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Evaluation of the Relationship Between Iron Deficiency Anemia and Febrile Seizures

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What is known on this subject?

The most common neurologic problem in children is febrile convulsion. This occurs in children between the ages of 6 and 72 months. The most common micronutrient deficiency is iron deficiency anemia, which is more common in children aged 6 to 24 months. The age range of the two groups covers each other.

What this study adds?

The study highlights that iron deficiency anemia is more common in patients undergoing febrile seizure.

ABSTRACT

Objective: Febrile convulsions are the most common neurologic problems in children. We investigated whether iron deficiency anemia affects febrile convulsions.

Material and Methods: This study was conducted as a retrospective cross-sectional study with 100 children aged between 6 months and 78 months who visited the Gaziantep University Şahinbey Practice and Research Hospital, Pediatric Emergency Department and Pediatric Outpatient Clinic between January 2016 and September 2019. Participants were examined in two groups in terms of the presence or absence of iron deficiency anemia.

Results: 50% (n=50) of the individuals included in the study had febrile seizures (FS) (case group), and 50% (n=50) did not have FS (control group). The rate of iron deficiency anemia was 22% (n=11) in the case group and 16% (n=8) in the control group.

Conclusion: We observed that the low hemoglobin level was more evident in children with febrile convulsions, but the difference was not statistically significant. It was determined that 22% of patients with FS had iron deficiency anemia, but there was not any notable difference from the control group.

Keywords: Anemia, febrile seizures, iron deficiency, pediatrics

Introduction

Seizures that occur in children six months to 6 years, are not associated with a central nervous system infection, have no history of febrile seizures (FS), and occur due to a high body temperature when no other cause for the seizure is found are defined as FS (1). The most common type of seizure in childhood and infancy is FS (2). In studies, the frequency of FS varies between 2 and 10% (3).

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Although the etiopathogenesis of FS is still not clear, recent studies have provided important insights into the genetic basis. On the other hand, studies have shown that iron and zinc deficiency, central thermoregulation disorders, an increase in excitatory amino acids, humoral immune system disorders, prenatal maternal problems, and growth and developmental delays may play a role in the etiology (4).

Our study aimed to determine whether iron deficiency anemia plays a role in the etiology of FS.

Material and Methods

The study included 100 patients aged between 6 and 78 months who presented to the Pediatric Emergency Department and the Polyclinic for Child Health and Diseases of the Şahinbey Research and Practice Hospital between January 2016 and September 2019. In the case group, 50 patients with FS were selected, and in the control group, 50 patients with high fever but without seizures were selected. Patients in the case group must be in the specified age group, must have no intracranial pathology and/or central nervous system infection, the seizure must not recur within 24 h, must be of the generalized type, must have no history of febrile convulsions in the child, must have no pathological neurological findings (such as cerebral palsy, mental motor retardation), and must have no electrolyte disturbance that could cause a seizure. Patients with complicated FS were not included in the study. The control group was selected from patients of the same age group who had a body temperature above 38 °C, were seizure-free, and had no known chronic disease. Prior to the study, approval was obtained from the Gaziantep University Clinical Research Ethics Committee, dated December 25, 2019, with decision number 2019/483. The study was conducted in accordance with the principles of the Declaration of Helsinki. This article is derived from the dissertation entitled "Evaluation of the Relationship Between Failure to Thrive or Anemia and Febrile Convulsion".

Laboratory parameters such as serum iron, ferritin, complete blood count, and total iron binding capacity (TIBC) were retrieved from the archive. Laboratory tests were performed in the biochemistry laboratory of Şahinbey Research and Practice Hospital. At our center, approximately 1 mL of venous blood was used to determine hematological parameters such as hemoglobin (HBG), hematocrit (HTC), mean red cell hemoglobin (MCH), mean red cell hemoglobin concentration (MCHC), mean red cell volume (MCV), and red blood cell count (RBC) as part of the complete blood count. The blood was placed in an EDTA-containing hemogram tube and automatically analyzed with the Cellpack kit using the optical or impedance method on a SYSMEX brand device (Sysmex Turkey Diagnostic Systems Limited Company, İstanbul, Turkey). For the measurement of serum iron, TIBC and ferritin, approximately 2.5 cm^3 of venous blood was placed in a plain dry tube and centrifuged at 4000 rpm for 10 min to separate serum. Subsequently, the electrochemiluminescence method was analyzed using a Beckman Coulter device (Beckman Coulter Diagnostics, Brea, California, USA) and a Beckman kit.

Statistical Anaysis

Statistical Package for Social Sciences (SPSS) version 22 was used to analyze the data. In addition to descriptive statistics, chi-square, Student's t-test, and Kruskal-Wallis analyses were performed. In descriptive statistics, numbers and percentages were used to describe nominal variables, and mean, standard deviation, and lowest and highest values were used to describe numerical variables. The 0.05 level was considered significan.

Results

One hundred children, the youngest at the age of 6 months and the oldest at the age of 78 months, were included in the study. The mean age of the children was 34.45±19.45 months (minimum: 6, maximum: 78); the mean age of the case group was calculated as 30.88±20.86 months (lowest age: 6, highest age: 78), and the mean age of the control group was calculated as 39.12±18.49 months (lowest age: 8, highest age: 76). While 50% (n=25) of the case group were male and 50% (n=25) were female, 68% (n=34) of the control group were male and 32% (n=16) were female.

Ferritin, iron, TIBC, HBG, HTC, MCV, MCH, MCHC, and RBC did not differ significantly between the study groups (p=0.360, p=0.313, p=0.362, p=0.164, p=0.185, p=0.242, p=0.976, p=0.651 and p=0.859, respectively) (Table 1).

The number of children with iron deficiency anemia in the case group was higher than that in the control group, but this difference was not significant (p=0.444). Iron deficiency anemia was present in 22% of the case group (n=11) and 16% of the control group (n=8) (Figure 1).

Discussion

The most common neurologic problem in childhood is FS, which is also the most frequent seizure in childhood (2). They usually have a benign course; however, it is essential to investigate the underlying causes in terms of etiology, as they may recur and develop into epilepsy in the future (2).

Anemia caused by iron deficiency is the most frequent lack of micronutrients, accounting for 50% in developing countries and 30% worldwide. Iron deficiency anemia is more common

in children aged 6 months to 2 years, which is the age range in which FS is most common (5,6,7). Iron deficiency anemia occurs in 46-66% of children under the age of 4 years in developing countries (8). Because it is an avoidable reason, the frequency of iron deficiency anemia can be reduced through good nutrition and iron supplements (7). Iron deficiency slows down the metabolism of neurotransmitters, such as aldehyde oxidase and monoamine, which can change a child's seizure threshold (9). In addition, the production of cytochrome c oxidase, an indicator of neuronal metabolic activity, decreases in anemia caused by iron deficiency (10). Iron deficiency anemia affects the growing brain by changing the neuronal development mechanisms of the hippocampus, impairing energy metabolism function, delaying myelin development, blunting auditory and visual action potentials, and causing alterations in synaptic neurotransmitter systems (including dopamine, gamma-aminobutyric acid, norepinephrine and glutamate) (11,12). Iron deficiency, which is easily treatable, is considered a risk factor for febrile convulsions in children (13).

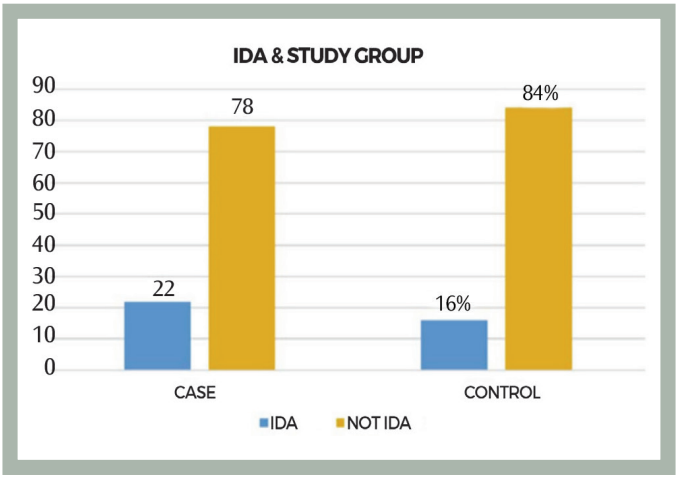

Figure 1. Distribution of Iron deficiency anemia by study groups (%)

In the study conducted by Gupta et al. (14) 2015 in Bhopal, 70 children suffering from FS were compared with 100 children in the control group, and it was found that the serum HGW amount of the children with seizures (<11 g/dL) was lower than the control group (12±0.37). In a study carried out by Fallah et al. (15) in Iran, it was found that the HGB level (11.46±1.18 g/dL) was lower in children with febrile convulsions than the control group (11.9±0.89 g/dL) (15). Similarly, in a study carried out by Sultan et al. (16) in 2013 in Pakistan, 68% of 31 children with FS were found to have low HGB, while 31 children who had fever but no seizures were found to have low HGB of 32%, and this difference was found to be statistically significant. In a study conducted by Omran et al. (17) in Iran in 2009, the average HGB was (11.75±1.15 g/dL) in the case group and (11.99±1.94 g/dL) in the control group; however, this difference was not significant. In our study, the mean serum HGW was found to be lower in children with febrile convulsions (11.50±1.78) than in the control group (11.94±1.30). Although this difference is not statistically significant, we believe that there might be a difference when studies with larger series are conducted (p=0.164).

In the study carried out by Ahmed (18) on Egyptian children, it was found that the mean HGB and HTC were significantly lower in cases with simple FS than in the control group. In a study by Srinivasa and Reddy (19) in India, the mean HGB and MCV values in children with FS were lower than those in the control group. Likewise, Aziz et al. (20) reported significantly lower HTC, MCV, and MCHC values in

Table 1. Distribution of blood values of individuals included in the study according to study groups

Blood value	Group				p value
	Case		Control		
	Average + SD	Minimum-maximum	Average + SD	Minimum-maximum	
Ferritin	36.62±41.71	2.30-214.20	43.62±45.30	2.20-223.70	0.360
Iron	56.32±28.88	9.80-119.00	50.36±29.93	12.00-171.00	0.313
TIBC	388.27±88.72	187.00-579.00	372.76±0.45	88.00-527.00	0.362
HBG	11.50±1.78	5.60-18.20	11.94±1.30	9.00-15.90	0.164
HTC	34.92±4.96	21.10-55.70	36.04±3.31	29.40-46.20	0.185
MCV	73.18±9.65	34.20-86.90	70.03±5.60	58.90-86.30	0.242
MCH	24.41±3.31	13.50-30.10	24.43±4.02	2.30-29.20	0.976
MCHC	32.87±1.76	26.50-36.20	33.01±1.32	30.10-35.80	0.651
RBC	4.73±0.54	3.36-6.46	4.75±0.44	4.05-6.23	0.859

TIBC: Total iron binding capacity, HBG: Hemoglobin, HTC: Hematocrit, MCV: Mean red cell volume, MCH: Mean red cell hemoglobin, MCHC: Mean red cell hemoglobin concentration, RBC: Red blood cell count, SD: Standard deviation

children with FS compared with the control group. In our study, although the mean levels of HTC, MCV, and MCHC in the serum of children with FS were lower than those in the control group, no statistical difference was demonstrated. We believe that a large series of studies is needed to prove the difference.

The relationship between FS and iron deficiency anemia was first investigated by Pisacane et al. (21) in this study, published in 1996, it was found that the rate of iron deficiency anemia was higher in children with FS than in the control group. The study by Fallah et al. (22) found a higher rate of iron deficiency anemia in children with FS than in the control group (22% vs. 10%) and in the study by Gupta et al. (14) (30.5% vs. 50.5%). It was found in the study by Vaswani et al. (23) (34.68% vs. 15.3%), Hartfield et al. (24) (16% vs. 5%), and Zareifar et al. (25) (56.6% vs. 24.8%). A high prevalence was also found in the study by Kumari et al. (26) (63.6% vs. 24.7%). Daoud et al. (13) a study in Jordan showed that the rate of iron deficiency anemia was higher in children with febrile convulsions than in children with fever but no convulsions, but this was not statistically significant. On the other hand, a study conducted by Talebian et al. (27) found that the rate of iron deficiency anemia was significantly lower in children with FS (13.3% vs. 20%) than in children with fever and without seizures. The study by Kobrinsky et al. (28) in Fargo and the studies by Derakhshanfar et al. (29), Bidabadi and Mashouf (30), and Abaskhanian et al. (31) in Iran found that the rate of iron deficiency anemia was lower in children with FS than in children with fever and without seizures. In our study, the rate of iron deficiency anemia was higher in the FS group (22%) than in the control group (16%), but not significant (p=0.444).

Assessment of anemia and planning of its treatment in patients admitted to hospital with FS may be important for prognosis. Comparison of seizure frequency during follow-up of patients treated for anemia with those who did not receive treatment may be important in clarifying the etiology.

Conclusion

We believe that iron deficiency anemia is more common in patients undergoing FS, but studies with a larger number of participants are needed to demonstrate a statistically significant association.

Ethics

Ethics Committee Approval: Gaziantep University Clinical Research Ethics Committee, dated December 25, 2019, with decision number 2019/483.

Informed Consent: Informed consent was obtained from the patient's relatives.

Authorship Contributions

Surgical and Medical Practices: H.C., M.K., Concept: H.C., Design: H.C., Data Collection or Processing: H.C., O.G., Analysis or Interpretation: H.C., M.K., M.T.T., Literature Search: H.C., Writing: H.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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