Original article

J Korean Child Neurol Soc 2018;26(4):210-214
https://doi.org/10.26815/jkcns.2018.26.4.210
pISSN 1226-6884•eISSN 2383-8973

철 결핍성 빈혈: 복합 열성경련과 열성경련의 재발의 가능한 위험인자

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Iron Deficiency Anemia: The Possible Risk Factor of Complex Febrile Seizure and Recurrence of Febrile Seizure

Purpose: A relationship between Febrile seizure (FS) and iron deficiency anemia (IDA) has been found in several studies. However, few studies have focused on the role of IDA in complex febrile seizures (CFS) and simple febrile seizures (SFS) and there is no report on whether IDA is a risk factor for recurrence. The aim of this study was to investigate the role of IDA in SFS and CFS and to examine the effect of IDA on recurrence.

Methods: Patients (n=166) who had been diagnosed with FS were enrolled in our study. Subjects were divided into the following groups for analysis: the SFS and CFS groups, recurrence and non-recurrence groups. The onset age was compared in each group of patients and laboratory test results based on IDA were compared.

Results: Between the SFS and the CFS groups, there was no significant difference in laboratory test results based on IDA. There was a significant difference in onset age between the two groups and the onset age tended to be lower in the CFS group (24.00 vs. 16.49 months) (P=0.004). Comparing recurrence and non-recurrence groups, the mean corpuscular volume was significantly different (P=0.043) with the recurrence group having a lower mean corpuscular volume level (78.92 vs. 77.48). The onset age in the recurrence group was lower (26.02 vs. 19.68 months).

Conclusion: This study suggests that onset age could be a risk factor for CFS, and IDA may not contribute to elevating the risk of CFS. However, IDA may play an important role in the recurrence of FS.

Key Words: Febrile seizure, Recurrence, Iron deficiency anemia

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Submitted: 24 August, 2018
Revised: 11 October, 2018
Accepted: 11 October, 2018

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Introduction

Febrile seizure (FS) is the most common pediatric neurological disorder that occurs in two to five percent of children under the age of five years[1]. The highest incidence of FS occurs at 18 months of age and FS is mostly common between the ages of six months and five years[2]. Although FS is benign and almost never causes brain damage, it causes emotional, physical, and mental distress, and affects the quality of life in a family[3]. There are many studies which have identified the risk factors of FS. The known provoking factors include fever, genetics, intrau-

terine risk factors (maternal nicotine and alcohol intake). Other studies have found an association between FS and vaccination. Furthermore, recent studies have also shown an association with iron deficiency anemia (IDA)[1]. The risk of recurrent FS is 15 to 70 percent and recurrence risk factors are age under 18 months, duration of fever, and fever temperature[4,5].

Although some studies have shown that IDA does not play a role in pediatric febrile seizure or even raise seizure threshold [6,7], many studies have reported that there is a significantly high number of FS patients with IDA[8-12]. However, few studies have focused on the role of IDA in complex febrile seizures (CFS) and simple febrile seizures (SFS)[13]. Additionally, to the best of our knowledge, there is no report on whether anemia is a risk factor for recurrence of FS. Therefore, the current study was designed to compare the prevalence of IDA between patients with SFS and those with CFS, and determine whether IDA is a risk factor for FS recurrence.

Materials and Methods

1. Patients

In this retrospective case control study, 714 patients between the ages of six months and five years who were diagnosed with FS at the Chung-Ang University Hospital in Seoul from January 2011 to April 2018 were reviewed according to their laboratory test results and medical records. Cases with central nervous system (CNS) infection, mental retardation, epilepsy, head trauma, hypoglycemia, and cases which did not include laboratory testing were excluded from the study. Children with a previous history of febrile or afebrile seizures were excluded from the study because they were unable to identify anemia at the time of the first episode. Only patients who were followed-up for two or more years were enrolled in the study[14,15]. Of the 714 patients, 2 patients had CNS infection, 7 patients were diagnosed as epilepsy and 1 patient had mental retardation. 165 patients were excluded because of previous history of seizures. Of the remaining patients, 373 patients who were not followed up for more than 2 years were also excluded from the study. 166 patients were finally included in the study. This study was approved by the Institutional Review Board of Chungang University Hospital in Seoul, Korea (1808-006-16198).

2. Definition and data extraction

The patients were divided into the following groups for analysis: the SFS and CFS groups, patients who experienced recurrence, and those who did not. A febrile seizure with a duration of less than 15 minutes, with no focal features, and occurring once within 24 hours was considered as an SFS, whereas CFS was defined as a febrile seizure lasting more than 15 minutes, with focal features, and occurring more than once within 24 hours[2]. Patients with recurrence of complex febrile seizures were assigned to the CFS group. Patients who did not experience recurrence during the follow-up period were assigned to the no recurrence group and those who did were assigned to the recurrence group[14]. The results of red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet, and mean platelet volume (MPV) were obtained from tests performed on the day of the first seizure. Low Hb, Hct, and MCV levels were defined as Hb<10.5, Hct<33, and MCV<70 in patients aged between six months and 24 months, and as Hb<11.5, Hct<34, and MCV<73 for patients aged between 24 and 60 months16). Seizure onset age, sex, previous medical history, type of seizure, and recurrence were obtained from patient medical records.

3. Statistical analysis

The SPSS statistical software version 18 was used to analyze the data. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the t-test. $P<0.05$ was considered statistically significant in all tests.

Results

1. Comparison between the SFS and CFS groups

For all 166 patients involved in the study, the mean patient age was 23.23±10.24 months. 149 were assigned to the SFS group and 17 to the CFS group. 2 patients assigned to the CFS group because they had three seizure attacks within 24 hours and 14 patients had two attacks within 24 hours. Mean follow-up period were 39.33 and 40.57 months in the SFS and CFS groups, respectively, which had no statistically significant difference between the two groups. The demographic characteristics and laboratory results of the SFS and CFS groups are shown in Table 1. There were no significant differences between the SFS and CFS groups regarding gender (P=0.731) and laboratory test results, but onset age was significantly higher in the SFS group (24.00 vs. 16.49 months) (P=0.004). Age under 18 months, low Hb, low Hct, and low MCV are compared between the SFS and CFS groups in Table 2. Patients under 18 months were significantly more in the CFS group than in the SFS group (P=0.017). There were no significant differences in the number of low Hb, low Hct, and low

MCV patients between the two groups. The odds ratio for patients younger than 18 months was 3.420 (95% confidence interval (CI) 1.196–9.775).

2. Comparison between the recurrence and non-recurrence groups

Seventy-three patients were assigned to the recurrence group and 93 patients were assigned to the non-recurrence group. The demographic characteristics and laboratory test results of the non-recurrence and recurrence groups are shown in Table 3. Onset age was significantly higher in the non-recurrence group (*P*=0.000). Surprisingly, there was a significant difference in MCV between the two groups, with the MCV being significantly lower in the recurrence group (78.92 vs. 77.48 fl) (*P*=0.043). Gender, RBC, Hct, MCHC, RDW, platelet, and MPV levels were similar between the two groups with no significant differences (*P*=0.932, *P*=0.507, *P*=0.549, *P*=0.611, *P*=0.917, *P*=0.680, *P*=0.329, respectively).

As mentioned earlier, age under 18 months, low Hb, low Hct, and low MCV were also compared between the two groups and significant differences in age (*P*=0.000) and low MCV level (*P*=0.049) were found (Table 4). There were more patients under 18 months of age in the recurrence group as well as more patients with low levels of MCV. In the recurrence group, the odds ratio for patients younger than 18 months was 3.689 (95% CI 1.909–7.131) and that for low MCV level was 2.329 (95% CI 1.951–2.779), which are both significant.

Discussion

We observed the role of anemia in the recurrence of febrile seizures in patients with SFS and CFS. To do this, several laboratory test results including RBC, Hb, Hct, MCV, MCHC, platelet, RDW, and MPV were compared between the SFS and CFS groups. Although the number of patients assigned to the CFS group was too low to draw statistically significant conclusions, the onset age was significantly lower in the CFS group than in the SFS group. RBC, Hb, and Hct levels in the CFS group were lower than those in the SFS group, but not statistically significant. In the Pearson's chi-square test, the odds ratio of the first seizure onset age <18 months was significantly higher in the CFS group with a value of

Table 1. Demographic Data and Laboratory Results of the Simple Febrile Seizure and Complex Febrile Seizure Groups

	SFS (n=149)	CFS (n=17)	*P* value*
Gender			
Male	94	10	0.731
Female	55	7	
Age (month)	24.00±10.27	16.49±7.23	0.004
Mean follow-up period (month)	39.33±0.91	40.57±2.48	0.661
Red blood cell (10^{12}/L)	4.62±0.33	4.67±0.32	0.526
Hemoglobin (g/dL)	12.33±0.81	12.45±0.74	0.488
Hematocrit (%)	36.23±2.18	36.47±2.33	0.672
MCV (fl)	78.31±4.70	78.09±2.74	0.853
MCHC (g/dL)	33.92±0.83	34.15±0.87	0.287
RDW (%)	13.28±0.99	13.31±0.82	0.907
Platelet (10^9/L)	263.93±78.67	264.94±90.05	0.961
MPV (fl)	9.03±0.68	8.86±0.45	0.323

SFS, Simple febrile seizure; CFS, Complex febrile seizure; MCV, Mean corpuscular volume; MCHC, Mean corpuscular hemoglobin concentration; RDW, Red cell distribution width; MPV, Mean platelet volume.
*P<0.05, statistically significant.

Table 2. Comparison of Frequency of Anemia and Age in the Simple Febrile Seizure and Complex Febrile seizure Groups

	SFS	CFS	OR (95% CI)	*P* value*
Onset age less than 18 months	52/149	11/17	3.420 (1.196-9.775)	0.017
Low hemoglobin	8/149	0/17	1.121 (1.062-1.183)	0.327
Low hematocrit	14/149	2/17	1.286 (0.266-6.209)	0.754
Low MCV	3/149	0/17	1.116 (1.059-1.176)	0.555

SFS, simple febrile seizure; CFS, complex febrile seizure; OR, odds ratio; CI, confidence interval; MCV, Mean corpuscular volume.
*P<0.05, statistically significant.

Table 3. Demographic Data and Laboratory Results of the Non-Recurrence and Recurrence Groups

	Non-recurrence (n=93)	Recurrence (n=73)	*P* value*
Gender			
Male	58	46	0.932
Female	35	27	
Age (month)	26.02±10.76	19.68±8.34	0.000
Mean follow-up period (month)	40.18±1.33	38.54±0.95	0.341
Red blood cell (10^{12}/L)	4.61±0.29	4.64±0.37	0.507
Hemoglobin (g/dL)	12.35±0.74	12.28±0.88	0.573
Hematocrit (%)	36.34±2.02	36.14±2.39	0.549
MCV (fl)	78.92±3.03	77.48±5.84	0.043
MCHC (g/dL)	33.97±0.75	33.91±0.93	0.611
RDW (%)	13.28±0.89	13.29±1.09	0.917
Platelet (10^9/L)	266.30±85.64	261.15±71.69	0.680
MPV (fl)	9.06±0.66	8.96±0.67	0.329

MCV, Mean corpuscular volume; MCHC, Mean corpuscular hemoglobin concentration; RDW, Red cell distribution width; MPV, Mean platelet volume.
*P<0.05, statistically significant.

Table 4. Comparison of Frequency of Anemia and Age in the Non-Recurrence and Recurrence Groups

	Non-recurrence	Recurrence	OR(95% CI)	*P* value*
Onset age less than 18 months	23/93	40/73	3.689 (1.909-7.131)	0.000
Low hemoglobin	4/93	4/73	1.290 (0.311-5.342)	0.725
Low hematocrit	7/93	9/73	1.728 (0.611-4.885)	0.298
Low MCV	0/93	3/73	2.329 (1.951-2.779)	0.049

OR, odds ratio; CI, confidence interval; MCV, Mean corpuscular volume.
*P<0.05, statistically significant.

3.420 (95% CI 1.196–9.775). No significant differences were found between other factors such as low Hb and Hct levels, and low MCV.

IDA is the most common micronutrient deficiency worldwide, occurring in 9–40% of children from 6–24 months of age[17]. Because iron in the hemoglobin structure plays an important role in transporting oxygen to the brain, some researchers believe that iron may reduce seizure threshold[8]. Additionally, iron is essential for many enzymes involved in the synthesis of neurotransmitters [18]. In iron deficiency, unusual behaviors, fatigue, mental retardation, attention deficit disturbance, arousal, decreased learning ability, cognitive impairment, and central nervous system symptoms can occur[19-22]. Many studies have investigated the role of IDA in febrile seizures and have found that IDA is a major risk factor in the aggravation of febrile seizures[8-12,23].

However, few studies have investigated the role of IDA in SFS and CFS. According to Ozaydin et al., Hb, Hct, MCV, platelet, RDW, and MPV levels were significantly lower in patients with CFS compared to patients with SFS[13]. On the contrary, in a study which compared anemia in SFS and CFS patients, Jun et al. showed that the anemia ratio was higher in the CFS group but not statistically significant, and there was no statistically significant difference between the two groups in Hb, MCV, and Hct levels[17]. Ozaydin et al. also studied the risk factors of CFS and found that a family history of epilepsy and febrile seizures, prematurity, and low birth weight could be risk factors[13]. In our study, we conclude that there is no statistically significant difference in Hb, Hct, and MCV levels between SFS patients and CFS patients, as in the study by Jun et al. Therefore, the results of this study suggest that IDA is just risk factor of febrile seizure and may not be a risk factor for CFS.

Febrile seizures have a high recurrence rate, ranging from 15 to 70 percent, depending on the risk factors involved[4,5]. The risk factors identified in previous studies were onset age under 18 months, duration of fever, and fever temperature[4]. To the best of our knowledge, there is no study yet on whether IDA is a risk factor for recurrence of febrile seizures. Similarly, in our study, the onset age was significantly lower in the recurrence group and the odds ratio for onset age under 18 months was 3.689 (95% CI 1.909–7.131), which was significant. The MCV was significantly lower in the recurrence group and the odds ratio was 2.329 (95 % CI 1.951–2.779) after analysis to confirm an association with anemia. There were no significant differences in RBC, Hb, Hct, MCHC, platelet, RDW, and MPV levels between the recurrence and the non-recurrence groups.

The limitations of this study include the low number of patients in the CFS group. Only 17 patients were assigned to the CFS group, which prevented us from making any statistically significant conclusions. This could explain why our results indicated that anemia is not related to CFS, which is in contrast to previous studies. Although we tried to evaluate the association between febrile seizure and IDA, data on the serum iron, total iron binding capacity (TIBC), ferritin, and transferrin saturation, which are diagnostic criteria for IDA, were not available for many patients. Therefore, we conducted our analysis with Hb, Hct, and MCV only.

Further studies involving serum iron, ferritin, TIBC, and transferrin saturation will provide further insight into the impact of IDA on the recurrence of febrile seizures. This will enable us to confirm if actively identifying and treating IDA in the diagnosis of febrile seizures can help prevent the recurrence of such seizures. In conclusion, this study suggests that onset age may be a possible risk factor for CFS, and IDA may not contribute to increasing the risk of CFS. We also found that IDA may play an important role in the recurrence of febrile seizures, considering that the recurrence group had significantly lower MCV levels than the no recurrence group, and the odds ratio of MCV levels lower than that specified in the IDA diagnostic criteria was significantly high.

요약

목적: 열성경련과 철 결핍성 빈혈간의 상관관계는 몇몇 연구에서 밝혀져 왔다. 하지만 단순 열성경련과 복합 열성경련에서 철 결핍성 빈혈의 역할을 확인한 연구는 적으며 열성경련 재발의 위험인자가 될 수 있는지 확인한 연구는 없었다. 본 연구의 목표는 단순 열성경련과 복합 열성경련에서 철 결핍성 빈혈의 역할을 알아보고 철 결핍성 빈혈이 열성경련의 재발에 미치는 영향을 확인하는 것이다.

방법: 2011년 1월부터 2018년 4월까지 중앙대병원에서 열성경련으로 진단받고 2년이상 추적관찰을 받았던 166명의 소아에 대해 연구를 진행하였다. 환자들은 다음과 같은 군으로 나뉘어 분석되었다: 단순 열성경련과 복합 열성경련, 재발이 있었던 환자와 없었던 환자. 각 그룹에서 발병시의 나이를 비교하였고 빈혈 여부를 확인하기 위한 진단검사 결과들을 비교하였다.

결과: 단순 열성경련과 복합 열성경련 군에서 철 결핍성 빈혈과 관련된 진단검사 결과는 두 군 간에 유의한 차이가 없었다. 발병 시 나이는 두 군 간에 유의한 차이를 보였고 복합 열성경련 군에서 낮은 경향을 보였다(24.00과 16.49개월) (P=0.004). 남성과 여성의 비율은 두 군 간에 차이가 없었다. 재발한 군과 재발이 없던 군을 비교할 때 평균 적혈구 용적이 유의한 차이를 보였고(P=0.043) 재발이 있던 군에서 유의하게 더 낮았다(78.92와 77.48 fl). 발병 시 나이는 재발이 있던 군에서 더 어렸다 (26.02와 19.68 개월).

결론: 본 연구에서 발병 시 나이가 복합 열성경련의 위험인자가 될

수 있음을 확인하였고 철 결핍성 빈혈이 복합 열성경련의 위험도를 올리지 않을 수 있다는 것을 알 수 있었다. 하지만 철 결핍성 빈혈은 열성경련의 재발과 연관이 있는 것으로 보인다.

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