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Research Article

Relationship of Serum Vitamin B12 Levels, Mean Platelet Volume And Iron Parameters of Febrile Convulsions in Children

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Abstract

Background and Aims: Recently, some studies have reported that low serum iron store and vitamin B12 levels can serve as a triggering factor for the febrile convulsion (FC) in children. It has been suggested that mean platelet volume (MPV) increase in simple FC (SFC) and decrease in complex FC (CFC) as an indicator of the inflammation. The aims of this study are to evaluate MPV in febrile patients with and without FC, and also investigate the relationship between vitamin B12, folic acid and iron parameters in FC groups.

Material and Methods: Total of 83 patients, aged between 6 months to 5 years, with FC and 92 cases with febrile illness without FC as a control group were included in the study. MPV levels of all patients evaluated. Serum iron parameters, vitamin B12 and folic acid levels were measured in FC patients who also had anemia.

Results: There was no significant difference between FC and control groups in terms of MPV. Serum ferritin and vitamin B12 levels of the CFC group were found significantly lower than SFC.

Conclusion: The results of the present study demonstrated that the decrease of ferritin and vitamin B12 may be risk factors for FC recurrences. Vitamin B12 levels should be considered for children presenting with FC like iron status screening.

Keywords: *Febrile Convulsion; Vitamin B12; Mean Platelet Volume; İron Parameters*

Introduction

Febrile convulsion (FC) is a seizure which is associated with fever and without any definite cause such as acute electrolyte imbalance, intoxication and a history of prior afebrile seizure [1]. FCs occur most frequently at 14 - 18 months of age, which correspond to the iron deficiency anemia (IDA) that seen frequently at 12 - 24 months of age [2]. In the last 20 years, there has been increasing interest in a possible role for iron deficiency (ID) in the causation of FCs. Animal studies have shown that ID negatively affects myelination and the synthesis of neurotransmitters [3]. It is known that iron is a cofactor for many enzymes in the body. It has a role in production and function of neurotransmitters and DNA duplications. Iron is found in the structure of hemoglobin has a role in the transport of oxygen to various tissues such as the brain. Iron deficiency increases the risk of seizures by stimulating neuronal function [2,4]. Some studies have shown that ID is a risk factor to FC [5-8] but some other studies have not been shown. [4,9]. The conclusions of previous studies regarding the association between IDA and FC have demonstrated that low serum levels of iron lower the seizure threshold [6,10] Sadeghzadeh., *et al.* [11] showed that anemia was not common among FC patients, however ID was more frequent in these patients. In addition, it is considered that fever increases this negative effect and facilitates the occurrence of seizure [5,12]. In contrast, some studies suggested that ID has seen lesser in children with FC and ID is thought to have a protective effect of seizure [13,15]. It is known that vitamin B12 deficiency causes many neuropsychiatric complications. In addition, it is suggested that lower vitamin B12 levels may have a role in the occurrence

and recurrence of seizure [16-18]. Osifo., *et al.* [19] have analyzed the vitamin B12 and folic acid levels in the cerebrospinal fluid and serum in patients with FC. In this study, low serum levels of vitamin B12 were detected in both control groups, including patients with febrile illness, and patients with FC. However, it was found that the decrease in serum vitamin B12 levels is deeper in the patients with FC.

The mean platelet volume (MPV) is a parameter measured by an automatic blood cell counter while clinicians generally don't pay attention to it during routine blood count. The platelet volume was found to be related to the platelet function and activation. There is a consensus that the MPV is determined while platelet production from megakaryocytes [20]. MPV increases as the platelet count decreases and it is thought that the large platelets are younger and more reactive. In other words, increased MPV is an indicator that thrombocytes have been activated [21]. In many major diseases, the MPV is studied as an inflammatory marker. It is demonstrated that the MPV were increased in the myocardial infarction and cerebrovascular diseases, conversely decreased in the systemic inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis and ulcerative colitis [22-25]. Ozaydin., *et al.* [26] reported lower MPV value in CFC patients than SFC [26] and Abuhandan., *et al.* [27] showed significantly higher MPV value in SFC than the control group.

In this study, we aimed to compare MPV levels in febrile patients with and without FC. Additionally, we investigated the relationship between serum iron parameters, vitamin B12 and folic acid levels in FC groups with anemia. To the best of our knowledge, there was no study which evaluates the relation between both MPV and serum vitamin B12 levels in FCs.

Material and Methods

Study Design

Eighty three patients diagnosed with FC who were admitted to SBU Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, SUAM between 15.05.2014 and 15.11.2014 were included. The ILAE classification system used for the FC diagnosis [1]. This study was approved by the local ethics committee.

Case Definition

The FC group was divided into two groups as Simple Febrile Convulsion (SFC) and Complicated Febrile Convulsion (CFC). The SFC is generalized onset, lasts less than 15 minutes, does not occur more than once in the 24 hours, has no neurological and post-ictal findings. The CFC has focal features at onset, lasts more than 15 minutes, occurs more than once in the 24 hours, has neurological and post-ictal findings. Febrile status epilepticus is defined as a seizure that lasts more than 30 minutes or recurrent febrile seizures in 30 minutes without any consciousness [1]. Patients' age, gestational age, birth weight, family history of consanguinity, FC and epilepsy were questioned. Gestational age was categorized as ≥ 37 weeks and < 37 weeks, family history of FC and epilepsy were categorized as present or absent. Patients with febrile illness who have not FC were taken as a control group. Patients with neurological disorders such as mental retardation, cerebral palsy and epilepsy were excluded from the study.

Laboratory Measurements

Hemoglobin (Hb), mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV) levels of all patients were evaluated. Anemia was defined as decrease of the Hb and Hct below 2 standard deviations of normal values for the age group, with Hb at < 10.5% for 6 - 24 months, and 11.5 g/dl for 24 - 72 months of age, Hct at < 33% for 6 - 24 months of age, and 34% 24 - 72 months of age, MCV < 70 fL for 6 - 24 months and < 75 fL for 24 - 60 months of age.

After data collection, firstly FC group was compared with control group for MPV. After that the difference of MPV values in SFC and CFC groups were determined. As second aim of our study, in patients who had FCs; anemia was detected complete blood count (CBC) following seizure. After the febrile episode blood test of serum iron, total iron binding capasity (TIBC), serum ferritin (SF), folic acid and vitamin B12 levels were done in FC patients with anemia. Transferrin saturation was calculated by dividing the serum iron by the TIBC. Serum iron levels < 25 mcg/dl, SF levels < 12 ng/ml and transferrin saturation < 15% were defined as IDA. Vitamin B12 levels below 250 pg/ml were defined as vitamin B12 deficiency. A specialist in biochemistry was checked for the status of iron, vitamin B12 and folic acid levels.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 20.0 (SPSS Chicaco, IL) was used in data analyses. The study data were calculated as percentages and the mean ± standard deviation. Chi-square test and Fisher's exact test were used for comparisons of categorical features of patients according to the eligibility. Non-parametric Mann-Whitney U test was used for comparing the average of two independent groups. Non-parametric Kruskal-Wallis test was used for the comparison of more than two independent samples. "p" value less than 0.05 was considered statistically significant.

Results

A total of 83 patients (47 male, 36 female) and 82 healthy controls (56 male, 36 female) were enrolled in the study (Table 1). The mean age of patients with SFC, CFC, and control groups were 23.3 ± 14.1 months, 24.9 ± 13.9 months, and 24.5 ± 16.1 months, respectively. The mean age and male-to-female ratio were similar in the 3 groups (p = 0.89, p = 0.77, respectively). Comparison of the SFC and CFC groups regarding family history of consanguinity, family history of epilepsy and family history of FC showed no statistically significant differences between the groups (p > 0.05). Among the 83 cases, 48 (57.8%) had SFC, while 35 (34.9%) of the patients were diagnosed as CFC. 6 (7.3%) cases of patients with febrile status epilepticus were considered in CFC group.

	Female n (%)	Male n (%)	Total n (%)	p
Simple Febrile Convulsion	20 (%41,7)	28 (%58,3)	48	0,77
Complex Febrile Convulsion	16 (%45,7)	19 (%54,3)	35	
Control Group	36 (39.1%)	56 (60.9%)	92	

Table 1: *Gender distribution of the three groups.*

The mean levels of Hb, Hct, MCV, MCH, RDW and MPV had no statistically significant differences between three groups (p > 0.05) (Table 2). Anemia was diagnosed in 28 (33.7%) of FC and 29 (31.5%) of control patients. There were no statistically significant differences among the groups in terms of the anemia, iron, TIBC, transferrin saturation and folic acid. However, ferritin levels were significantly higher in SFC group (30.58 ng/ml) than those in CFC group (13.78 ng/ml) (p < 0.001). Vitamin B12 levels were 430.73 pg/ml in patients with SFC, 408.75 pg/ml in patients with CFC and the differences between these two groups were statistically significant (p < 0.006) (Table 3). One patient had lower vitamin B12 than 250 pg/ml in the CFC group. Peripheral blood smears evaluation of 11 (22.9%) in SFC and 8 (22.8%) in the CFC patients with anemia were compatible with hipochromic microcytic anemia.

	SFC (n: 48) (mean ± SD)	CFC (n: 35) (mean ± SD)	Control Group (n:92) (mean ± SD)	p
Hb (g/dl)	11,41 ± 0,84	11,44 ± 0,90	11,57 ± 1,34	0,75
Htc (%)	34,08 ± 2,33	34,55 ± 2,32	34,89 ± 3,47	0,37
MCV (fl)	74,34 ± 5,12	74,63 ± 4,03	74,56 ± 4,98	0,92
MCH (pg)	24,86 ± 2,06	24,86 ± 1,87	24,71 ± 2,16	0,89
RDW (%)	14,17 ± 1,95	14,32 ± 1,40	14,13 ± 1,37	0,57
MPV (fl)	8,33 ± 0,73	8.18 ± 0,91	8.16 ± 0.7	0.49

Table 2: *Comparison of the mean values and standart deviation of hematologic parameters among the three groups.*

	SFC (n = 16) (mean ± SD)	CFC (n = 12) (mean ± SD)	p
Iron (µg/dl)	25,91 ±9,64	32,00 ± 11,07	0,43
Total Iron Binding Capacity	360,00 ±33,89	333,50 ± 37,81	0,23
Ferritin (ng/ml)	30,58 ± 16,91	13,78 ± 12,49	< 0.001
Transferrin saturation (%)	7.09 ± 2.50	9.90 ± 4.31	0.21
Vitamin B12 (pg/ml)	430.73 ± 72.95	408.75 ± 187.82	0.006
Folat (ng/ml)	12.88 ± 2.72	12.91 ± 2.19	0.56

Table 3: *Iron profiles, vitamin B12 and folate levels of patients who have febrile seizure and concommitant anemia.*

Discussion

The results of this study showed that mean age and male-to-female ratio of the diagnosis of FC were found to be consistent with the literature. However, there have rarely been reported studies that have been demonstrated male predominance [28,29]. In addition, there was no significant difference between FC groups in terms of consanguinity, family history of FC and epilepsy, which is similar to the some studies [26,30].

In addition to anemia, the most important consequence of ID, recent studies have suggested that ID may play a significant role in FC [6-8]. ID affect many systems at the cellular level and can lead to neurological problems such as neuromotor delay, ischemic stroke, venous thrombosis, and breathe holding spells. Iron plays a role in neurotransmitter metabolism, myelin formation, and brain energy metabolism. It was shown that ID influences cytochrome C oxidase activation and metabolism of monoamine and aldehyde oxidase. Iron contents of globus pallidus, substantia nigra and cerebellar nuclei are high. Their neurons contain the inhibitory neurotransmitter such as GABA. Similarly, experimental studies have demonstrated that iron plays a role in the regulation of GABA [31].

It may be therefore hypothesized that the disruption of normal neurotransmitter activity caused by ID may be the mechanism that predisposes children with ID to FCs. There have been many studies investigating the relationship between ID and FC. However, the results were conflicted and inconclusive. Further experimental study in this area using an animal model of FC and ID to attempt to elucidate the mechanism is warranted. Hartfield., *et al.* [2] showed that children with FCs were almost twice as likely to be iron deficient as compared with age-matched controls with fever. They suggested that ID is one of the risk factors for FC to be included along with others such as family history, rate of fever rise, and specific viral illness. The chance of a child having FC may increase as the number of riskfactors in a given patient accumulates.

According to the World Health Organization data, IDA is seen 36% of developing countries and 8% of developed countries [32,33]. Also FC often occur from 1 month to 5 year-old including the period of infancy that IDA is most commonly seen. Because iron is important for the function of various enzymes and neurotransmitters in the central nervous system, low SF may lower the seizure threshold [3,13-15]. Özaydın., *et al.* [26] showed that Hb, Htc and MCV values were significantly lower in patients with CFC, and also RDW was higher in this group. Bidabadi., *et al.* [9] compared FC patients to controls in their studies and there were no significant differences for Hb, Htc and MCV values. Piscane., *et al.* [5] detected that Hb and MCV were lower in the patients with FC compared to controls. In their comparative study of age- and sex-matched children, reported a significantly higher rate of IDA, defined on the basis of low serum iron concentration, among children with FC than in the control group. In children younger than 2 years of age, 30% of those with FC had anemia compared to 14% in the control group. However, SF levels were not measured in that study. Momen., *et al.* [34] reported no relationship between IDA and first FC in children younger than 5 years of age in Iran. In our study, we found no significance regarding the mean levels of Hb, Htc, MCV, MCH and RDW between SFC, CFC and controls. In addition, there is no significant difference between FC and control groups in the prevalence of anemia.

King., *et al.* [35] investigated the relationship of FC with ID. In this study reported that the results were very heterogeneous because of the different definitions of the anemia and ID. Traditional measures of iron status (ferritin, serum iron, TIBC, transferrin saturation, and FEP) are influenced by infection and are therefore not reliable indicators of iron status in the setting of acute infection [36]. Ferritin can be increased with inflammation because it is an acute phase reactant, this situation is very important especially children with FC. Also, serum iron, TIBC and transferrin saturation may give false negative results while determining iron status. Another situation is the most of the studies about the relationship between FC and ID are made in developing countries and ID is more common in these countries [37]. Both MCV and RDW are available as part of the CBC, so those two parameters are economical and avoid further phlebotomy attempts after a screening CBC. Both MCV and RDW have been demonstrated to be sensitive, specific, and stable in children with the presence of febrile illness [38]. It should be considered to perform MCV and RDW only in children with anemia or anemia history because of the high incidence of ID in children with FC. Therefore, after a febrile period, iron parameters were performed in children with FC who had anemia determined by CBC.

In the present study, iron parameters, vitamin B12 and folic acid levels were not measured in patients without anemia. Because we aimed to assess the association of iron parameters, vitamin B12 and folic acid levels in patients who have both anemia and convulsion. Ferritin and vitamin B12 levels in the CFC group were found to be significantly lower than SFC group. In many previous studies SF levels were found lower in FC group and it was suggested that ID may be a risk factor for FC [6,39,40]. Recently in a study it was determined that European children with FC have lower ferritin than those with fever alone, and ID, but not anemia. They concluded that iron status screening should be considered as a routine for children presenting with or at high risk for FC [41]. Ozaydin., *et al.* [26] showed that SF levels were found to be statistically significantly lower in CFC group compared to the SFC group, in line with our study [23]. Zareifar., *et al*. [43] claimed that SF level was the only value that was significantly lower in children with SFC than in the control group and the same findings were also reported by Daoud., *et al* [40]. Moreover, Papageorgiou., *et al.* [41] claimed that any differences in ferritin levels between SFCs and controls could not be attributed solely to fever.

Neurological symptoms of vitamin B12 deficiency are heterogeneous and including irritability, lethargy, apathy, regression of neuromotor development and convulsions [17,18]. The most important cause of vitamin B12 deficiency in infants, feed with only breast milk by mothers who consumed a small amount of animal protein. Vitamin B12 deficiency is usually seen in young children (under 2 years) with low socioeconomic groups and the main reason is to consume less diet or breast milk [42]. Developmental mechanisms of neurological symptoms are not fully known in vitamin B12 deficiency. But, vitamin B12 plays a role as a cofactor in homocysteine remethylation and methyl malonyl CoA degradation. It is thought that methionine synthesis is interrupted and guanidoasetat accumulation leads to neurotoxicity in vitamin B12 deficiency. Homocysteine and methylmalonic acid levels increase in vitamin B12 deficiency. Those parameters are playing a role in demyelization, axonal degeneration and neuronal death. Experimental studies reported that homocysteine, which is one of sulfur-containing amino acids, and its metabolite such as homocysteic acid induce convulsion. Some studies showed that EEG abnormalities and epilepsy concomitance in vitamin B12 deficiency [43]. A potential mechanism for epileptogenesis in vitamin B12 deficiency is not clear, but it is asserted that the neurons with damaged myelin sheath may be more sensitive against excitatory effects [44].

Recently Ozkale., *et al*. found that mean vitamin B12 level in the FC group was significantly lower than the control group. Low serum vitamin B12 may reduce a child›s threshold for seizure and may be a risk factor for FC. In their study the FC patients with 3 or more had significantly lower serum folic acid than the subgroups with two or one episode only. They concluded that low serum folic acid level may be predisposed to recurrent FC [45]. In our study we didn't found any difference between the SFC and CFC groups regarding the mean folic acid levels. In our study mean values of vitamin B12 were found statistically significant difference between the SFC and CFC groups ($p < 0.01$). This was consistent with the study that showed the relation between vitamin B12 deficiency and FC by Osifo., *et al*. too [30]. We thought that the low levels of vitamin B12 may have a role in the recurrence of FC.

Many studies have been suggested that MPV plays an important role as a marker of inflammation and it can reflect disease activity and efficacy of anti-inflammatory treatment of chronic inflammatory diseases. MPV values between SFC and CFC patients were first compared by Ozaydin., *et al.* [26] and hypothesized that what if epilepsy is an inflammatory disease of the brain and also MPV decrease in inflammatory cases, MPV should be lower in CFC than SFC. Finally, they found lower levels of MPV in CFC group because CFS is considered to be a major risk factor of epilepsy and naturally more inflammatory changes occur in the brain [26].

Although the pathogenesis of FC is not exactly known, the cytokines are thought to be in part of the pathogenesis of FC in recent years. During infection proinflammatory cytokines such as IL-1 beta, TNF alpha and IL-6 are suggested to be the cause of the fever by stimulating the synthesis of prostaglandins and hypothalamic receptors [46]. It is proposed that IL-1 and IL-6 biallelic polymorphisms may have a role in the pathogenesis of FC but it is not conclusively proven [47,48]. It has been reported that TNF-alpha, IL1, IL-6 and IFgamma increase may be responsible for MPV decrease in CFC patients and particularly IL-6 is a mediator to cause secondary thrombocytosis [49]. In a study, MPV values of the SFC groups found to be higher than the control group. In the event of acute inflammation and infection, which create an immune response, increased MPV, which is associated with structural changes in thrombocytes, even showing an anti-microbial effect, shows infectionactivity causing SFC [27]. In the current study, we found no significant differences between SFC, CFC and control groups regarding the MPV values.

According to the results, especially subjects with CFC should be examined for iron and vitamin B12 deficiency if anemia was detected by CBC. Moreover, we suggested that it should be performed long term studies regarding FC recurrence in children who has FC or a family history of FC after iron and vitamin B12 replacement.

Conclusion

In our study, the ferritin and vitamin B12 levels in anemic children with FC were found significantly lower in CFC than SFC. As a result of this, the decrease of ferritin and vitamin B12 may be risk factors for FC. There are needs for prospective, long term studies with larger patient groups to evaluate MPV, iron parameters, vitamin B12 levels and their effects on FC type.

Bibliography

1. Commision on Epidemiology and Prognosis International League Againist Epilepsy: "Guidelines for epidemiologic studies on epilepsy". *Epilepsia* 34.4 (1993): 592-596.

2. Hartfield DS., *et al*. "Association Between Iron Deficiency and Febrile Seizures in Childhood". *Clinical Pediatrics* 48.4 (2009): 420-426.

3. Lozoff B., *et al*. "Long-lasting neural and behavioral effects of iron deficiency in infancy". *Nutrition Reviews* 64.5 (2006): S34-43.

4. Heydarian F and Vatankhah H. "The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old". *Neurosciences* 17.3 (2012): 226-229.

5. Pisacane A., *et al*. "Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years". *BMJ* 313.7053 (1996):343.

6. Naveed-ur-Rehman and Billoo AG. "Association between iron deficiency anemia and febrile seizures". *Journal of the College of Physicians and Surgeons Pakistan* 15.6 (2005): 338-340.

7. Guzman AR., *et al*. "La anemia: un posible factor de riesgo para la primera convulsifactor de riesgolevalua". 7 (2005): 62-65.

8. Kumari PL., *et al*. "Iron deficiency as a risk factor for simple febrile seizures--a case control study". *Indian Pediatrics* 49 (2012): 17-19.

9. Bidabadi E and Mashouf M. "Association between iron deficiency anemia and first febrile convulsion: A case-control study". *Seizure* 18.5 (2009): 347-351.

10. Sharif MR., *et al*. "The Relationship Between Iron Deficiency and Febrile Convulsion: A Case-Control Study". *Global Journal of Health Science* 8.2 (2016): 185-189.

11. Sadeghzadeh M., *et al*. "Iron Status and Febrile Seizure-A Case Control Study in Children Less Than 3 Years". *Iranian Journal of Child Neurology* 6.4 (2012): 27-31.

12. Shukla A., *et al*. "Latent iron deficiency alters gammaaminobutyric acid and glutamate metabolism in rat brain". *Experientia* 45.4 (1989): 343-345.

13. Kobrinsky NL., *et al*. "Does iron deficiency raise the seizure threshold?". *Journal of Child Neurology* 10.2 (1995): 105-109.

14. Abaskhanian A., *et al*. "The association between iron deficiency and the first episode of febrile seizure". *Journal of Babol University of Medical Sciences* 11 (2009): 32-36.

15. Derakhshanfar H., *et al*. "Association between iron deficiency anemia and febrile seizure in children". *Medicinski Glasnik* 9.2 (2012): 239-242.

16. Celik T., *et al*. "Vitamine B12 deficiency in a child presenting with epileptic spasms". *Journal of Pediatric Neurology* 12.4 (2014).

17. Bak M., *et al*. "Neurological manifestations of vitamin B12 defi ciency in 15 infants". *Journal of Pediatric Neurology* 7 (2009): 275-278.

18. Taskesen M., *et al*. "Neurological presentations of nutritional vitamin B12 deficiency in 42 breastfed infants in Southeast Turkey". *Turkısh Journal of Medıcal Scıences* 41.6 (2011): 1091-1096.

19. Osifo BO., *et al*. "Cerebrospinal fluid folate and cobalamin levels in febrile convulsion". *Journal of the Neurological Sciences* 68.2-3 (1985): 185-190.

20. Mangalpally KK., *et al*. "Platelet activation patterns in platelet size sub-populations: differential responses to aspirin in vitro". *Journal of Thrombosis and Thrombolysis* 30.3 (2010): 251-262.

21. Bath PM and Butterworth RJ. "Platelet size: measurement, physiology and vascular disease". *Blood Coagulation and Fibrinolysis* 7.2 (1996): 157-161.

22. Gülcan M., *et al*. "Mean platelet volume is increased in patients with deep vein thrombosis". *Clinical and Applied Thrombosis/Hemostasis* 18.4 (2012): 427-430.

23. Çay N., *et al*. "Platelet Activity Indices in patients With Deep Vein Thrombosis". *Clinical and Applied Thrombosis/Hemostasis* 18.2 (2012): 206-210.

24. Yüksel O., *et al*. "An overlooked indicator of disease activity in ulcerative colitis: mean platelet volume". *Platelets* 20.4 (2009): 277-281.

25. Kisacik B., *et al*. "Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis". *Joint Bone Spine* 75.3 (2008): 291-294.

26. Özaydın E., *et al*. "Differences in iron deficiency anemie and mean platelet volume between children with simple and complex febrile seizures". *Seizure* 21.3 (2012): 211-214.

27. Abuhandan M., *et al*. "Evaluation of Selenium Levels and Mean Platelet Volume in Patients with Simple Febrile Convulsion". *Iranian Journal of Pediatrics* 24.4 (2014): 401-405.

28. Akbar MA., *et al*. "Evaluation of iron status in 9 months to 5 years old children with febrile seizure". Iranian *Journal of Child Neurology* 4.2 (2010): 45-50.

29. Abdur Rehman KN and Al Trushi AM. "The association between iron deficiency anaemia and febrile seizure". *Duhok Medical Journal* 4 (2010): 60-66.

30. Okumura A., *et al*. "Unconsciousness and delirious behaviour in children with febrile seizures". Pediatric Neurology 30.5 (2004): 316-319.

31. Li D. "Effects of iron deficiency on iron distribution and gamma-aminobutyric (GABA) metabolism in young rat brain tissues". *Hokkaido Journal of Medical Science* 73.3 (1998): 215-225.

32. Andrews N., *et al*. "Disorders of iron metabolism and sideroblastic anemia in Nathan and Oski's Hematology of infancy and childhood". Orkin S, Nathan D. l7th edition. Philedelphia: Saunders (2009): 521-570.

33. Khusun H., *et al*. "World health organization hemoglobin cutt-off points for the detection of anemia are valid for an Indonesian population". *The Journal of Nutrition* 129.9 (1999): 1669-1674.

34. Momen AA and Hakimzadeh M. "Case–control study of the relationship between anemia and febrile convulsion in children between 9 months and 5 years of age". *Scientific Medical Journal of Ahwaz University of Medical Sciences* 1.4 (2003): 50-54.

35. King D King A. "Question 2: Should children who have a febrile seisure be screened for iron deficiency?". *Archives of Disease* 99.10 (2014): 960-964.

36. "Recommendations to prevent and control iron deficiency in the United States". *Morbidity and Mortality Weekly Report* 47 (1998): 1-36.

37. McLean E., *et al*. "Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005". *Public Health Nutrition* 12.4 (2009): 444-454.

38. Aslan D., *et al*. "Importance of rdw value in differential diagnosis of hypochrome anemias". *American Journal of Haematology* 69 (2002): 31-33.

39. Vaswani M., *et al*. "Iron Deficiency as a Risk Factor for First Febrile Seizure". *Indian paediatrics Journal* 3 (2009): 1-3.

40. Daoud AS., *et al*. "Iron status: a possible risk factor for the first febrile seizure". *Epilepsia* 43.7 (2002): 740-743.

41. Papageorgiou V., *et al*. "Association between iron deficiency and febrile seizures". *European Journal of Paediatric Neurology* 19.5 (2015): 591-596.

42. Zareifar S., *et al*. "Association between iron status and febrile seizures in children". *Seizure* 21.8 (2012): 603-605.

43. Roschitz B., *et al*. "Nutritional infantile vitamin B12 deficiency: pathobiochemical considerations in seven patients". *Archives of Disease in Childhood Fetal Neonatal Edition* 90.3 (2005): 281-282.

44. Graham SM., *et al*. "Long-term neurological consequences of nutritional VB12 deficiency in infants". *Journal of Pediatrics* 121.5 (1992): 710-714.

45. Özkale Y., *et al*. "Serum vitamin B12, folic acid, and homocysteine levels in children with febrile seizure". *The Turkish Journal of Pediatrics* 57.4 (2015): 345-352.

46. Akaike A., *et al*. "Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons". *European Journal of Pharmaceutical Sciences* 241.1 (1993): 1-6.

47. Waruiru C and Appleton R. "Febrile seizures: an update". *Archives of Disease in Childhood* 89.8 (2004): 751-756.

48. Leung A and Robson L. "Febrile Seizures". *Journal of Pediatric Health Care* 21 (2007): 250-255.

49. Millichap JG and Millichap JJ. "Role of viral infections in the etiology of febrile seizures". *Pediatric Neurology* 35.3 (2006): 165-172.

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