ORIGINAL ARTICLE

Serum Iron Levels and Iron Deficiency Anemia in Febrile Seizures

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ABSTRACT

Background: Febrile seizures are common convulsive events in young children, typically triggered by fever without evidence of intracranial infection or other identifiable causes. Iron deficiency anemia (IDA), a prevalent nutritional disorder in developing countries, has been suggested as a potential risk factor for febrile seizures due to its effects on brain metabolism and neurotransmitter function. Low serum iron levels may further contribute to increased neuronal excitability.

Objective: To determine the mean serum iron level and the frequency of iron deficiency anemia in children presenting with febrile seizures.

Methods: This cross sectional study was conducted in the Department of Pediatric Medicine, Jinnah Hospital Lahore during 6 months period from January 2018 to July 2018. The 120 children, aged between 6 months and 6 years, with febrile seizures, were enrolled by the use of non-probability consecutive sampling. Parents/guardians gave informed consent prior to being included. A structured proforma was used to record demographic data, including age, gender and pertinent clinical history. Complete blood count (CBC) and serum iron estimation were done for all the participants. Iron deficiency anemia was classified by age dependent hemoglobin levels and serum iron levels were classified by the established cut off points. The data collected were analysed using SPSS version 18 and association between variables was assessed by stratification and appropriate statistical tests.

Results: A total of 120 subjects were analyzed. The mean age was 24.97 ± 12.45 months, with a range of 6 to 59 months. Among them, 68 (56.67%) were male and 52 (43.33%) were female. The mean hemoglobin level was 9.99 ± 1.64 g/dL, and the mean serum iron level was 42.05 ± 9.20 µg/dL. 57.5% of the children were found to have iron deficiency anemia and 70% low levels of serum iron. There was a significant association between younger age and iron deficiency anemia ($p = 0.014$) but no association with gender, or with iron supplementation.

Conclusion: This study found that levels of iron and iron deficiency anemia were high among children with febrile seizures. These results suggest a strong association between iron deficiency and febrile seizures, highlighting the importance of early detection and management of iron deficiency to potentially reduce the risk of febrile seizures in children.

Keywords: Iron deficiency anemia, febrile seizures, serum iron, pediatric population, anemia prevalence

INTRODUCTION

Febrile seizures are seizures that happen in children who are young and are caused by a fever. The children most frequently affected are those between 6 months and 6 years of age and the peak incidence is in the second year of life.[1] The fever is typically due to a common childhood infection, including upper respiratory tract infections, influenza or otitis media. The majority of febrile seizures are generalized tonic-clonic convulsions.[2,3,4] In an episode a child is usually unconscious, and the arms and legs may shake rapidly. Alternatively, symptoms can be eye deviation, stiffness in the limbs or focal twitching in one side or a particular area of the body.[5] At times, the child's movements may not be discernable and the child goes unconscious.

Most febrile seizures are less than 5 minutes in duration and are accompanied by a fever of about ≥38.3°C (101°F). Though these seizures may be frightening for the parent or caregiver, simple febrile seizures (which last no more than 15 minutes) do not result in permanent neurological damage.[6,7,8] Fever is not a feature of epileptic seizures and a febrile seizure does not mean the child has epilepsy[5]. But, long seizures that last over 15 minutes can slightly raise the risk of later developing epilepsy. There can also be a familial history of febrile seizures.[9,10] To make the diagnosis, the possibility of infection of the central nervous system, metabolic disorders, and a history of afebrile seizures must be ruled out.[11]

There are two types of febrile seizures-simple and complex. Simple febrile seizures are generalized, do not occur within 24 hours, last less than 15 minutes and are in otherwise healthy children.[12,13,14] Extensive testing (EEG, neuroimaging or laboratory testing) is typically not necessary in these instances.[15,16] But it is important to do a clinical assessment to determine the cause of fever.[17] Lumbar puncture is not routinely indicated in well-appearing children, except in the presence of a clinical suspicion of meningitis. The pathogenesis of febrile seizures is still under investigation and genetic susceptibility is believed to play a role.[18,19] Furthermore, the important role of micronutrients, including zinc, selenium and iron, has increasingly been investigated, but their exact relationship with febrile seizures is still being studied.[9,11]

Anemia is a decrease in the number of red blood cells (RBCs) or hemoglobin in the blood and thus the blood's ability to carry oxygen.[21] Symptoms of anemia may be subtle when the condition develops over a prolonged period of time, and may involve fatigue, weakness, shortness of breath and decreased exercise tolerance.[22,23] Acute anemia may have more prominent signs and symptoms, like dizziness, fainting, confusion or increased thirst. Pallor is a clinical finding and only seen in moderate to severe cases.[24,25]

There are three general types of anemia: anemia of decreased red blood cell production, anemia of increased red blood cell destruction, and blood loss. Iron deficiency, Vitamin B12 deficiency, thalassemia and bone marrow disorders are all causes for decreased production. In certain diseases (e.g., sickle cell disease, malaria, autoimmune hemolytic anemia), additional destruction can take place.[26,27] Anemias are divided into microcytic, macrocytic, and normocytic kinds, based on the size of red blood cells.[28]

IDF is one of the most widespread micronutrient deficiencies in the world, with at least 1/3 of the world's population being IDF. Iron is important in developing brain for neurotransmitter synthesis, myelination, and neuronal development. Iron deficiency could affect the development of the hippocampus, energy metabolism, myelination, and neurotransmitter systems, such as dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate, and norepinephrine, and lead to neurological symptoms and increased susceptibility to seizures.[11]

Iron deficiency anemia (IDA) has been suggested to be a risk factor for febrile seizures, presumably because both conditions are frequently seen in children under two years of age.[29,30] In a study conducted by Sharif et al, 45% of children with febrile seizures were found to be iron deficient with mean serum iron level of 45.92±26.02 µg/dl.[3] Likewise, Sherjil et al. found 31% and Muhammad Ashfaq et al. found 74%.[31] Most studies have, however, concentrated on iron deficiency anemia per se and there are few data on mean serum iron levels. However, other studies by Nadia et al., Derakhshanfar H et al. and Parsa Yousefichaijan et al. have found no association or even a decreased risk of febrile seizures in anemic children.[6,7,8]

This study's rationale is that, for some reason, iron deficiency anemia has been reported as a potential risk factor for febrile seizures, but in some cases, serum iron levels may be important even without overt anemia present. This factor is rarely considered because serum iron is not routinely evaluated. Thus, the purpose of this study is to evaluate the iron deficiency anemia in febrile seizure children as well as to assess serum iron levels. Children with febrile seizures may have low serum iron and anemia, indicating a possible role for iron deficiency in reducing seizure thresholds. This study will yield baseline data for the local population and can be compared with international studies. Prevention of febrile seizures in children may be possible with early detection and correction of iron deficiency.

METHDOLOGY

The aim of present study was to estimate the mean serum iron level and prevalence of iron deficiency anemia (IDA) in children who presented with febrile seizures. For the above said objective, descriptive cross sectional study design was used. This design was chosen because it enabled the study of the exposure (iron status) as well as the outcome (febrile seizures) in a specific population. A study was conducted in the Department of Pediatric Medicine of Jinnah hospital, Lahore from January 2018 to July 2018 for six months.

A non-probability consecutive sampling technique was used to recruit study participants. With a 95% confidence level, a sample size of 120 children was calculated, using a margin of error of 9%, and a prevalence of 45% of iron deficiency anemia among children who have febrile seizures. Children were included regardless of gender if they had febrile seizures as per operational criteria and they ranged in age from 6 months to 6 years. Children that had had tonic-clonic convulsions with documented fever over 101°F but recovered within 30 minutes of the convulsion and without any symptoms of meningeal irritability (neck stiffness, photophobia, excessive irritability) were classified as having febrile seizures. Further, no history of afebrile seizures, or central nervous system (CNS) infections was found on clinical evaluation, blood culture and cerebrospinal fluid (CSF) analysis.

In this study, children with previously diagnosed neurological disorders (epilepsy, cerebral palsy, central nervous system infections (CNS) – meningitis, encephalitis) were excluded. In addition, children with medical history of hematologic disease or other known causes of anemia, including thalassemia, sickle cell anemia, sideroblastic anemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency and hemolytic anemia were excluded from the study based on their medical, laboratory and red blood cell morphology data.

Operational definitions were clearly defined to standardize measurements. Serum iron level was determined from blood samples and normal levels were defined as > 40 µg/dL for children < 1 year of age and > 50 µg/dL for children > 1 year of age. Any values outside of these are considered iron deficient. Iron deficiency anemia was considered to be hemoglobin levels below 10.5g/dl in children 6 months to 2 years of age and below 11.5g/dl in the children aged 2 to 5 years.

After informed consent of the parent/guardians of participants and approval of the institutional ethical committee, data was collected. Demographic information (age, gender, parental education and socio-economic status) were recorded using a structured questionnaire. Also, any clinical history relevant to the iron supplementation was recorded. Five milliliters (mL) of venous blood were withdrawn from every individual using aseptic precautions and transported to the laboratory in the hospital for routine blood count (CBC) and serum iron estimation. Patients were diagnosed with IDA and treated as per the hospital treatment set guidelines.

All the collected data were entered and analyzed by the Statistical Package for Social Sciences (SPSS) version 18 for data analysis. The descriptive statistics were used for continuous variables like age, haemoglobin level and serum iron level to calculate the mean and standard deviation. Categorical variables, such as gender and iron deficiency anemia, were analysed in terms of frequency and percentage. Stratification was used to adjust for possible effect modifiers including age, sex and iron supplementation in the last 6 months. The chi-square test was used to examine associations between categorical variables while the independent sample t-test was used for comparisons between the mean serum iron levels in the different variables, post-stratification. A value of $p \leq 0.05$ was deemed to be statistically significant.

RESULTS

In our study 120 Subjects were included. Mean age was 24.97 SD +12.45. The minimum age was 06 months and the maximum was 59 months. 54.2 % were < 24 months of age and 45.8 % were > 24 months of age. (Table no:1)

56.67% (68) were male and 43.33% (52) were female (Graph no:1)

Mean hemoglobin was 9.99 SD + 1.64. The lowest haemoglobin level was 7.10 and the highest was 13. 57.5%

(69) were anemic and 42.5% (51) were not anemic. (Table no: 2)

Mean Fe was 42.05 SD +9.20. Minim Fe was 26 and Maximum Fe was 63. As per table no:3, 70% (84) children were having iron deficiency while 30% (36) were not having iron deficiency.

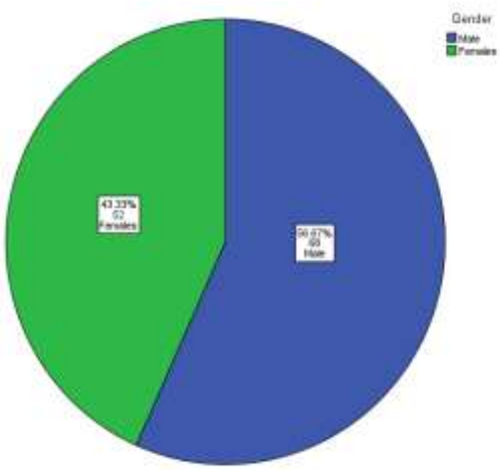
9.2% had iron deficiency with iron supplementation and 90.8% were without iron supplementation. (Table no: 4).

A cross tabulation was carried out between age and anemia. 63.8% (44) of respondents with anemia were < 24 month of age and 36.2% (25) were > 24 months of age. 41.2% (21) of respondents without anemia were < 24 months of age and 58.8% (30) were > 24 months of age . Chi-square was applied. (X2=6.029 P =.014). (Table no: 5).

Cross tabulation was performed for gender vs. iron deficiency anemia. 52.2% (36) male and 47.8% (33) female were anemic and 62.7% (32) male and 37.3%(19) female were not anemic.

Chi-square was applied. (X2=1.335 P =.248). (Table no: 6)

The level of anemia was cross tabulated to iron supplementation. Of the anemic patients 8.7% (6) were on iron supplementation while 91.3% (63) were not taking iron supplementation and of the non-anemic 9.8% (5) were taking iron supplementation and 90.2% (46) were not taking iron supplementation. Chi-square was applied. (X2=.043 P =.835). (Table: 7)



Graph 1: Gender of subjects

Table 1: Age of subjects

Age (months)	Frequency	Percent
< 24 months	65	54.2
> 24 months	55	45.8
Total	120	100.0
Mean = 24.97 SD= 12.45 Min= 6 Max = 59		

Table 2: Iron Deficiency Anemia among subjects

Anemia	Frequency	Percent
Yes (Hb< 10.5 mg /dl (< 2 years) < 11.5 mg /dl (> 2 years)	69	57.5
No (Hb> 10.5 mg / dl (< 2 years) > 11.5 mg /dl (> 2 years)	51	42.5
Total	120	100.0
Mean HB = 9.99 mg dl SD= 1.64 Min= 7.10 Max = 13		

Table 3: Iron deficiency among subjects

Iron Deficiency	Frequency	Percent
Yes (FE < 40.0 mg /dl (< 1 years) < 50 mg /dl (> 1 years)	84	70.0
No (FE > 40.0 mg /dl (> 1 years) > 50 mg /dl (> 1 years)	36	30.0
Total	120	100.0
Mean Fe = 42.05 SD= 9.20 Min= 26 Max = 63		

Table 4: Iron Supplementation among subjects

Iron Deficiency	Frequency	Percent
Yes	11	9.2
No	109	90.8
Total	120	100.0

Table 5: Iron Deficiency Anemia and age cross tabulation

Age	Anemia		Total	Chi-square P value
	Yes (Hb< 10.5 mg /dl (< 2 years) < 11.5 mg /dl (> 2 years)	No (Hb> 10.5 mg / dl (< 2 years) > 11.5 mg /dl (> 2 years)		
< 24 months	44	21	65	X^2 =6.029 P =.014
	63.8%	41.2%	54.2%	
> 24 months	25	30	55	
	36.2%	58.8%	45.8%	
Total	69	51	120	
	100.0%	100.0%	100.0%	

Table 6: Iron Deficiency Anemia and Gender cross tabulation

Gender	Anemia		Total	Chi-square P value
	Yes (Hb< 10.5 mg /dl (< 2 years) < 11.5 mg /dl (> 2 years)	No (Hb> 10.5 mg / dl (< 2 years) > 11.5 mg /dl (> 2 years)		
Male	36	32	68	X^2 =1.335 P =.248
	52.2%	62.7%	56.7%	
Females	33	19	52	
	47.8%	37.3%	43.3%	
Total	69	51	120	
	100.0%	100.0%	100.0%	

Table 7: Iron Deficiency Anemia and iron supplementation cross tabulation

Iron supplementation	Anemia		Total	Chi-square P value
	Yes (Hb< 10.5 mg /dl (< 2 years) < 11.5 mg /dl (> 2 years)	No (Hb> 10.5 mg / dl (< 2 years) > 11.5 mg /dl (> 2 years)		
Yes	6	5	11	X^2 =.043 P =.835
	8.7%	9.8%	9.2%	
No	63	46	109	
	91.3%	90.2%	90.8%	
Total	69	51	120	

DISCUSSION

A febrile seizure is a seizure that arises between the ages of 6 months and 5 years that is related to fever without evidence of intra-cranial infection or cause. While febrile seizures are not epilepsy per se, they are a disorder that can lead to the development of epilepsy in which seizures occur without fever.[32,33] The accepted criteria for feeble seizures is that the child has a seizure accompanied by a fever that exceeds 38 degrees Celsius, the child is under five years of age and over six months old, the child has no central nervous system (CNS) infection or inflammation, the child has a normal level of systemic metabolic abnormality that could cause seizures, and the child has no history of any previous afebrile seizures. There are two types of febrile seizures based on clinical features: simple and complex. The most common form of febrile seizures is simple febrile seizures, which are generalized, brief (less than 15 minutes) and occur only once in a 24-hour period.[34,35] Most simple febrile seizures end in less than 5 minutes, so a proposed threshold for simple vs complex has been suggested as 10 minutes.[36] Complex febrile seizures are seizures which have a focal onset (such as shaking of one arm or one side of the body), that last longer than 15 minutes, or that happen more than once in a 24 hour period. The difference between simple and complex is prognostic with most of the studies suggesting that patients with complex features have a greater risk of recurrent febrile seizures and a slightly increased risk of future non-febrile seizures. Febrile seizures are age dependent, probably due to a differential sensitivity of the developing nervous system to the effects of fever plus a genetic susceptibility. Besides age, the most reported risk factors are high fever, viral infection, recent immunization, iron deficiency anemia and family history of febrile seizure.[37]

The non-epileptic event or movement, central nervous system (CNS) infection (such as meningitis or encephalitis, which may cause a fever and seizure), or rare genetic types of epilepsy that are known to cause a fever and seizure are forms of differential diagnosis for febrile seizure.[38]

Most children with a normal exam and a benign history of simple febrile seizures do not require any tests. Evaluation should be directed towards assessment and diagnosis of the underlying febrile illness and parent education regarding risk of recurrent febrile seizures and low risk for future epilepsy. If a child has prolonged or focal febrile seizures (especially if this is their first convulsion), a more tailored approach is needed because there is a slightly increased risk of a different cause of their seizures (such as meningitis, or a structural or metabolic condition) and also a slightly increased risk of future afebrile seizures. EEG and magnetic resonance imaging (MRI) in the outpatient setting may be useful for further risk stratification of future epilepsy in children with complex febrile seizures but are typically not performed in the acute setting.[39, 40] The management of the outpatient evaluation of complex febrile seizures is not uniformly adopted, and a plan for each individual patient should be formulated by the treating clinician in conjunction with a pediatric neurologist for interpretation of abnormal testing results. Iron deficiency is defined as an inadequate amount of body iron for normal physiologic functions. Sometimes it is defined by the level of ferritin in the bloodstream, which is less than 12 micrograms/L in children under 5 years and less than 15 micrograms/L in those 5 years of age or older. Iron is an essential nutrient. About 75 percent is bound in the heme proteins hemoglobin and myoglobin. The rest is stored in storage proteins (ferritin and hemosiderin), and a relatively small amount (3 percent) is bound in critical enzyme systems (catalase and cytochromes). In healthy adults, only 5% or less of iron requirements is derived from food, the balance being supplied by the receding of RBCs. The rest is from the recycling of older RBCs by macrophages in the RE system. This means that just about 1mg of iron is absorbed and excreted every day. But for infants and children, since growth and body (muscle) expansion is taking place at a fast rate, 30 percent of the daily iron requirement must be obtained from the diet.The mechanism of iron homeostasis is mainly digestive at the level of absorption and transport, not at the level of urinary or digestive excretion. The peptide hormone hepcidin plays a primary role in regulating the uptake of iron into plasma by controlling the expression of the transmembrane protein ferroportin which is expressed on the basolateral surface of enterocytes and used for iron uptake from the intestine.

Body iron stores (transferrin and ferritin), erythropoietic rate and dietary iron bioavailability regulate serum hepcidin expression, and consequently intestinal iron absorption.[40] Low iron stores leads to hepcidin suppression so that iron can be absorbed and transported by ferroportin. On the other hand, iron deficiencies lead to lower hepcidin levels and better iron uptake. Occupational and community health nurses should be aware that healthy term infants at birth have iron stores of about 75 mg/kg (two-thirds of which is hemoglobin) and a mean hemoglobin level of 15-17 g/dL. These babies are usually iron sufficient up to 5–6 months of age. A number of conditions in the peripartum period can heighten the risk of iron deficiency anemia (IDA) in the first 3-6 months of life by decreasing the perinatal iron stores or by altering how the baby acquires iron, such as maternal iron deficiency, fetal-maternal haemorrhage (FMH), twin-twin transfusion syndrome (TTTS), other blood loss in the perinatal period, low birth weight, erythropoietin (EPO) therapy for low birth weight babies, and inadequate dietary iron intake in early infancy.

80% of maternal fetal transfer takes place during the 3rd trimester. Therefore, the importance of maternal iron deficiency in pregnancy and pre-term birth are factors that puts the infant at risk for iron deficiency. IDA in infancy and early childhood is most commonly associated with dietary problems.[41] The following are common causes of an imbalance in iron metabolism: inadequate iron intake, dietary sources of iron with low bioavailability, unmodified cow's milk (non-formula cow's milk) before 12 months of age, occult blood loss from cow's milk protein induced colitis and obesity. The first cause of iron deficiency among infants younger than 12 months is in most cases breastfeeding without iron fortification of infant milk or formula or early switch to cow milk. It is important that unmodified (non-formula) cow's milk is introduced as early as possible in infancy as this is an important risk factor for IDA. Unmodified cow's milk exacerbates intestinal bleeding in infants than other infant feedings such as formula or breast feeding. The main site of dietary iron absorption is the duodenum. Diseases involving the duodenum, such as celiac disease and surgical resection of the proximal small intestine (such as in children and infants with short bowel syndrome) can cause malabsorption of iron. Recommended dietary allowances (RDA) for iron are based on requirements for absorbed iron, the proportion of dietary iron that is absorbed, and estimated iron losses (eg, due to menstruation). In infants and children, a significant part of this requirement is related to growth.In infants and children a large share of this requirement is related to growth, for hemoglobin mass and tissue iron. Iron requirements for children less than 12 years of age are 1-8 mg/day (maximum 15 mg/day). The form of iron consumed (heme versus non-heme) and the other foods consumed at the same time affect iron absorption.

The researches were done to elaborate the relationship between the febrile seizures and iron deficiency anemia. The study conducted by Sharif et al showed 45% iron deficiency anemia in the children with febrile seizures and serum iron was 45.92+26.02. While in our study, 69% of patients with febrile seizures showed iron deficiency anemia with mean serum iron of 42.05+9.20, the ratio of iron deficiency anemia in febrile seizure was higher in our study as compared to previous study done by Sharif et al and iron deficiency anemia in febrile seizure in our study was almost comparable to the study done by Muhammad Ashfaq et al which was 74%of febrile seizure patients had iron deficiency anemia. The results of our study revealed a high co-relation between iron deficiency anemia and febrile seizures, while Nadia et al, Derakhshanfar H et al and Parsa Yousefichaijan et al type of studies revealed no correlation.

CONCLUSION

The results of the current study indicate that low iron is very common and iron deficiency anemia is common among children with febrile seizures. A large number of patients had decreased mean serum iron, and a diagnosis of iron deficiency anemia was made in many, suggesting good correlation between iron deficiency and febrile seizures. These findings indicate that FD could be a significant risk factor and could be modified in the development of febrile seizures.

Prompt diagnosis of serum iron levels via early detection and treatment of IDA in children could help prevent and minimise febrile seizures, especially in low and middle-income countries where nutritional deficiencies predominate. This association is recommended to be tested in further large-scale studies to reinforce the association and to examine the effects of iron supplements in the prevention.

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