% of the kids taking valproic acid experienced a second febrile seizure, compared to 35% of the control group. Valproic acid therefore appears to be much more efficacious than placebo and at least as effective as phenobarbital in avoiding the recurrence of febrile seizures [38]. The recurrence of febrile seizures is not observed to be prevented by carbamazepine or phenytoin.

Benefits of intermittent anticonvulsant therapy

Diazepam

In a double-blind controlled trial, it was found that giving oral diazepam to patients who had previously experienced febrile seizures could lessen their likelihood of recurring. When a child had a febrile seizure in the past, they were either given oral or rectal diazepam (0.33mg/kg every eight hours for 48 hours) or a placebo. Diazepam reduced the probability of febrile seizures per person-year by 44% [39]. In a more recent trial, kids with previous instances of febrile seizures received oral diazepam during a fever and were compared to kids in a control group who weren't given any medication. There was a 30% recurrence rate in the control group versus 11% in the oral diazepam group [40].

Midazolam

The feasibility and safety of stopping a simple febrile seizure that lasts no more than five minutes with rectal diazepam as well as with intranasal and buccal midazolam have been shown in the literature [41].

Intermittent antipyretics

79 kids who experienced their first febrile seizure were treated by Camfield, et al., [42] with either a daily Phenobarbital with antipyretic regimen or a placebo plus antipyretic regimen. The Phenobarbital-treated group had a considerably low

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recurrence risk, indicating that the antipyretic drug is unsuccessful at preventing febrile seizures from recurring.

Iron deficiency

In practically every nation on earth, a sizable portion of the population-and frequently the majority-is affected by iron deficiency. Human newborns frequently suffer from iron deficiency anaemia, especially between the ages of 6 and 24 months [43]. Half of the anaemia in children under 4 years old in underdeveloped nations is due to iron deficits anaemia.

Ninety of the 112 nations that provided information to the WHO in 1992 have programmes in place to prevent iron insufficiency, notably iron supplementation for expectant mothers [44]. In a WHO publication [45], the scientific agreement on the avoidance of iron deficits anaemia was discussed. Since then, however, fortification technology has advanced considerably and understanding of the effects of iron deficiency-even in the dearth of anaemia-has changed. A condition known as iron deficiency is characterized by the absence of mobilizable iron reserves and the presence of symptoms indicating a compromised iron delivery to tissues, which involves erythron. Anaemia is a symptom of the more severe phases of iron insufficiency. The exact same sort of transferrin receptors is found on cell surfaces with respect to the actual need for iron in all tissues, which is how their iron needs are expressed. Therefore, an inadequate supply of iron to all other tissues is also linked to a deficient supply to the erythron. The words anaemia, iron deficiency, and iron deficiency anaemia are occasionally used interchangeably since anaemia is the most prevalent sign used to test for iron deficiency. However, there are mild to moderate forms of iron shortage where tissues still function poorly despite the absence of anaemia.

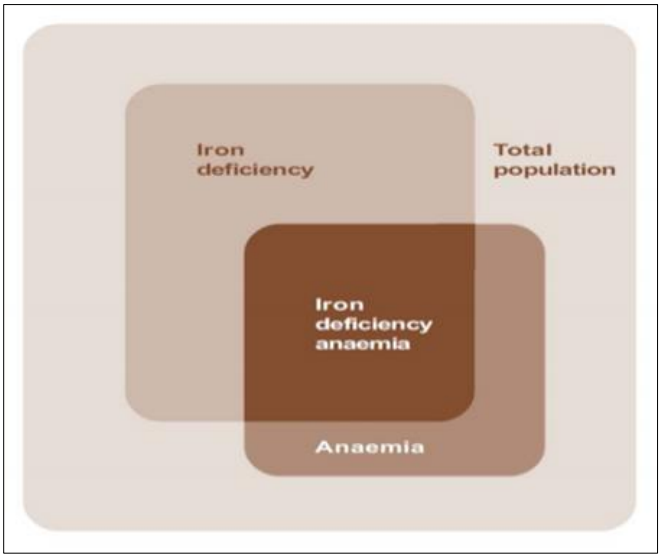

Figure 1: Source adapted from Yip R. Iron nutritional status defined. In: Filer IJ, ed. Dietary Iron: birth to two years. New York, Raven Press, 1989:19-36.

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Figure 1 [46] shows the connection between anaemia and iron deficiency in a population. The observed population also affects how much the rates of total anaemia and iron deficiency anaemia overlap.

The largest overlap happens in populations where dietary iron absorption is poor or where blood loss is frequently seen as a result of hookworm infestation. Long before the etiology of anaemia was understood, the pallor of anaemia was linked to fatigue and weakness

Today, it is acknowledged that mild to moderate iron shortage has negative functional effects even when there is no anaemia [47].

1. The cognitive function, behaviour, and physical development of babies, preschoolers, and school-aged children are negatively impacted by iron deficiency.
2. Immune health and infectious morbidity across all age groups.
3. The utilization of energy sources by muscles, which affects teenage and adult physical capacity and productivity across all age groups.

Cognitive impairment

Iron has been demonstrated to be crucial to brain function in laboratory animals. The brain contains iron in a number of locations, sometimes in significant amounts. Animals with an iron deficiency exhibit altered neurotransmitter levels as well as behavior that is typically unresponsive to iron replenishment. Infants in India with iron deficient anaemia have demonstrably slower psychomotor growth and worse cognitive ability [48]. Teenage girls whose diets included iron supplements reported feeling less worn out, having more focus in class, and having better moods [49]. Cognitive function can be affected by iron deficiency at any stage of life. According to estimates, between 10 and 20 percent of preschoolers in industrialized nations and between 30 and 80 percent in underdeveloped nations are anaemic at age one. When these kids reach school age, they will do poorly on tests of language, motor, and coordination skills, which is equivalent to a 5-to 10-point IQ loss. They will also have delayed psychomotor development.

Resistance to infection

Iron deficiency has a negative impact on the immune system, which increases the risk of morbidity from infectious diseases in populations with low iron stores [50]. Leukocytes' ability to kill ingested bacteria and lymphocytes is diminished in these circumstances, as is their potential to multiply when triggered by a mitogen.

Additionally, in such circumstances, there is a reduction in the number of cells involved in cell-mediated immunity [51] as well as a diminished skin test responses to common antigens [52].

Growth

Children in Indonesia who received more iron experienced growth improvements [53]. Evidently, local circumstances determine whether an impact of iron supplementation is seen or not. These include age at iron depletion, other dietary variables, and the frequency of illnesses and diarrhea.

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Endocrine

Triiodothyronine (T_3) synthesis and thyroid function in general, as well as the synthesis and metabolism of catecholamines and other neurotransmitters, are all affected by iron shortage. This impairs one's ability to regulate one's body temperature in a cold environment [54].

Prevalence

Children and women in non-industrialized countries are disproportionately affected by iron deficiency, which is the sole nutritional deficit that is also remarkably common in almost all industrialized countries.

Although there are no current global statistics on iron deficiency, it may be assumed that most preschoolers and expectant mothers in non-industrialized countries and at least 30-40% in industrialized nations are iron deficient using anaemia as an indirect sign [55,56].

	Industrialized countries	Non-industrialized countries
Children (0-4 years)	20.1	39
Children (5-14 years)	5.9	48.1
Pregnant women	22.7	52
All women (15-59 years)	10.3	42.3
Men (15-59 years)	4.3	30
Elderly (+60 years)	12	45.2

Table 1: Percentage of total affected population in industrialized and non-industrialized countries.

Category of public health significance	Prevalence of anaemia (%)
Severe	>or=40
Moderate	20-39.9
Mild	5-19.9
Normal	<or=4.9

Table 2: Prevalence of anaemia in different categories of public health significance.

Epidemiology [56]

Age, gender, physiological, pathological, environmental, and socioeconomic factors all have a significant impact on how common iron deficiency is.

Age

Because foetal red blood cells are destroyed shortly after delivery, full-term infants often have adequate iron reserves in the liver and hematopoietic tissue at birth. Iron accumulates in these tissues as a result, especially if the chord is tied after it stops beating. Even for infants who are exclusively breastfed, iron insufficiency frequently appears after six months of age if additional foods do not contain enough absorbable iron.

Gender

The prevalence of iron deficiency in children

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is the same across the board, with the exception of adolescent girls who have greater prevalence due to menstruation losses.

Physiological states

Growth rate is inversely correlated with the body weight-based need for iron. Accordingly, iron deficiency is most prevalent in children in preschool and during puberty, as well as to women in the reproductive stage as a consequence of physiological losses.

Pathological states

Common infections, particularly those that are recurring and persistent, can affect hematopoiesis and lead to anaemia. Blood loss is directly caused by hemolysis from malaria and by some parasitic illnesses, including hookworm, trichuriasis, amoebiasis, and schistosomiasis (both vesical and intestinal variants). The loss of blood exacerbates an iron deficit.

Groups	Age (years)	Mean body weight (Kg)	Required iron intake for growth (mg/day)	Median iron losses (mg/day)	
				Basal	Menstrual
Children	0.5-1	9	0.55	0.17	
	1-3	13.3	0.27	0.19	
	4-6	19.2	0.23	0.27	
	7-10	28.1	0.32	0.39	
Males	11-14	45	0.55	0.62	
	15-17	64.4	0.6	0.9	
	18+	75		1.05	
Females	11-14b	46.1	0.55	0.65	
	11-14	46.1	0.55	0.65	0.48
	15-17	56.4	0.35	0.79	0.48
	18+	62		0.87	0.48
Post menopause		62		0.87	
Lactating		62		1.15	

Table 3: Iron requirements and recommended iron intakes. A-Total absolute requirements include requirement for growth, basal losses and, in female, menstrual losses; B-Non-menstruating; C-Bioavailability of dietary iron during this period varies greatly.

Environmental factors

A diet may be deficient in iron or it may include sufficient levels of iron with a high bioavailability. It's possible that other nutrients required for hematopoiesis are lacking as well. Folic acid, vitamins A, B12, and C, protein, copper, and other minerals are some of them. Trauma can cause acute or chronic blood loss, which can lead to anaemia and iron deficiency.

Socioeconomic status

The majority of people with iron deficiency belong to low socioeconomic class groups.

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Requirement [56]

Table 3 provides an overview of suggested iron intakes and iron requirements.

Vulnerability

With each step of the life cycle, different populations are much more susceptible to iron deficiency. This variation is brought on by shifts in iron reserves, intake volume, and requirements for development or iron losses.

The most vulnerable demographics are often women of childbearing age, particularly during pregnancy, and children aged 6 months to 5 years.

Due to low iron intake in the diet and accelerated development in the first year, iron deficiency is most common among children under the age of five over the 2nd year of life.

Both school-age children and adults may experience severe iron shortage in regions where hookworm infestation is common.

Iron state indicators

Anaemia due to iron shortage is the extreme end of depletion.

Most non-anemic persons in that category who have rates more than 30-40% will be sufficiently iron-deficient to be at risk of negative functional repercussions [57].

For determining and tracking iron status, a number of trusted laboratory indices are available.

Only the hemoglobin and hematocrit tests, however, can be regularly carried out in field situations.

Only countries with sufficient resources or under certain research or survey conditions can do more accurate, numerous biochemical assays of iron status [58].

Studies that simultaneously measured iron status and carried out other available iron-related tests have demonstrated the value and restriction of utilizing anaemia as a surrogate for iron status.

These additional examinations include measurements of mean corpuscular volume, mean corpuscular hemoglobin, serum ferritin, erythrocyte protoporphyrin, mean corpuscular saturation, and (more recently) transferrin receptors.

The individual tests or methods for determining iron status are described in the following sections.

Sr. ferritin

The most precise biochemical test that corresponds to relative total body iron reserves is the serum ferritin level. In a lack of infection, a low serum ferritin level, which indicates depleted iron reserves, is a prerequisite for iron deficiency.

Being an acute-phase reactant protein, serum apoferritin is enhanced in response to any inflammatory or viral activity.

Therefore, in a lack of these situations, serum ferritin in the average range merely represents iron sufficiency. The best way to find out if your iron stores are low is to measure your serum ferritin levels.

The Table 4 lists the cut off values for sr. ferritin to identify iron deficiency.

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Iron stores	Serum ferritin (µg/l)			
	Less than 5 years of age		More than 5 years of age	
	Male	Female	Male	Female
Depleted iron stores	<12	<12	<15	<15
Depleted iron stores in the presence of infection	<30	<30	-	-
Severe risk of iron overload	-	-	>200 (adult male)	>150 (adult female)

Table 4: Cut off values for sr. ferritin to diagnose iron deficiency.

Serum iron, transferrin, and transferrin saturation

A decrease in serum iron (SI) levels is followed by an increase in transferrin total iron-binding capacity (TIBC) levels, which results in a net decrease in transferrin saturation (i.e., SI/TIBC).

However, there is a sizable diurnal variation in both serum iron and transferrin saturation. Additionally, there is a clear overlap between normal and iron-deficient people in these indices. The value of these indicators in making or disproving an iron deficiency diagnosis is reduced by this overlap.

Serum transferring receptors

A more recent addition to the range of iron deficiency diagnostics is the detection of serum transferrin receptors.

However, few data from epidemiological studies have been obtained regarding the effectiveness of this test in differentiating between patients who are iron-replete and those who are iron-deficient.

Red cell indices

The two most sensitive indicators of iron deficiency among all the red cell indices determined by electronic blood counts are mean corpuscular volume and mean corpuscular hemoglobin.

Reduced mean corpuscular volume that occurs together with anaemia is a late symptom of iron insufficiency.

Table 5 provides reference values for mean corpuscular volume and mean corpuscular hemoglobin.

Bone marrow iron stain

The standard by which other iron tests are measured has always been a bone marrow stain. Lack of stainable iron indicates a lack of iron reserves.

Because of this, serum ferritin, another indicator of iron storage, and the bone marrow stain have the strongest correlations [59]. Bone marrow iron-staining is not helpful in straightforward population-based studies for obvious reasons.

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	Female and male			
	1-1.9 years	**2-4.9 years**	**5-7.9 years**	**8-11.9 years**
RBC count				
Mean	4.34	4.34	4.41	4.52
-2SD	3.8	3.7	3.1	3.8
MCV (fl)				
Mean	79	81	82	84
-2SD	67	73	74	76
MCH (pg)				
Mean	27.4	28.1	28.6	28.7
-2SD	22	25	25	26
MCHC (g/l)				
Mean	34.4	34.5	34.5	34.5
-2SD	32	32	32	32

Table 5: Reference values for mean corpuscular volume and mean corpuscular hemoglobin.

Defining iron deficiency when multiple indices are available

Serum ferritin measurement in a lack of illness is the best way to identify an iron deficit. When it is practical to measure a number of indices, a definition of iron deficiency based on numerous markers is helpful for population-based assessment. Hemoglobin, serum transferrin receptors, serum ferritin, or bone marrow iron, would make the ideal combination. This combination would represent, in that order, functional impairment, tissue avidity for iron, and iron storage. Usually, resource-constrained environments cannot implement this strategy.

Materials and methods

- This prospective case-control study was carried out at the hospital between December 2013 and June 2015.
- The following formula is used to compute sample size, keeping the study's power at 90% and its level of significance at 5%.

  $$n = \left[\frac{p1(1-p1) + p2(1-p2)}{(p1-p2)2}\right] \times f(\alpha, \beta)$$

  N=children needed in each group (sample size).

  P1-proportion of events in cases group.

  P2-proportion of events in control group.

  α=significance level.

  β=1-power of the study.
- The sample size is calculated as 100 in each group using the proportions from the prior study and the calculation above.

According to the following inclusion and exclusion criteria, the kids were included in the study.

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Inclusion criteria

The study included children between the ages of 6 months and 5 years who had a fever (>38 °C) and a history of seizures, as well as normal serum glucose, sodium, potassium, and calcium levels.

Children between the ages of 6 months and 5 years who visit the hospital with a fever but no seizures are used as controls.

Exclusion criteria

- Children aged <6 months and >5 years.
- Children presenting with atypical febrile seizures.
- Children presenting with seizures other than febrile seizures or those having signs of CNS infection.
- Kids with a history of epilepsy, developmental delays, or birth asphyxia.
- Children receiving treatment with iron supplements
- Children with severe (≥ grade 3) malnutrition.
- Those diagnosed with hemolytic anaemia, coagulation disorders and hematological malignancies.
- Parents of children (cases and controls) provided written informed consent.

  All the questions were answered, doubts were cleared and signature of the parents was taken. The study was approved by the ethical committee of the hospital.
- A simple febrile seizure is defined as a convulsion that lasted less than 15 minutes and had no specific neurological abnormalities or symptoms.
- A thorough history was gathered, including the length of the fever, when the seizures started, how long they lasted, any accompanying complaints (for the reason of the fever), and any prior episodes of febrile seizures in the patient's family.
- Examination is done to rule out any dysmorphic features, signs of CNS infection, and to assess the development of the child.
- Vitals were recorded. Axillary temperature was measured using mercury thermometer by placing in axilla for 3 minutes.
- Those who are suspected to have CNS infection are included in study, only after ruling out CNS infection by CSF analysis.
- Blood investigations were done in the form of CBC to identify anaemia based on Hb%.
- To rule out other similar causes of anaemia, iron deficiency is identified in these children based on laboratory parameters like MCV,MCH, Sr. ferritin.
- Iron deficiency anaemia was defined as decrease of the Hb and Hct below 2 standard deviations (SD) of normal values for age group, as presence of Hb<11gm/dl, MCV<67fl for 6-23 months and <73fl for 24-60 months old, MCH<22pg for 6-23 months and <25pg for 24-60 months old and sr. ferritin of <12ug/l as per WHO guidelines.

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- Based on the above criteria number of iron deficient children were identified in both cases and controls groups.

Statistical methods

In the current statistical study, descriptive statistical analysis has been done. The Chi-square tests are utilized to compare discrete variables that are reported as counts (%). The unpaired, two-sided t test is used to compare continuous variables and is used to quantify continuous variables as mean ± SD. The 5% level of significance is used to determine significance. 95% confidence intervals and adjusted odds ratios were computed. according to these models. The cutoff for statistical significance was P <0.05.

Results

- Among the cases 52 were males and 48 were females which is almost equal to 1:1 ratio, as shown in Table 6.
- The mean age group for febrile seizure in the study for cases is 29.2 with confidence interval of 29.2 ± 13.02 where as in controls mean is 29.5 with confidence interval of 29.5 ± 11.38 as shown in Table 7.
- The median age for cases is 25 and for controls is 27 as shown in Table 8.
- 60 children among cases had low hemoglobin compared to 40 children among controls showing significant anaemia among cases (p=0.016) as shown in Table 9.
- Serum ferritin levels are low in 47 cases compared to 31 in controls showing significant association (p=0.029) as shown in Table 10.
- Among the total number of cases and controls, 13 in each group showed mild malnutrition which is statistical insignificant as shown in Table 11.
- Table 12 shows the MCV distribution among cases and controls, which is significantly low in cases (p=0.01).
- MCH value among cases is significantly low as compared to control (p=0.04) as shown in Table 13.
- Table 14 shows the frequency of iron deficiency distributed among cases and controls, which correlates with sr. ferritin levels.
- Among the vital measured, there is significant amount of tachycardia noted in cases with no significant difference regarding respiratory and temperature rate at the time of admission (Tables 15-17).

Sex	Group				Total	
	Control		Case			
	Count	%	Count	%	Count	%
Female	33	33	48	48	81	40.5
Male	67	67	52	52	119	59.5
Total	100	100	100	100	200	100

Table 6: Frequency distribution of sex among cases and controls.

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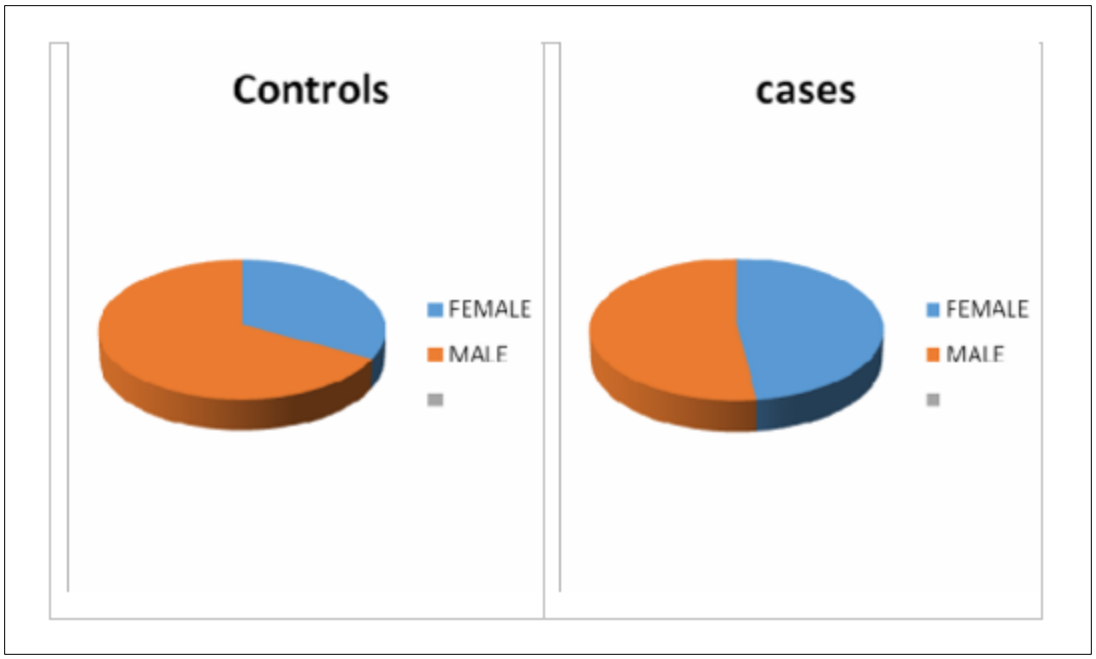

Figure 2: Frequency distribution of sex among cases and controls.

	Control (n = 100)		Case (n = 100)		t	df	p value
	Mean	S D	Mean	S D			
Age in months	29.5	11.38	29.2	13.02	0.2	198	0.84

Table 7: Frequency of age distribution among cases and controls.

Group	N	Minimum	Maximum	Median
Control	100	9	60	27
Case	100	7	59	25
Total	200	7	60	25.5

Table 8: Age in months.

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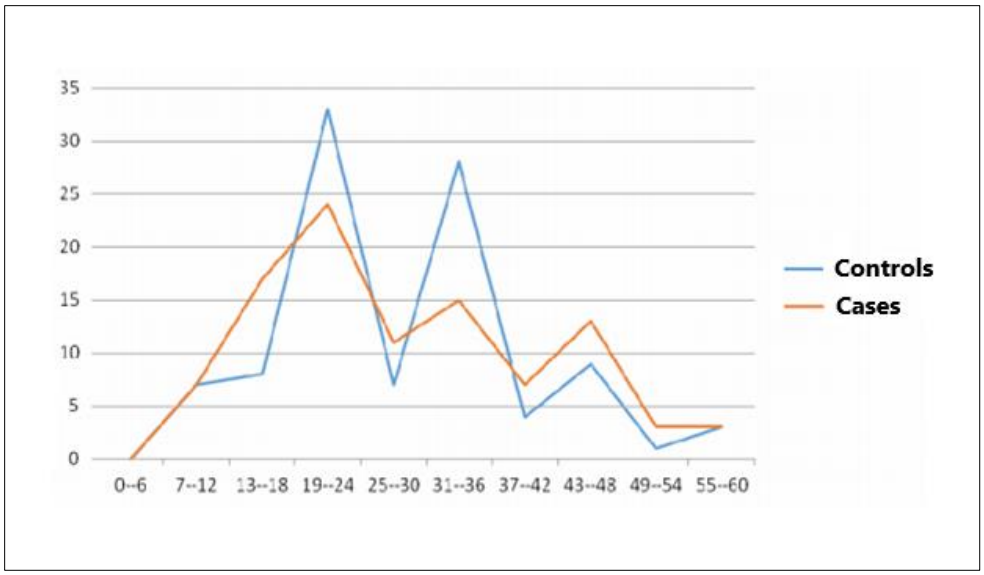

Figure 3: Frequency of age distribution among cases and controls.

	Group				Total	
	Control		Case			
HB class	**Count**	**%**	**Count**	**%**	**Count**	**%**
Low	42	42	60	60	102	51
Normal	58	58	40	40	98	49
Total	100	100	100	100	200	100

Table 9: Hb% Frequency of distribution among cases and controls (p=0.016).

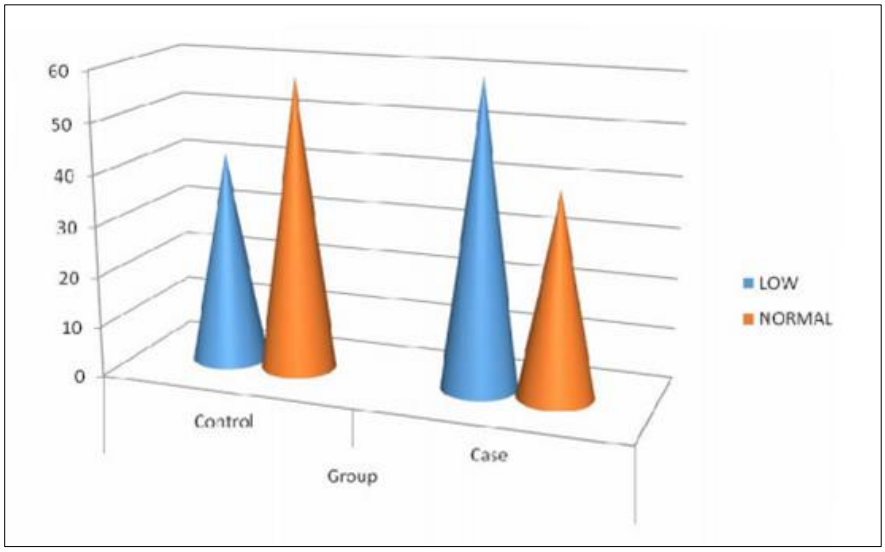

Figure 4: Hb% Frequency of distribution among cases and controls (P=0.016).

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Sr. Ferritin	Group				Total	
	Control		Case			
Class	Count	%	Count	%	Count	%
Low	31	31	47	47	78	39
Normal	69	69	53	53	122	61
Total	100	100	100	100	200	100

Table 10: Frequency of distribution of low sr. ferritin among cases and controls (p=0.029).

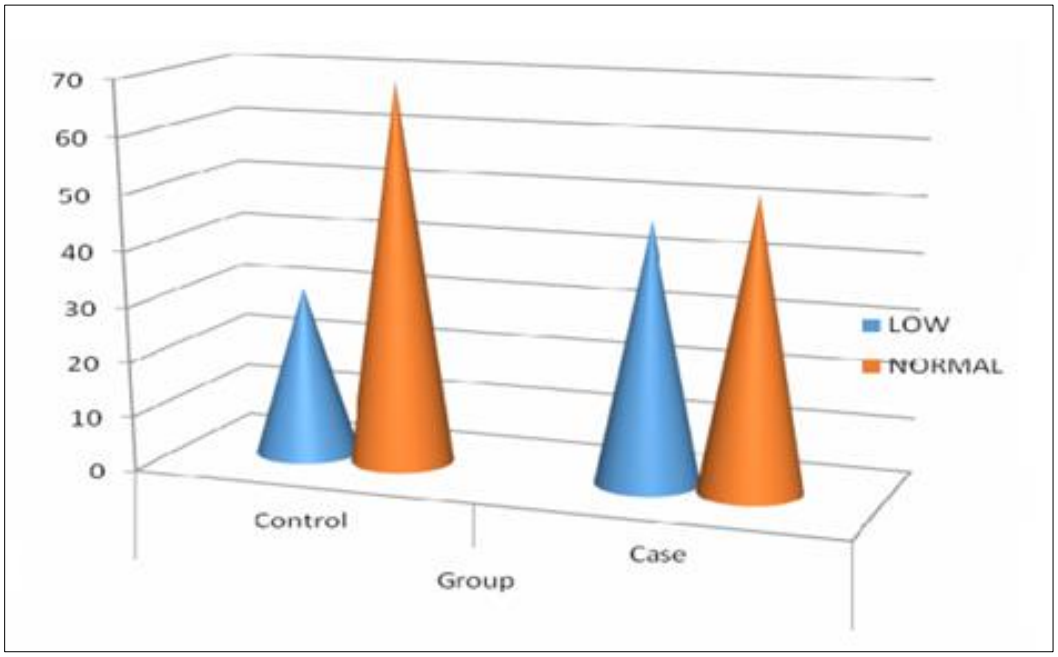

Figure 5: Frequency of distribution of low sr. ferritin among cases and controls (p=0.029).

Growth	Group				Total	
	Control		Case			
	Count	%	Count	%	Count	%
Mild	13	13	13	13	26	13
Normal	87	87	87	87	174	87
Total	100	100	100	100	200	100

Table 11: Frequency distribution of malnutrition among cases and controls (p=1.000).

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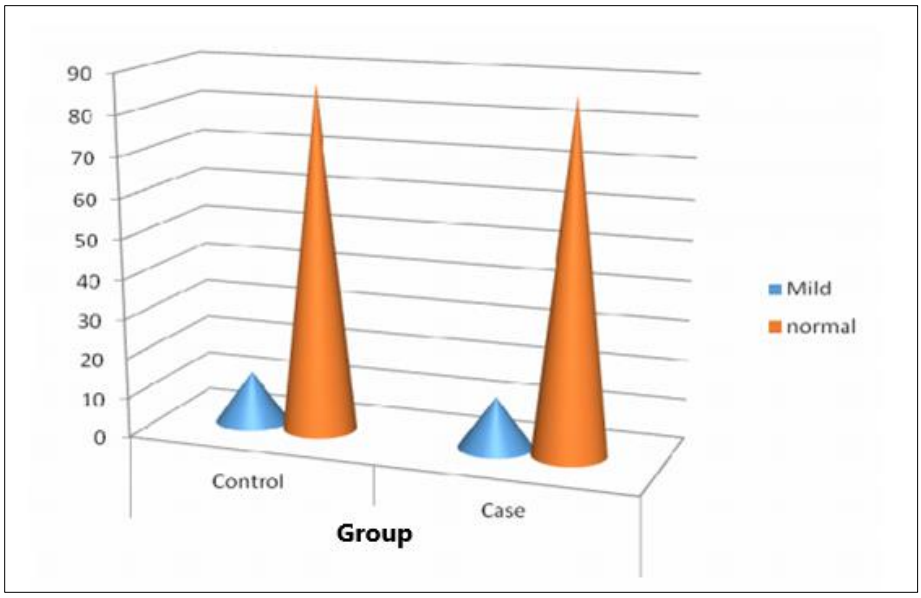

Figure 6: Frequency distribution of malnutrition among cases and controls (p=1.000).

	Group				Total	
	Control		Case			
MCV Class	Count	%	Count	%	Count	%
Low	35	35	59	59	94	47
Normal	65	65	41	41	106	53
Total	100	100	100	100	200	100

Table 12: Frequency of distribution of low MCV among cases and controls (p=0.001).

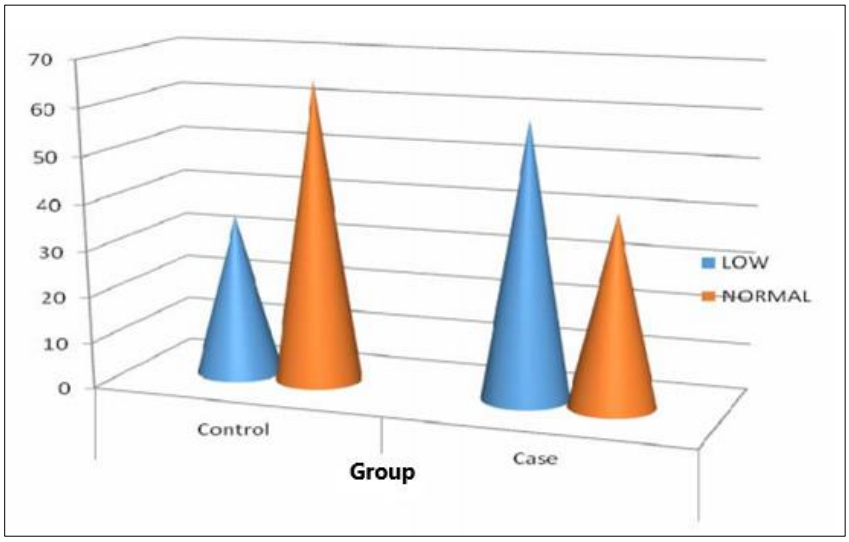

Figure 7: Frequency of distribution of low MCV among cases and controls (p=0.001).

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	Group				Total	
	Control		Case			
MCH Class	Count	%	Count	%	Count	%
Low	36	36	57	57	93	46.5
Normal	64	64	43	43	107	53.5
Total	100	100	100	100	200	100

Table 13: Frequency of distribution of MCH among cases and controls (p=0.004).

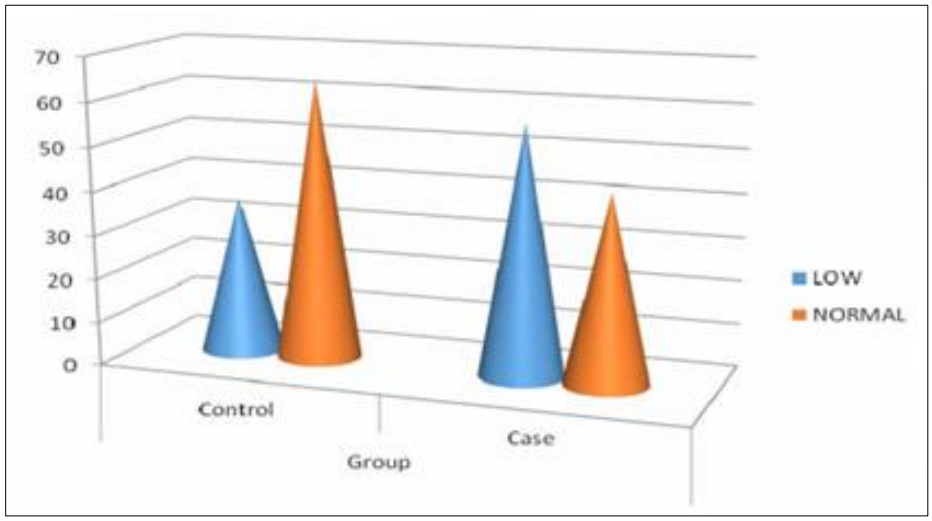

Figure 8: Frequency of distribution of MCH among cases and controls (p=0.004).

	With iron deficiency	Without iron deficiency	Total
Cases	43	57	100
Controls	29	71	100
Total	100	100	200

Table 14: Frequency of iron deficiency among cases and controls. Odds ratio=2.8.

	Group				Total	
	Control		Case			
PR Class	Count	%	Count	%	Count	%
High	69	69	45	45	114	57
Normal	31	31	55	55	86	43
Total	100	100	100	100	200	100

Table 15: Frequency distribution of tachycardia among cases and controls (p=0.001).

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	Group				Total	
	Control		Case			
RR Class	Count	%	Count	%	Count	%
High	61	61	52	52	113	56.5
Normal	39	39	48	48	87	43.5
Total	100	100	100	100	200	100

Table 16: Frequency distribution of tachypnea among cases and controls (p=0.254).

Group	N	Minimum	Maximum	Median	Mean	Std. Deviation
Control	100	100	104	101.3	101.454	1.1245
Case	100	98.6	104	100.8	100.956	1.4343
Total	200	98.6	104	101	101.205	1.3095

Table 17: Temperature variation among cases and controls. Temp in F.

Discussion

As found from the epidemiology, febrile convulsion is a common condition as well as iron deficiency. Since febrile convulsions are more frequent in children aged 18 to 24 months, this demographic is particularly vulnerable and should be targeted for prevention.

The metabolism and proper operation of the enzymes needed for neurochemical processes depend on iron. Since iron deficiency is a modifiable risk factor, it is crucial to determine whether there is a correlation between the two. The purpose of this study was to determine whether there is any conclusive correlation between a lack of iron and uncomplicated febrile seizures.

All of the subjects had breast milk or formula until they were 6 months old; solid foods like cereal and rice; a progressive introduction of vegetables by 7 months; and supplementary juices of fruits (apple, banana, lemon, etc.) as well as veggies. By the end of the initial year of life, most newborns automatically adjust to a routine of three meals each day. The age groups in cases and controls were almost matched. Whereas there is significant difference found among sex ratio between cases and controls, M:F is 1:1 among cases where as it is 2:1 among controls. But it hasn't influenced the study as there is no significant difference of incidence of iron deficiency among males and female less than 5 years who are included in the study. In the study majority of convulsion occurred among children between 2-4 years age group. There is no significant difference among the cases and controls regarding the temperature at the time of admission which may not be significant as most of the children with simple febrile seizures present following the seizure episode which implies that temperature measured was not during the time of seizure. The number of children with iron deficiency as defined by the Hb%, MCV, MCH and serum ferritin as per WHO are found to be

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more among cases as compared to controls with odds ratio of 2.89 suggesting that, there is significant association between iron deficiency and simple febrile seizures.

The findings were comparable to those of Vaswani, et al., [2] who from August 2005 to July 2006 conducted a case control study in 50 children between the ages of 6 months and 6 years who were admitted to the pediatric ward at King Edward Memorial Hospital, Parel, Mumbai, India, with their first episode of febrile seizure. Children on iron therapy, neurological illnesses, developmental delay, or prior febrile or afebrile convulsions were excluded. Children admitted with febrile illnesses who were matched for age and sex were chosen as the control group. Serum ferritin, MCV, and MCH indices of red blood cells, as well as hemoglobin, were estimated. They found that children with their first febrile seizure had considerably lower blood ferritin levels than did controls, which is nearly identical to the study.

The findings of the study are also consistent with Pisacane, et al., [1] case control study of 156 children diagnosed with febrile convulsions who were admitted to Castella Mare di Stabia Hospital in Naples between January 1, 1993, and June 30, 1995. They were healthy kids who had never experienced afebrile seizures or a condition affecting the central nervous system. Two groups of controls were chosen-a group of healthy children randomly chosen from the provincial birth register for an iron deficiency survey in Greater Naples in 1994, and a sample of children admitted to the same ward during that time with a diagnosis of respiratory and gastrointestinal infection. All patients underwent standard hematological examinations. Finally, they noted in their study's conclusion that anaemia can be related to the severity of a febrile illness, whereas low iron levels are linked to febrile seizures. However, contrast to the study, which included children between the ages of 6 and 60 months, the age range only covered 6 to 24 months.

From August 2009 to February 2010, Leela Kumari and colleagues [3] conducted a case control study in the Department of Paediatrics at the SAT Hospital in Thiruvananthapuram. The study had 154 case cases and 154 control cases. Children between the ages of 6 months and 3 years who presented to the paediatric emergency department and hospital wards during the study period were considered cases. According to the study's findings, iron deficiency significantly increases the incidence of uncomplicated febrile seizures in children between the ages of 6 months and 3 years. Additionally, they noted that among Indian children between the ages of 6 months and 3 years, iron deficiency is a modifiable risk factor for uncomplicated febrile seizures. Simple febrile seizures among kids of this age group may be prevented by early detection and prompt treatment of iron deficiency.

The role of iron in the CNS may help to explain the aforementioned observations, and an iron deficit may lead to neurologic impairment. As a cofactor in brain cells, iron may have an impact on the synthesis of dopamine, GABA, and serotonin. Some neurotransmitters, like as monoamine and aldehyde oxidase, are lowered, and GABA activity is changed. Additionally, these

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patients may have problems with oligodendrocyte myelinogenesis and DNA replication [60,61]. Fever is hypothesized to exacerbate the negative effects of inadequate iron levels in developing brain cells by lowering the threshold level for convulsions, which could lead to convulsion attacks [62].

According to the following mechanisms, iron deficiency and anaemia may be significant contributors to seizures:

1. Changes in the metabolism of GABA, an inhibitory neurotransmitter.
2. Changes in the metabolism of neurons.
3. Reductions in the activity of certain enzymes, such as monoamine and aldehyde oxidases.
4. Deteriorations in oxygenation and energy metabolism.

However, Kobrinsky pointed out that in Fargo, iron deficiency was less common in children with FS, but Hb, hematocrit, and MCV were greater, and researcher hypothesized that iron deficiency anaemia might shield kids from developing FS.

According to Derakhshanfar, et al., study, iron deficiency anaemia was more common in the control group at Mofid Hospital in Tehran, Iran, where FS children's Hb, Hct, MCV, serum iron, and plasma ferritin were greater and TIBC was lower than in febrile children without seizures [63].

According to Talebian, et al., in Kashan, anaemic children appeared to have a lower chance of developing FS than children without anaemia [64]. In Momen, there was no discernible difference between the prevalence of iron deficient anaemia in FS children and febrile children without seizure [9]. These variances could be explained by variations in the control group's age, dietary habits, geographic location, and sample sizes.

The current study's strengths included the use of uniform diagnostic criteria for detecting febrile seizures and iron insufficiency, concurrent enrollment of controls and cases, and the absence of exposure-related recollection bias. The study's limitation-that it was conducted in a hospital-is that the prevalence of the exposure and outcome factors may vary from what they would be in a community.

Summary

- Based on inclusion and exclusion criteria, 200 children from St. Martha's Hospital were separated into 100 cases and 100 controls for this study.
- It was found that most of the children having febrile seizures are between 2 years to 4 years.
- The ratio of males to females in simple febrile seizures group is almost 1:1.
- No sex difference regarding the prevalence of simple febrile seizures.
- Indicating 60% of children among cases and 42% of children among controls were having anaemia. P value calculated for the same showed significant association (p=0.016).
- 47% of children among cases and 31% of children among controls were having low ferritin levels for which p value was calculated which is significant (p=0.029).

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- There is no significant difference regarding the temperature at the time of presentation among cases and controls.
- The MCV and MCH values were also significantly low in cases compared to controls.
- The odds ratio between cases and controls based on low sr. ferritin, low MCV, and low MCH was 2.89, demonstrating a substantial relationship between iron deficiency and uncomplicated febrile seizures.

Conclusions

There is considerable amount of iron deficient children among both cases and controls.

- Simple febrile seizures and iron deficiency are significantly correlated.
- Simple febrile seizures in children at risk for iron shortage may be avoided with early identification and iron supplementation.
- Children particularly between 6 to 24 months who are at high risk should be screened regularly for iron deficiency.

Recommendations

1. All children who are at risk for iron deficiency should be screened regularly.
2. Prophylactic iron supplementation should be given till 5 years of age particularly between 6-24 months.
3. Work up for iron deficiency in children at risk for simple febrile seizure at every possible opportunity and intervene accordingly.
4. Treatment with Iron supplementation should be given to all children with iron deficiency.
5. Fortification of regular foods with iron.

References

1. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron Deficiency Anaemia and Febrile Convulsions: Case-Control Study in Children Under 2 Years. BMJ. 1996;313(7053):343. PubMed | CrossRef
2. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron Deficiency as a Risk Factor for First Febrile Seizure. Indian Pediatr. 2010;47(5):437-9. PubMed | CrossRef
3. Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron Deficiency as a Risk Factor for Simple Febrile Seizures-A Case Control Study. Indian Pediatr. 2012;49(1):17-9. PubMed | CrossRef
4. Swaiman KF, Ashwal S, Ferriero DM, Schor NF. Febrile Seizures-Preface to the Fourth Ed. Swaiman's Ped Neurol. 2006:1079-89. CrossRef
5. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does Iron Deficiency Raise the Seizure Threshold? J Child Neurol. 1995;10(2):105-9. PubMed | CrossRef
6. Moumen AA, Hakim ZM. Case-Control Study Of The Relationship Between Anemia And Febrile Convulsion In Children Between 9 Months To 5 Years. Of Age. Scient Med J Ahwaz Univer Med Sci. 2003;35:50-54.
7. Daoud AS, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron Status:A Possible Risk Factor for the First Febrile Seizure. Epilepsia. 2002;43(7):740-3. PubMed | CrossRef
8. Consensus statement. Febrile Seizures: Long-Term Management of Children with Fever-Associated Seizures. Pediatrics. 1980;66(6):1009-12. PubMed | CrossRef
9. Freeman JM. Febrile Seizures: A Consensus of their Significance, Evaluation, and Treatment. Pediatrics. 1980;66(6):1009. PubMed | CrossRef

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DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(3)-132

10. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile Seizures: Clinical Practice Guideline for the Long-Term Management of the Child with Simple Febrile Seizures. Pediatrics. 2008;121(6):1281-6. PubMed | CrossRef
11. Practice Parameter: Long-Term Treatment of the Child with Simple Febrile Seizures. American Academy of Pediatrics. Committee on Quality Improvement, Subcommittee on Febrile Seizures. Pediatrics. 1999;103(6):1307-9. PubMed | CrossRef
12. Baumann RJ. Technical Report: Treatment of the Child with Simple Febrile Seizures. Pediatrics. 1999;103(6):e86. PubMed | CrossRef
13. Graves RC, Oehler K, Tingle LE. Febrile Seizures: Risks, Evaluation, and Prognosis. Am Fam Physician. 2012;85(2):149-53. PubMed
14. Berg AT, Steinschneider M, Kang H, Shinnar S. Classification of Complex Features of Febrile Seizures: Interrater Agreement. Epilepsia. 1992;33(4):661-6. PubMed | CrossRef
15. Berg AT. Are Febrile Seizures Provoked by a Rapid Rise in Temperature? Am J Dis Child. 1993;147(10):1101-3. PubMed | CrossRef
16. Shinnar S, Glauser TA. Febrile Seizures. J Child Neurol. 2002;17(1):S44-52. PubMed | CrossRef
17. Nelson KB, Ellenberg JH. Predictors of Epilepsy in Children Who have Experienced Febrile Seizures. N Engl J Med. 1976;295(19):1029-33. PubMed | CrossRef
18. Nelson KB, Ellenberg JH. Prognosis in Children with Febrile Seizures. Pediatrics. 1978;61(5):720-7. PubMed | CrossRef
19. Berg AT, Shinnar S, Hauser WA, Leventhal JM. Predictors of Recurrent Febrile Seizures: A Metaanalytic Review. J Pediatr. 1990;116(3):329-37. PubMed | CrossRef
20. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk Factors for a First Febrile Seizure: A Matched Case-Control Study. Epilepsia. 1995;36(4):334-41. PubMed | CrossRef
21. Offringa M, Bossuyt PM, Lubsen J, Ellenberg JH, Nelson KB, Knudsen FU, et al. Risk Factors for Seizure Recurrence in Children with Febrile Seizures: A Pooled Analysis of Individual Patient Data from Five Studies. J Pediatr. 1994;124(4):574-84. PubMed | CrossRef
22. Hirose S, Mohney RP, Okada M, Kaneko S, Mitsudome A. The Genetics of Febrile Seizures and Related Epilepsy Syndromes. Brain Dev. 2003;25(5):304-12. PubMed | CrossRef
23. Berkovic SF, Scheffer IE. Genetics of the Epilepsies. Epilepsia. 2001;42 Suppl 5:16-23. PubMed | CrossRef
24. Kiviranta T, Tuomisto L, Airaksinen EM. Histamine in Cerebrospinal Fluid of Children with Febrile Convulsions. Epilepsia. 1995;36(3):276-80. PubMed | CrossRef
25. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive Attention and Behavior Outcome of School-Age Children with a History of Febrile Convulsions: A Population Study. Epilepsia. 2000;41(4):412-20. PubMed | CrossRef
26. Ellenberg JH, Nelson KB. Febrile Seizures and Later Intellectual Performance. Arch Neurol. 1978;35(1):17-21. PubMed | CrossRef
27. Verity CM, Butler NR, Golding J. Febrile Convulsions in a National Cohort Followed Up from Birth. II-Medical History and Intellectual Ability at 5 Years of Age. Br Med J (Clin Res Ed). 1985;290(6478):1311-5. PubMed | CrossRef
28. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors Prognostic of Unprovoked Seizures after Febrile Convulsions. N Engl J Med. 1987;316(9):493-8. PubMed | CrossRef
29. Berg AT, Shinnar S, Darefsky AS, Holford TR, Shapiro ED, Salomon ME, et al. Predictors of Recurrent Febrile Seizures-A Prospective Cohort Study. Arch Pediatr Adolesc Med. 1997;151(4):371-8. PubMed | CrossRef
30. Practice parameter: the neurodiagnostic evaluation of the child with a first simple febrile seizure. American Academy of Pediatrics. Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. Pediatrics. 1996;97(5):769-773. PubMed
31. Maytal J, Steele R, Eviatar L, Novak G. The Value of Early Postictal EEG in Children with Complex Febrile Seizures. Epilepsia. 2000;41(2):219-21. PubMed | CrossRef

Citation: Vuppu DK, Reddy VI, Rahul SCH. Iron Deficiency as a Risk Factor for Simple Febrile Seizures. J Regen Biol Med.2023;5(3):197-223.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(3)-132

32. Doose H, Ritter K, Völzke E. EEG Longitudinal Studies in Febrile Convulsions. Genetic Aspects. Neuropediatrics. 1983;14(2):81-7. PubMed | CrossRef
33. Kajitani T, Ueoka K, Nakamura M, Kumanomidou Y. Febrile Convulsions and Rolandic Discharges. Brain Dev. 1981;3(4):351-9. PubMed | CrossRef
34. Kajitani T, Kimura T, Sumita M, Kaneko M. Relationship Between Benign Epilepsy of Children with Centro-Temporal EEG Foci and Febrile Convulsions. Brain Dev. 1992;14(4):230-4. PubMed | CrossRef
35. Wolf SM, Carr A, Davis DC, Davidson S, Dale EP, Forsythe A, et al. The Value of Phenobarbital in the Child Who has had a Single Febrile Seizure: A Controlled Prospective Study. Pediatrics. 1977;59(3):378-85. PubMed | CrossRef
36. Minagawa K, Miura H. Phenobarbital, Primidone and Sodium Valproate in the Prophylaxis of Febrile Convulsions. Brain Dev. 1981;3(4):385-93. PubMed | CrossRef
37. Herranz JL, Armijo JA, Arteaga R. Effectiveness and Toxicity of Phenobarbital, Primidone, and Sodium Valproate in the Prevention of Febrile Convulsions, Controlled by Plasma Levels. Epilepsia. 1984;25(1):89-95. PubMed | CrossRef
38. Wallace SJ, Smith JA. Successful Prophylaxis Against Febrile Convulsions with Valproic Acid or Phenobarbitone. Br Med J. 1980;280(6211):353-4. PubMed | CrossRef
39. Rosman NP, Colton T, Labazzo J, Gilbert PL, Gardella NB, Kaye EM, et al. A Controlled Trial of Diazepam Administered During Febrile Illnesses to Prevent Recurrence of Febrile Seizures. N Engl J Med. 1993;329(2):79-84. PubMed | CrossRef
40. Verrotti A, Latini G, di Corcia G, Giannuzzi R, Salladini C, Trotta D, et al. Intermittent Oral Diazepam Prophylaxis in Febrile Convulsions: Its Effectiveness for Febrile Seizure Recurrence. Eur J Paediatr Neurol. 2004;8(3):131-4. PubMed | CrossRef
41. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of Intranasal Midazolam with Intravenous Diazepam for Treating Febrile Seizures in Children: Prospective Randomised Study. BMJ. 2000;321(7253):83-6. PubMed | CrossRef
42. Camfield PR, Camfield CS, Shapiro SH, Cummings C. The First Febrile Seizure-Antipyretic Instruction Plus Either Phenobarbital or Placebo to Prevent Recurrence. J Pediatr. 1980;97(1):16-21. PubMed | CrossRef
43. Angulo-Kinzler RM, Peirano P, Lin E, Algarin C, Garrido M, Lozoff B. Twenty-Four-Hour Motor Activity in Human Infants with and without Iron Deficiency Anemia. Early Hum Dev. 2002;70(1-2):85-101. PubMed | CrossRef
44. World Health Assembly, 45. National Strategies for Overcoming Micronutrient Malnutrition. World Health Organization. 1992.
45. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikantia SG. World Health Organization. Preventing and Controlling Iron Deficiency Anaemia through Primary Health Care: A Guide for Health Administrators and Programme Managers. World Health Organization. 1989. CrossRef
46. Yip R. Iron Nutritional Status Defined. In: Filer IJ, Ed. Dietary Iron: Birth to Two Years. New York, Raven Press Ltd., 1989:19-36.
47. Scrimshaw NS. Functional Significance of Iron Deficiency: An Overview. In Annual Nutrition Workshop Series. 1990;3:1-13.
48. Seshadri S, Gopaldas T. Impact of Iron Supplementation on Cognitive Functions in Preschool and School-Aged Children: The Indian Experience. Am J Clin Nutr. 1989;50(3):675-86. PubMed | CrossRef
49. Ballin A, Berar M, Rubinstein U, Kleter Y, Hershkovitz A, Meytes D. Iron State in Female Adolescents. Am J Dis Child. 1992;146(7):803-5. PubMed | CrossRef
50. Hershko C, Karsai A, Eylon L, Izak G. The Effect of Chronic Iron Deficiency on Some Biochemical Functions of the Human Hemopoietic Tissue. Blood. 1970;36(3):321-9. PubMed | CrossRef
51. Walter T, Arredondo S, Arévalo M, Stekel A. Effect of Iron Therapy on Phagocytosis and Bactericidal Activity in Neutrophils of Iron-Deficient Infants. Am J Clin Nutr. 1986;44(6):877-82. PubMed | CrossRef
52. Bhaskaram C, Reddy V. Cell-Mediated Immunity in Iron and Vitamin-Deficient Children. Br Med J. 1975;3(5982):522. PubMed | CrossRef

Citation: Vuppu DK, Reddy VI, Rahul SCH. Iron Deficiency as a Risk Factor for Simple Febrile Seizures. J Regen Biol Med.2023;5(3):197-223.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(3)-132

53. Soewondo S, Husaini M, Pollitt E. Effects of Iron Deficiency on Attention and Learning Processes in Preschool Children: Bandung, Indonesia. Am J Clin Nutr. 1989;50(3):667-74. PubMed | CrossRef
54. Beard JL. Iron Deficiency, Thyroid Function and Thermoregulation. In Annual Nutrition Workshop Series 1989;3:71-80.
55. World Health Organization. Maternal Health and Safe Motherhood Programme and World Health Organization. Nutrition Programme. The Prevalence of Anaemia in Women : A Tabulation of Available Information, 2nd Ed. World Health Organization. 1992.
56. Iron Deficiency Anemia: Assessment, Prevention and Control: A Guide for Programme Managers. WHO/NHD. 2001;3:17-22.
57. Yip R. Iron Deficiency: Contemporary Scientific Issues and International Programmatic Approaches. J Nutr. 1994;124(8):1479S-90S. PubMed | CrossRef
58. Summary of a Report on Assessment of the Iron Nutritional Status of the United States Population. Expert Scientific Working Group. Am J Clin Nutr. 1985;42(6):1318-30. PubMed | CrossRef
59. Hallberg L, Bengtsson C, Lapidus L, Lindstedt G, Lundberg PA, Hultén L. Screening for Iron Deficiency: An Analysis Based on Bone-Marrow Examinations and Serum Ferritin Determinations in a Population Sample of Women. Br J Haematol. 1993;85(4):787-98. PubMed | CrossRef
60. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The Association Between Iron Deficiency and Febrile Seizures in Childhood. Clin Pediatr (Phila). 2009;48(4):420-6. PubMed | CrossRef
61. Naveed-ur-Rehman, Billoo AG. Association Between Iron Deficiency Anemia and Febrile Seizures. J Coll Physicians Surg Pak. 2005;15(6):338-40. PubMed | CrossRef
62. Daoud AS, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron Status: A Possible Risk Factor for the First Febrile Seizure. Epilepsia. 2002;43(7):740-3. PubMed | CrossRef
63. Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association Between Iron Deficiency Anemia and Febrile Seizure in Children. Med Glas (Zenica). 2012;9(2):239-42. PubMed
64. Talebian A, Momtazmanesh N, Moosavi SGH, Khojasteh MR. The Relationship Between Anemia and Febrile Seizure in Children under 5 Years Old. Iran J Pediatr 2006; 16(1):79-82.

Citation: Vuppu DK, Reddy VI, Rahul SCH. Iron Deficiency as a Risk Factor for Simple Febrile Seizures. J Regen Biol Med.2023;5(3):197-223.
DOI: https://doi.org/10.37191/Mapsci-2582-385X-5(3)-132