



## Development of Febrile Seizures in Children with Iron Deficiency Anemia

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### Abstract

A febrile seizure is a seizure that occurs in children with a temperature of 38 °C or more, common in pediatric patients between the ages of 6 to 60 months without intracranial infections, metabolic disorder, or a history of seizures without fever. In 50% of children the first febrile seizure occurs at 2 years and in 90% before 3 years, anemia is also a frequent pathology in pediatric patients, in fact, the figures of the World Health Organization (WHO), point out that iron deficiency anemia attacks children under five years of age, occurring worldwide around 799 million, an average, in the last 10 years, of 42%. And in Latin America, the figure is 23%. Iron deficiency anemia can predispose to the development of febrile seizures because iron plays a crucial role in the transport of oxygen to all tissues, its deficiency also produces a dysfunction of myelination, tyrosine, and tryptophan synthesis hydroxylase, which are necessary for the release of neurotransmitters, therefore, if said neurotransmitters are not released, the brain synapse can be altered and lead to a seizure. Therefore, it is important and relevant to recognize these concepts and the intimate relationship between them, in addition to the risk factors that can trigger them, in order to promote the reduction of the risk of presenting these diseases in vulnerable groups such as pediatric patients.

### Keywords

Iron Deficiency, Anemia, Iron, Febrile Seizure, Infant Population

### Introduction

Febrile seizure is the most common seizure disorder in pediatric age and can be found in 2% to 5% in children 6 months to 5 years of age [1]. In 50% of

children, the first febrile seizure occurs at 2 years and in 90% before 3 years [2].

The International League to Fight Epilepsy (ILAE)

states that febrile seizures are “a seizure that occurs in childhood after 1 month of age, associated with febrile illness not caused by an infection of the Central Nervous System, without neonatal seizures. previous or unprovoked seizure and that does not meet criteria to include another cause of symptomatic seizure”, that is to say, in a nutshell, it is understood as a sudden and uncontrolled electrical alteration in the brain that usually appears between 6 and 60 months of age with a temperature greater than 38° C that is not due to infection of the central nervous system or any metabolic imbalance and that occurs without previous afebrile seizures [3]. Additionally, it is considered benign in the pediatric age according to the World Health Organization (WHO) [4,5].

Iron is essential for the functioning of some neurotransmitters, such as monoamine oxidase and aldehyde oxidase, this is important to mention because, in anemia, a reduced erythrocyte count or hemoglobin value (Hb) is generally observed by below the 5th percentile of the normal hemoglobin value specified for age in healthy individuals and according to the WHO can be classified as mild, moderate and severe (Fig-1) [6]. In addition, it is one of the pathologies along with seizures that are usually frequent in pediatric ages, in fact, the figures of the World Health Organization (WHO), indicate that iron deficiency anemia attacks children who do not exceed

five years of age. age, occurring worldwide around 799 million, an average, in the last 10 years, of 42% and in Latin America, the figure is 23% [7]. Likewise, anemia when it is due to iron deficiency can predispose to the development of febrile seizures [8]. Therefore, it is important and relevant to recognize these concepts and the intimate relationship between them, in addition to the risk factors that can trigger them, in order to promote the reduction of the risk of presenting these diseases in vulnerable groups such as pediatric patients.

The diagnosis of febrile seizure is clinical, based on parameters or criteria (Table-1) that guide the clinician to follow a correct examination and subsequent diagnostic resolution. In addition to the criteria, some factors have been found that increase the risk of developing febrile seizures by up to 30%; Such factors should be borne in mind when taking the patient's history. Most febrile seizures are unique and isolated, however, 30% of children will experience a second event and approximately 10% will develop three or more associated with risk factors (Fig-2) such as developmental delay, discharge from a neonatal unit after 28 days, day care attendance, viral infections, a family history of febrile seizures, certain vaccines, and nutritional deficiencies, including iron and zinc [5]. Iron deficiency is the most common nutritional deficiency worldwide and a major public health

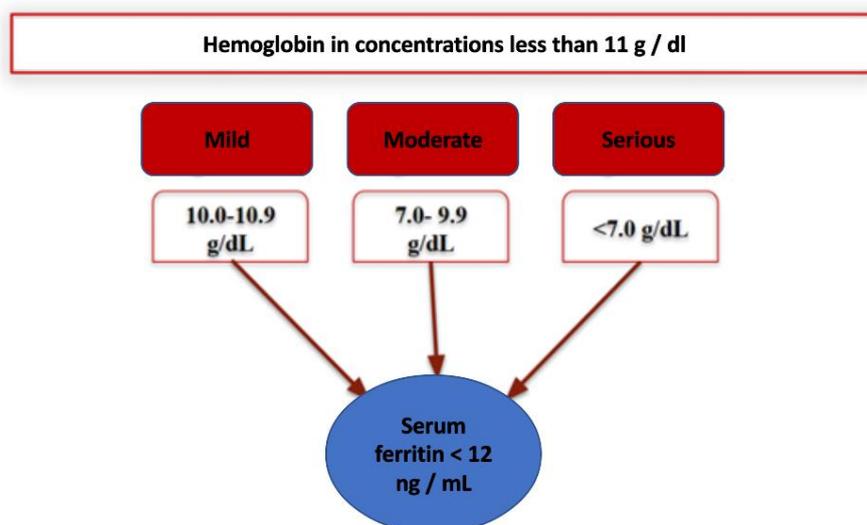


Fig-1:

Classification of iron deficiency anemia according to WHO in children under 5 years of age.

problem, especially in developing countries. There is no clear data on how many individuals are affected by iron deficiency worldwide, but it is estimated that identification is present in most pre-schoolers and pregnant women. About 8% of young children in the United States are iron deficient, and 2-3% have iron deficiency anemia. As age increases, the prevalence decreases until adolescence [9].

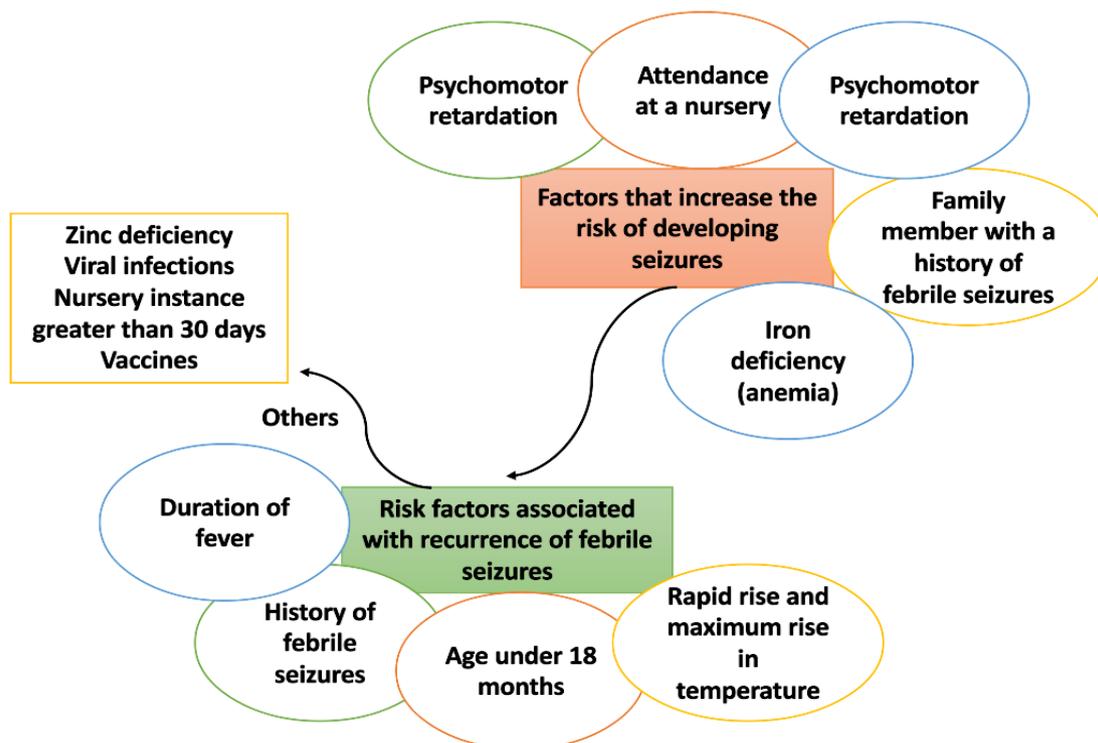
One of the important parts of red blood cells is iron, without it the blood could not carry out oxygen transport effectively. Through a balanced diet, our body gets iron and can also reuse iron from old red blood cells. The iron deficiency that causes anemia

occurs when the reserves found in the body decrease [7].

Iron deficiency is the largest nutritional deficiency in the world, it is an important micronutrient for almost all cells in the human body, it is a cofactor for several enzymes, it has a role in neurotransmitter production, hormonal function and DNA duplication, due to its presence in the hemoglobin structure, in addition, as mentioned, it plays a crucial role in the transport of oxygen to all tissues, so its deficiency produces a dysfunction of myelination, a decrease in tyrosine and synthesis of tryptophan hydroxylase, which are

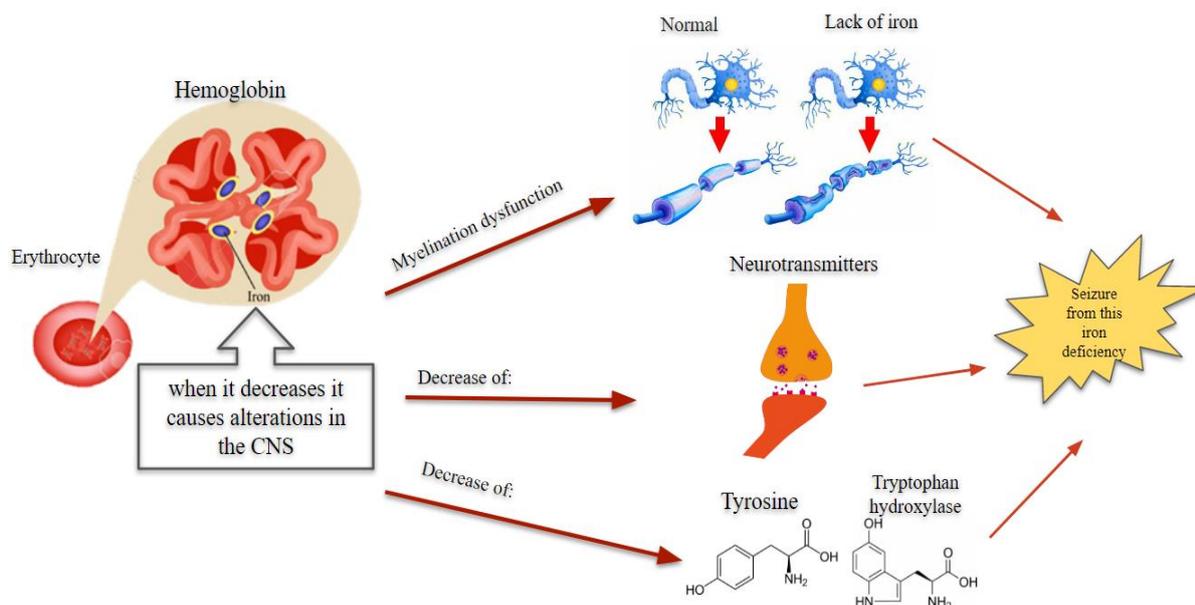
**Table-1: Diagnostic parameters of febrile seizure in children**

Seizure associated with elevated temperature > 38°C
A child usually older than 3 months and younger than 6 years old
Absence of CNS infection or inflammation
Absence of acute systemic metabolic disturbance that can lead to seizures
No previous history of febrile seizures.



**Fig-2:**

*Risk factors for the development and recurrence of febrile seizures in children with anemia.*



**Fig-3:**

*Representation of iron deficiency anemia as a development of febrile seizures in children*

components necessary for the release of neurotransmitter substances (**Fig-3**). In addition, this nutrient is responsible for the production of serotonin, dopamine, GABA, for all this and the great function it has at the CNS level, when it decreases, it can alter the brain synapse, increasing excitatory glutamate, decreasing or inhibiting GABA, causing a decrease in monoamines, and together with hypoxemia can induce a seizure due to this iron deficiency [10].

## Materials and Methods

In this review article, a detailed bibliographic search of information published since 2014 was carried out, in the databases PubMed, Elsevier, Scielo, national and international libraries. We used the following descriptors: Iron deficiency, Anemia, Iron, Febrile seizure, Child population the data obtained ranged between 2 and 15 records after the use of the different keywords. The search for articles was carried out in Spanish and English, limited by year of publication, and studies published since 2014 were used.

## Results

Several articles were identified that met the inclusion criteria for the development of the research. Naveed's study was developed at Agan Khan University Hospital, Karachi, where they found the association of febrile seizures in children and iron deficiency anemia

as evidenced by their studied parameters, that is, hemoglobin  $<10$  g / dl ( $p$ -value =  $<0.000$ ), hematocrit  $<30\%$  ( $p = <0.01$ ), MCV  $<70$  fL ( $p = <0.002$ ), MCH  $<24$  pg ( $p = <0.001$ ) and serum ferritin  $<10$  ng / ml ( $p = <0.000$ ) [11]. Therefore, iron deficiencies and other trace elements such as zinc affect the functioning of some enzymes of the central nervous system, altering the physiological mechanisms, in such a way that they contribute to the development of seizures. In a case-control study carried out in 100 babies and children from the Assiut University pediatric hospital, they found values of hemoglobin (HB), hematocrit (HTC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and concentration of Statistically significantly lower mean corpuscular hemoglobin (MCHC) in the cases than in the control group. Reporting iron values of  $39.68 \pm 18.00$  in the cases and  $78.21 \pm 42.95$  in the controls [12]. This association is probably linked to the imbalance between arousal and inhibition within the brain. However, brain involvement differs significantly on the likelihood of seizures depending on the iron deficiency exposure. According to the results found by Michael Rudy et al. where they found that mice that were exposed postnatally to DI (and that had acute DI) had a lowered seizure threshold and increased susceptibility to certain types of seizures. In contrast, mice that were exposed to DI only during pregnancy had an increased

seizure threshold and a low incidence of seizures [13]. In addition, not only the values of the hemograms present significant alterations. According to the report by Krystina et al. In the study group the mean body temperature was 39.0° C and in the control group 38.6° C. A statistically significant difference was found between the study body temperature and the control group ( $p = .005$ ). The mean C-reactive protein level in the study group was 15.73 mg / L and in the control group it was 58.20 mg / L. There was a statistically significant difference ( $p < .001$ ). There was a statistically significant difference between the number of lymphocytes and neutrophils ( $p < .001$ ). There was also a statistically significant difference between hemoglobin, hematocrit, and platelet numbers [14].

Another study confirms that children with febrile seizures suffer from iron deficiency anemia and low serum iron levels. This means that low serum iron and the presence of anemia can serve as a reinforcing factor for febrile seizures in children [3]. William's study confirms the above, his results suggest that the relationship between anemia and first febrile seizure was statistically significant, for two independent samples with a difference in hemoglobin  $p: 0.009$ , difference in mean corpuscular volume  $p: 0.01$ , mean corpuscular hemoglobin  $p: 0.03$  and concluded that a high percentage of children with febrile seizure (85.6%) have iron deficiency anemia and this is related to simple febrile seizure [15]. Therefore, a preventive treatment with iron is suggested. According to what was reported in 2013 by Ricardo et al. Where the group that received the preventive treatment did not present seizures and found that when means were compared, the differences were significant ( $p < 0.001$ ) for Hb, Ht, VCM, mean corpuscular hemoglobin and temperature between groups. Hematological correlations in the study group were significant between seizure, Hb, Hto ( $r = 0.569$ ,  $p < 0.001$ ) [16]. A study published in 2021 at the VITALES EsSalud II hospital carried out between 2014 and 2019 demonstrated the association between iron deficiency anemia as a risk factor for febrile seizures (ORa = 2.39; 95% CI = 1.09-5, 25;  $p = 0.03$ ) [17].

## Discussion

In the present review of the literature, cases of the

association between febrile seizures and the mechanisms involved were described, generating some discussion points according to what has been published with other studies. Iron deficiency may play an important role in the production of seizures through the decrease of the inhibitory neurotransmitter GABA, the change in the metabolism of neurons, and the deterioration of oxygenation and energy metabolism of the brain [18]. Furthermore, iron is essential for the biosynthesis of lipids and cholesterol, which are an important substrate in the synthesis of myelin, as well as of metabolic enzymes whose concentration is high in oligodendrocytes; iron has also been involved in the activity of the GABAergic system [19].

As in the case of the report by Cárdenas et al. They sought to find if iron deficiency anemia is a factor that predisposes febrile seizure events in children under 5 years of age and their results showed that children who presented seizures (33%), 19% (22) had iron deficiency anemia and 14% (16) did not present iron deficiency anemia. Of the children who did not present seizures (67%), 39% (45) did present iron deficiency anemia, and 27% (31) did not present iron deficiency anemia, therefore they concluded that iron deficiency anemia is not a risk factor for febrile seizure, with odds ratio of 0.94 which was not significant. They also indicate that age ( $p = 0.12$ ), sex ( $p = 0.415$ ) are not related to the presence of seizures [20]. Which is in agreement with the results of Sandoval et al. When no significant differences were found in both groups with respect to age, sex and family history of febrile crisis. However, in their study they found the presence of anemia with a percentage of 61% in the seizure group and 31% in the group with fever without seizures; there being a statistically significant difference between the two groups ( $p = 0,000$ ) and an OR = 3,481 (95% CI, 1,941 - 6,243). Concluding that anemia is a factor associated with Febrile Seizure in infants and preschool children [21]. However, Gonzalez et al. In 2020 they reported that anemia is not a risk factor for febrile seizure ( $p: 0.261$ ; OR: 1.59 CI: 95% [0.71 - 3.58]), since of the total number of patients with febrile seizure 38.5 % had anemia and of the total number of patients without febrile seizure, 28.2% had anemia. Of the total of patients with anemia, 56.8%

were mild and 43.2% were moderate, suggesting that anemia is not a risk factor for febrile seizures in a Public Hospital. Despite the fact that they found that male sex is a factor associated with febrile seizures ( $p$ : 0.031; OR: 2.37 CI: 95% [1.07 - 5.22]) [22].

Therefore, there is controversy regarding the role of iron status in the appearance of CF. A case-control study with 50 cases and 50 controls, with an age range of 6 to 60 months, reported significantly lower levels of HB, serum iron, and serum ferritin among cases than in controls, suggesting that iron deficiency anemia was more common in children with CF; this is in agreement with our results [23]. A systematic review found that iron deficiency anemia was significantly associated with febrile seizures in children (OR 1.98; 95% CI 1.26-3.13;  $P$  = 0.003). The subgroup meta-analysis according to the diagnostic markers for iron deficiency anemia (IDA) revealed a moderate association between IDA and FS based on plasma ferritin (OR, 3.78; 95% CI, 1.80- 7.94;  $P$  <0.001) and MCV (OR, 2.08; 95% CI, 1.36-3.17;  $P$  = 0.001). This situation possibly occurs because more than half with 64.3% of the mothers of children under 5 years of age with anemia who attend the Francisco Bolognesi Health Center have a regular level of knowledge about iron deficiency anemia, as suggested by Cano and cabbage [24]. Apart from iron deficiency there are other factors associated with febrile seizures as indicated by Patricia et al. where they found that the male gender was the most affected with 51.3%, acute diarrheal disease and herpetic gingivostomatitis were responsible for fever in 31.3% and 15.65%, respectively, concluding that infectious diseases they are the main causes of these seizure events in this series of cases [25].

Other risk factors for febrile seizures are male gender, age between 6-24 months, genetic predisposition (a history of a first or second degree relative with CF), specific infections (respiratory, urinary, human herpes virus type 6B) and attendance at centers day care, fever level reached, perinatal history, iron deficiency or iron deficiency anemia [26].

## Conclusion

We conclude that iron deficiency anemia and the development of febrile seizures exist to some degree of controversy. However, a series of studies have reported its significant statistical association, probably due to the role of iron in the functioning of some neurotransmitters, which is why iron supplementation is suggested as a treatment and preventive measure in both pediatric and female patients. pregnant mothers.

## Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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