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Differences in iron deficiency anemia and mean platelet volume between children with simple and complex febrile seizures

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ABSTRACT

Objective: The relationship between iron deficiency anemia and febrile seizures (FSs) were examined in several studies before. The aim of our study is to find out the differences regarding iron deficiency anemia, demographic characteristics and mean platelet volume (MPV) which is an inflammatory marker between simple and complex febrile seizure groups.

Methods: In this study, the authors investigated the recordings of 493 children with a diagnosis of simple and complex febrile seizure, aged between 6 months and 6 years, followed between 2002 and 2010 retrospectively.

Results: Mean age and male/female ratio were similar in two groups. There was no significant difference regarding with age, gender and family history of FS between two groups. We found significant difference statistically with respect to gestational age, consanguinity, family history of epilepsy and birth weight between two groups. The mean levels of Hb, Htc, MCV were lower and Plt and RDW levels were higher in children with CFS than SFS group, the differences were statistically significant (p: 0.001).

A higher proportion of children with CFS (16.2%) had iron deficiency anemia compared to SFS group (12.1%). Mean platelet volume (MPV) of CFS (7.99 ± 0.96 fL) were significantly lower than that of SFS group (8.77 ± 0.75) ($p < 0.001$).

Conclusions: The results of this study suggests that iron deficiency anemia is more frequently seen among the patients with CFS than the patients with SFS. The lower levels of MPV as an inflammatory marker, supports the idea that CFS is a brain inflammatory disease and the consequence of this inflammatory mechanism is the development of the epilepsy. Further studies are necessary to highlight the relationship between iron metabolism, inflammation and seizures.

1. Introduction

The febrile seizure (FS) is the most frequent seizure disorder in childhood. FSs are defined as seizures that occur in association with fever in children from 6 months to 5 years of age, with no evidence of a central nervous system infection or other identifiable causes of seizure and no history of afebrile seizures.[1]

Both genetic and environmental factors have been shown to contribute to the pathogenesis of FS and generalized epilepsy with febrile seizures plus (GEFS+); a familial epilepsy syndrome in which patients can have classic FS, FSs that persist beyond 5 years of age (i.e., FS+), and/or epilepsy.[2] The inheritance model in FS is still unclear but polygenic inheritance is suspected. In large families, the FS susceptibility trait is inherited by the autosomal dominant pattern with reduced penetrance.[3]

Loci reportedly linked to FSs and GEFS+ have been identified through analysis of large multiplex families in which the mode of inheritance was consistent with an autosomal dominant model. Four putative FS loci, namely FEB1 (chromosome 8q13-q21),[4] FEB2 (chromosome 19p13.3),[5] FEB3 (chromosome 2q23-q24)[6] and FEB4 (chromosome 5q14-q15)[7] have been mapped. In GEFS+ families, a mutation in the voltage-gated sodium channel β_1 subunit gene (SCN1B)[8] at chromosome 19q13.1 and 2 mutations of the same α_1 subunit gene (SCN1A)[9] at chromosome 2q24 were identified.The most consistently identified risk factor for FS is the presence of a close family history (among first-degree relatives) of FS.[10] Previous reports have indicated an elevated risk of FS development in children with underlying brain disorders associated with various factors such as premature birth, delayed discharge from the

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neonatal intensive care unit and developmental delay. However, a causal link between these factors and FS has not been established.[11–14]Iron deficiency anemia is a very common nutritional insult among human infants, especially between 6 and 24 months. In recent years, the number of studies investigating the relationship between iron deficiency anemia and FS has been increasing. Some studies support the existence of such a relationship some do not.[15–19]

The structure of the brain can become abnormal because of iron deficiency either in utero or in early postnatal life, because iron is essential for proper neurogenesis, as well as for differentiation of certain brain cells and brain regions.[20–22] The hippocampus and striatum are 2 areas of the rodent brain identified as morphologically altered in the event of iron deficiency. There is a decreased arborization of dendrites that decreases the number and complexity of interneuronal connections. A second morphological alteration is the location and functioning of oligodendrocytes which are responsible for producing myelin. These cells are particularly sensitive to iron deprivation; deficiency results in an altered composition and amount of myelin in the white matter. These alterations appear to be persistent and levels do not return to normal later in life.[23,24] Published data suggest that the biology of early developmental iron deficiency strongly indicates irreversible changes in brain structure and function and that an intervention needs to occur in the first 6 months of postnatal life, but the developmental trajectories for brain development are different in rodents and humans; current studies will be able to identify critical periods for different brain regions.[25]

Mean platelet volume (MPV) has been studied as a simple inflammatory marker in several diseases. Some studies have reported that MPV increases in myocardial infarction and cerebrovascular disease, while it contrarily decreases in active rheumatological diseases including rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and ulcerative colitis (UC).[26,27]

To the best of our knowledge, there is no publication reporting the relationship between FSs and MPV levels. Our hypothesis is simple. If epilepsy is a brain inflammation disorder and MPV decreases in the inflammatory conditions discussed above, we should find lower MPV levels in the complex febrile seizure (CFS) group compared to the simple seizure (SFS) group because CFS is a major risk factor of epilepsy and naturally more inflammatory changes occur in the brain. In our study, we compared 2 patient groups, SFS and CFS, with respect to demographic characteristics, iron deficiency anemia and MPV levels.

2. Methods

The study included 493 children with the diagnosis of febrile seizure who were followed by the Pediatric Neurology Department, between 2002 and 2010. Files of patients with an age ranging between 6 months and 6 years, who were admitted to the Emergency Service with a febrile seizure attack and then consulted with the Pediatric Neurology Department within two weeks were analyzed retrospectively. The patients were divided into two groups: SFS and CFS. A single seizure of <15 min in duration in the presence of fever without focal features was defined as a simple febrile seizure, whereas seizures were defined as complex if they lasted > 15 min, had focal features, or repeated more than once in 24 h. The first group included 337 children and the second group 156 children. Age, sex, gestational age, birth weight, consanguinity, family history of FS or epilepsy, and type of seizure were recorded for all patients. The measurements of hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), red cell distribution width (RDW) and mean platelet volume (MPV), serum iron, total iron binding capacity (TIBC) and ferritin levels were obtained from the files. The blood samples were taken two weeks after the occurrence of the seizure. Anemia was defined as a decrease of the Hb and Hct below 2 standard deviations of normal values for the age group, with Hb at < 10.5 g% for 6–24 months and 11.5 g% for 24–72 months of age, Hct at <33% for 6–24 months and <34% for 24–72 months of age, MCV < 70 fL for 6–24 months and <75 fL for 24–72 months of age.[28] Iron deficiency anemia was determined by transferrin saturation of <15% and a ferritin level of <10 ng/ml.[29] This study was approved by the local ethics committee.

SPSS 13.0 for Windows was used to analyze the data. Results were expressed as mean ± standard deviation. For continuous variables, Student's *t*-test was used to compare differences between groups. The Chi-square test was used for comparison of categorical variables. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of the MPV level to identify CFS with maximum sensitivity and specificity. For all tests, statistical significance was defined as a *p*-value of less than 0.05.

3. Results

The mean age and male-to-female ratio were similar in the 2 groups. The demographic characteristics of the patients with SFS and CFS are shown in Table 1.

There was no significant difference regarding age, sex and family history of FS between the groups. We found a significant statistical difference with respect to gestational age, consanguinity, family history of epilepsy and birth weight between the 2 groups.

The mean levels of Hb, Hct, MCV and MPV were significantly lower and Plt and RDW levels were significantly higher in children with CFS than in those of the SFS group ($p = 0.001$) (Table 2).

Data for serum iron, TIBC and ferritin levels were located in the records of 116 patients. A higher proportion of children with CFS (25/156, 16.2%) had iron deficiency anemia (transferrin

Table 1
The demographic characteristics of the patients with SFS and CFS.

	SFS *n*: 337	CFS *n*: 156	*p*
Age (month)	38.42 ± 32.15	34.08 ± 21.45	0.126
Gender			
Girls	123	67	0.171
Boys	214	89	
Gestational age			
37 week <	23	20	**0.028**
37 week >	314	89	
Consanguinity			
Absent	288	120	**0.020**
Present	49	36	
Family history of epilepsy			
Absent	316	136	**0.016**
Present	20	19	
Family history of FC			
Absent	216	106	0.403
Present	121	50	
Birth weight (g)	3228.64 ± 631.05	3078 ± 742.20	**0.021**

$p < 0.05$, statistically significant.

Table 2
Mean values and standard deviations of Hb, Hct, MCV, Plt, RDW and MPV among SFS and CFS patients.

	SFC *n*: 337	CFC *N*: 156	*p*
Hemoglobin	11.93 ± 1.27	11.13 ± 1.25	0.001
Hematocrit	35.70 ± 3.13	33.75 ± 3.88	0.001
MCV	75.78 ± 5.65	73.00 ± 6.41	0.001
Platelet	315.63 ± 98.52	368.48 ± 119.64	0.001
RDW	14.13 ± 2.00	15.44 ± 2.58	0.001
MPV	8.77 ± 0.75	7.99 ± 0.96	0.001

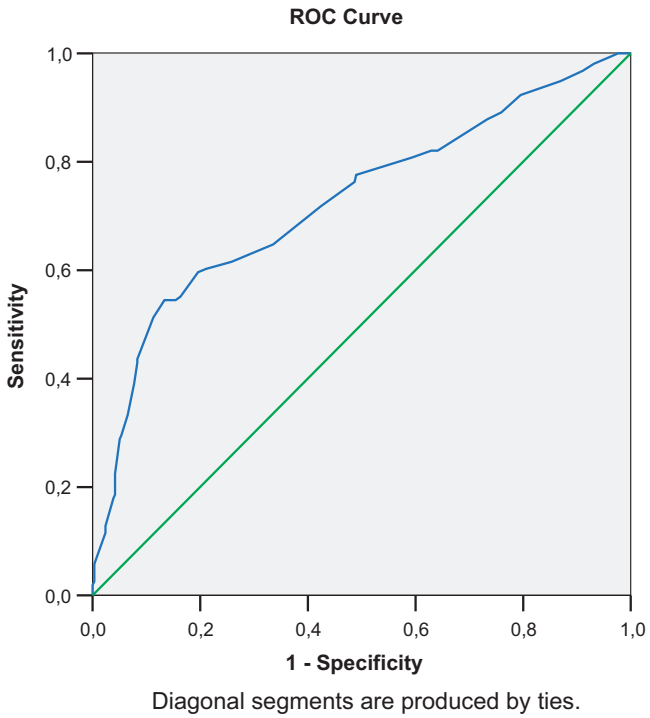

Fig. 1. ROC curve of mean platelet volume (MPV).

saturation < 15%, ferritin level < 10 ng/ml) compared to the SFS group (41/337, 12.1%).

The MPV of the CFS group (7.99 ± 0.96 fL) was significantly lower than that of the SFS group (8.77 ± 0.75) ($p < 0.001$) (Table 2). ROC curve analysis suggested that the optimum MPV level cut-off points for CFS was 8.25 fL and this level can be used in the differential diagnosis of SFS and CFS with a sensitivity and specificity of 60% and 80% respectively (AUC: 0.72) (Fig. 1).

4. Discussion

Is there a relationship between iron deficiency anemia and FS? Past studies have had conflicting results and this is still a controversial issue. In Turkey, the prevalence of iron deficiency anemia in the children has decreased after the 'Turkey Like Iron' campaign by the Ministry of Health to combat iron deficiencies in infants. Since 2004, daily iron supplementation of 1 mg/kg has been given to all infants aged between 4 months and 1 year of age but IDA still remains a common problem in Turkey.[30]

In our study, we had no control group because our aim was to examine the association of seizure type (complex versus simple FS) with Hb, MCV, RDW, MPV, and iron levels. Febrile seizures are classified as either simple or complex according to their clinical features, offering a limited predictive value in terms of later recurrences or afebrile seizures. To the best of our knowledge, there has been no prior study evaluating MPV levels as an inflammation marker in the differential diagnosis of these 2 groups.

Among the numerous biological effects of iron, there is considerable evidence that iron is also important for neurological functions such as neurotransmitter metabolism, myelin formation and brain energy metabolism.[31] In both animal models and cell culture experiments, there have been reproducible findings that dopamine and norepinephrine metabolism is altered by iron deficiency and only early repletion of iron status after gestational iron deficiency overcomes the lasting effects.[32,33] Studies involving metabolism in the hippocampus and striatum of iron-deficient rodent brain tissue suggest that fuel utilization in the iron-deficient brain is different from that in control brains.[21,34] Studies investigating the fuel utilization of the iron-deficient brain of humans have not been conducted, but the brain is the most oxidative organ of the body and usually requires glucose as a fuel, while it has long been known that iron deficiency alters glucose homeostasis.[35] The 3 aspects (morphological, biochemical and bioenergetic) of brain biology[25] impacted by iron deficiency are evidence that iron is important for neurological functions and that deficiencies may cause the development of febrile seizures but the results of previous studies are conflicting.

Looking over the literature studies, Pisacane et al. reported a significantly higher rate of iron deficiency anemia among children with FS than in controls. Hartfield revealed that a total of 9% of studied patients had ID and 6% had IDA compared to 5% and 4% of controls respectively. Kobrinsky et al., in a case–control study, showed that anemia raises the threshold for the first FS and that iron deficiency may protect against the development of febrile seizures. Bidabadi et al. suggested that IDA was less frequent among patients with FS as compared to the controls and that there was not a protective effect of ID against febrile seizures.[15–18] The differences observed among these studies may be due to the differences in ethnicities, the sample sizes of the groups, age groups and nutritional status. In the present study, 12.1% of the SFS group and 16% of the CFS group had IDA. The mean levels of Hb, Hct, MCV were significantly lower and RDW levels were significantly higher in children with CFS than in those of the SFS group.

A positive family history of FS among first-degree relatives is the most important risk factor for developing FS.[36] In our study there was no significant difference regarding age, sex, or family history of FS between the SFS and CFS groups, but the frequency of a positive family history of FS for all groups was 34.1%, which is consistent with the literature. Prematurity and low birth weights were naturally more frequent in the CFS group, as these are risk factors for hypoxia, sepsis, necrotizing enterocolitis triggering the proinflammatory cytokines and inflammation; a family history of epilepsy was also significantly related with CFS.

In a recent study, Malik et al. observed dramatic changes in iron metabolism under acute phase conditions.[37] Their study demonstrated that transferrin receptor-1 (TfR1) and other iron-regulatory proteins (hepcidin, ferritin-H, iron-regulatory protein-1 and heme oxygenase-1) known to be expressed in the liver are also expressed in the brain in rat model. They suggested that the induction of cytokines in the brain might be attributable to the production of reactive oxygen species (ROS) generated by oxidative stress as a result of increased iron concentration, as has been observed in other neurodegenerative disorders, or that a positive feedback mechanism might exist that is specific for the brain, at least for interleukin-6 (IL-6) gene expression. Dramatic changes in iron metabolism may play a role in the development of the seizures.

Mean platelet volume is a marker of platelet function and activation and it is also influenced by inflammation.[38] Increased levels of TNF-α, IL-1, IL-6 and IFN-γ may be responsible for low MPV levels in patients with CFS. Some authors argue that it is IL-6 among these mediators that is the primarily responsible cytokine in secondary thrombocytosis.[39] Our study showed that the sensitivity and specificity of MPV in the differential diagnosis of SFS and CFS were moderate; therefore, it is obvious that more inflammatory processes occur in the brains of the patients with CFS.

5. Conclusion

In the current study, we statistically evaluated the differences of hematological parameters, including MPV and demonstrated a significant difference between the parameters in SFS and CFS patients. Iron deficiency anemia is more frequently seen among patients with CFS than in patients with SFS. We do not exactly know whether IDA causes susceptibility to febrile seizures or not. Decreased MPV levels are present in patients with CFS and these results may be related to the immaturity of the hematopoietic system in children or to active inflammatory states. More advanced investigations are needed to highlight the relationships among iron metabolism, inflammation and seizures.

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