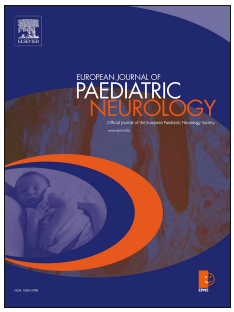
Accepted Manuscript



Association between iron deficiency and febrile seizures

Valia Papageorgiou, Euthymia Vargiami, Eleutherios Kontopoulos, Panagiotis Kardaras, Marina Economou, Miranta Athanassiou-Mataxa, Fenella Kirkham, Dimitrios I. Zafeiriou, MD, PhD, Professor in Child Neurology and Developmental Pediatrics

PII: S1090-3798(15)00106-3

DOI: 10.1016/j.ejpn.2015.05.009

Reference: YEJPN 1916

To appear in: *European Journal of Paediatric Neurology*

Received Date: 31 December 2014

Revised Date: 3 May 2015

Accepted Date: 25 May 2015

Please cite this article as: Papageorgiou V, Vargiami E, Kontopoulos E, Kardaras P, Economou M, Athanassiou-Mataxa M, Kirkham F, Zafeiriou DI, Association between iron deficiency and febrile seizures, *European Journal of Paediatric Neurology* (2015), doi: 10.1016/j.ejpn.2015.05.009.

Association between iron deficiency and febrile seizures

Abbreviated title: Iron and febrile seizures

Valia Papageorgiou[1], Euthymia Vargiami[1], Eleutherios Kontopoulos[1], Panagiotis Kardaras[2], Marina Economou[1], Miranta Athanassiou-Mataxa[1], Fenella Kirkham[3,4], Dimitrios I Zafeiriou[1]

[1]1st Department of Pediatrics, Aristotle University of Thessaloniki, Hippokratio General Hospital, Thessaloniki, Greece

[2]3rd Department of Pediatrics, Aristotle University of Thessaloniki, Hippokratio General Hospital, Thessaloniki, Greece

[3]Division of Clinical and Experimental Sciences, University of Southampton, UK

[4]Neurosciences Unit, UCL Institute of Child Health, London, UK

Disclosures

Both Fenella Kirkham and Dimitrios Zafeiriou were equally listed as last authors.

Manuscript word count: 2493

Abstract word count: 250

Title character count: 50

Correspondence should be directed to:

Dimitrios I Zafeiriou, MD, PhD
Professor in Child Neurology and Developmental Pediatrics
1st Department of Pediatrics
Aristotle University of Thessaloniki
Egntia St. 106
54622 Thessaloniki, Greece
Tel.-Fax: +30 2310 241845
Mobile: +30 6944 330587
E-mail: jeff@med.auth.gr

Highlights

- Greek children with FS have lower levels of plasma ferritin and higher levels of TIBC than controls, implying an association with iron deficiency although haemoglobin levels were non-significantly higher
- In children with complex FS, the levels of plasma ferritin are significantly lower and TIBC significantly higher than controls.
- Children in whom the index febrile seizure was a recurrence were more likely to be iron deficient but with a higher haemoglobin and mean cell haemoglobin concentration than those with a first seizure

Abstract

Objective: The relationship between iron status and febrile seizures has been examined in various settings, mainly in the Developing World, with conflicting results. The aim of this study was to investigate any association between iron deficiency and febrile seizures (FS) in European children aged 6-60 months.

Design: Prospective, case-control study

Setting: Greek population in Thessaloniki

Patients: 50 patients with febrile seizures (cases) and 50 controls (children presenting with fever, without seizures).

Interventions: None

Main outcome measures: Haematologic parameters (haemoglobin concentration, haematocrit, mean corpuscular volume, red cell distribution width), plasma iron, total iron-binding capacity, plasma ferritin, transferrin saturation and soluble transferrin receptors were compared in cases and controls.

Results: Plasma ferritin was lower (median [range]: 42.8 (3-285.7) vs 58.3 (21.4-195.3 ng/ml; p=0.02) and Total Iron Binding Capacity (TIBC) higher (mean [Standard Deviation] 267 [58.9] vs 243 [58.45] µg/dl, p=0.04) in cases than in controls. Results were similar for 12 complex FS cases (ferritin 30 (3-121 vs 89 (41.8-141.5 ng/lL; TIBC 292.92 [68.0] vs 232.08 [36.27] µg/dL). Iron deficiency, defined as ferritin <30ng/ml, was more frequent in cases (24%) than controls (4%; p=0.004). Ferritin was lower and TIBC higher in 18 with previous seizures than in 32 with a first seizure although haemoglobin and mean cell haemoglobin concentration were higher.

Conclusions: European children with febrile seizures have lower Ferritin than those with fever alone, and iron deficiency, but not anaemia, is associated with recurrence. Iron status screening should be considered as routine for children presenting with or at high risk for febrile seizures.

Introduction

Febrile seizures (FS) are the most common type of seizures in children (2-5%) (1-3). FS, although frightening to caregivers, are benign, and the risk for epilepsy following an episode of simple FS is no greater than that of the general population (4). There is a substantial literature examining risk factors including: positive family history for FS or epilepsy (5), maternal smoking or alcohol consumption during pregnancy (6), herpes type 6 or 7 infection (7) and nutritional deficiencies including zinc (8) and iron (9). Iron plays a critical role in the metabolism of several neurotransmitters as well as in myelination (10-12) and deficiency is associated with a number of neurological conditions in children including developmental delay, stroke, breath-holding attacks and cranial nerve palsies (11,12). Iron deficiency (ID) might therefore lower the seizure threshold (14) but there is controversy over whether there is an association with FS (9, 13-24), most conducted in the Developing World (24). In this study we investigate whether there is any association between ID and occurrence of FS in Greek preschoolers.

Patients and Methods

The present study is a prospective, case-control study following patients from March 2009 to March 2011. Consecutive children with FS (simple and complex) admitted to the 1st Pediatric Clinic, "Hippokratio" General Hospital, Thessaloniki, Greece, aged 6-60 months were considered for inclusion in the study. A total of 50 children with FS (cases) were enrolled. A reference group of 50 children (controls) were selected among children hospitalized for a febrile illness, but without seizures. Controls were matched to cases on gender and age (6-60 months). Exclusion criteria were: age <6 months or >60 months, history of afebrile seizures, any anti-epileptic drug usage, history of serious head trauma or central nervous system infection, chronic disease and neurologic deficit or developmental delay. The University's Ethics review board approved the use of human subjects and written informed consent was obtained from parents or legal guardians.

For each case and control a thorough personal history was taken. Information on the perinatal period included gestation, type of delivery (caesarian section or vaginal), birth weight, smoking or alcohol consumption during pregnancy and perinatal problems. Personal history documented included: breast-feeding duration, vaccination status, history of various illnesses, number of febrile episodes per year, previous surgeries, past admissions to hospital, history of head trauma, any drug usage and developmental milestones. Details

regarding family history were obtained as to presence of hereditary disease and/or positive history for febrile and afebrile seizures.

FS were defined according to the National Institute of Health consensus statement (2) and categorized as simple or complex (3). Simple FS were generalized, lasting <15 minutes, occurring only once in 24 hours and not provoking any neurological abnormality after the episode, in an otherwise neurologically healthy child. FS were complex if they were focal, of longer duration (>15 minutes), occurred more than once in 24 hours and/or caused neurologic deficit (such as Todd's paralysis). FS or multiple episodes of FS lasting >30 minutes without the patient gaining consciousness in the meantime were defined as Febrile Status Epilepticus (FSE) (3).

Morning venous blood samples were collected from all cases and controls for Haemoglobin, Haematocrit, Mean Cell Volume (MCV), red cell distribution width (RDW), plasma iron, total iron binding capacity (TIBC), plasma ferritin, soluble Transferrin factor Receptor (sTfR) and transferrin saturation, during the first 3 days of fever. Haemoglobin, Haematocrit, MCV and RDW were part of a complete blood count (Abbott analyzer, Cell Dyn 3700). Plasma iron and TIBC were measured by using Olympus Medicon AU2700 analyzer. Transferrin saturation was calculated using the formula: (plasma iron/TIBC)x100. Plasma ferritin was measured using an immuno-enzyme method with microparticles (AxSym System, Abbott). For the quantitative measurement of sTfR the enzyme-linked immunosorbent (ELISA) assay was used (Quantikine, R&D systems, Minneapolis, MN). Anaemia was defined as haemoglobin levels ≤10.5 g/dl for children 6-24 months and ≤11.5 g/dl for children 24-60 months (22, own unpublished data). ID was defined as plasma ferritin levels ≤30ng/ml, in the context of a febrile-infectious disease (25).

All continuous variables (e.g Haemoglobin, MCV) were compared among cases and controls using independent t-tests unless the data were skewed data when the Mann-Whitney test was used, while categorical variables were compared using χ^2. Statistical significance was set at $p \leq 0.05$. Statistical analysis was performed with use of the Statistical Package for the Social Sciences (SPSS) (PASW 18.0).

Results

Demographics

There were a total of 50 cases and 50 controls; there were no differences in age or gender (Table 1). Among the 50 cases, 36 (72%) had simple FS, while 14 (28%) had either complex FS or FSE. Among the twelve cases with complex FS, two (17%) seizures were prolonged (>15'), seven (58%) were recurrent during the

same day, one (8%) was recurrent and focal and two (17%) were prolonged and recurrent during the same day.

Cases and controls all had normal clinical examination and psychomotor development. Respiratory tract infections were the most common cause of fever and there were no differences in aetiology between cases and controls (Table 1).

Indices of iron deficiency in cases and controls

Plasma ferritin levels were significantly lower in cases than in controls (Table 2). TIBC was significantly higher in cases than in controls (Table 2). MCH and MCHC were significantly higher in cases than controls (Table 2) while Haemoglobin concentration was higher in cases than in controls, although the difference failed to attain statistical significance (Table 2).

ID was found in 14 of the 100 children in the study (14%). In particular, 24% of cases (12/50) were iron deficient and only 4% (2/50) of the controls (Fisher's Exact test, p=0.004).

Indices of iron deficiency in complex febrile seizures

For the 12 cases with complex FS and their matched controls, haematological status is provided in Table 3. In this subgroup also, plasma ferritin levels were significantly lower (Table 3) and TIBC was significantly higher in cases in comparison to controls (Table 3). Six of 12 (50%) of the children with complex and one the two of the children with febrile status epilepticus were iron deficient compared with 5/36 with simple febrile convulsions and 2/50 controls (χ^2, p<0.0005).

Recurrent febrile seizures

In our sample there were 18 (36%) cases with positive history for FS, i.e. the index seizure was a recurrence. Among them, 13 (72%) had one previous episode, one (6%) had 2 episodes, 3 (17%) had 3 episodes and only one (6%) had 4 past episodes. Ferritin was lower in those with previous seizures (median 33.45; range 3-136.8 ng/mL) than in those with a first seizure (median 46.1; range 20-286.1 ng/mL). Haemoglobin and MCHC, which were not correlated, were associated with recurrence in univariable logistic regression (Table 4) while ferritin, TIBC, family history of febrile seizures and complex febrile seizures failed to reach statistical significance and in multivariable logistic regression adjusted for age, only high haemoglobin (odds ratio 2.33, 95% confidence intervals 1.11, 4.89; p=0.025) and MCHC (odds ratio 3.11, 95% confidence

intervals 1.20, 8.07; p=0.02) were independently associated with recurrence. The presence of ID was not associated with recurrence (Fisher's Exact Test, p=0.171).

Discussion

In the present study the median age of children with FS was 25.6±13.2 months, which is in accordance with the literature. Of the previously reported associations we examined (5-7, 9, 13-24, 26), only positive family history for FS (5) and iron deficiency (9, 13-24) were risk factors in our prospective case control study. Consistent with a previous retrospective study (27) but not another prospective study including children with malaria (23), iron deficiency was also more common in those with complex febrile convulsions, suggesting exacerbation in a genetically predisposed individual. In line with previous studies showing that about one third recur (26, 28), in our study, 36% of the cases had previously had one or more episodes of FS, and Recurrences appeared in majority over the next 24 months after the first febrile seizure. Ferritin and TIBC were lower in this group but paradoxically, as in the main study, haemoglobin was higher in the cases than the controls in line with a previous large study in Iran (16).

ID is one of the most prevalent nutritional problems worldwide, especially in developing countries, affecting up to 2 billion people (29). It is the commonest dietary insufficiency and haematological disease of infancy and childhood (30). Iron is one of the most important elements of the body, especially of the CNS, having numerous biological effects. The consequences of its deficiency, especially during infancy or childhood, are multiple and show a wide variety of importance. They range from mild to extremely severe, depending on the age that they appear and the magnitude of iron insufficiency. Iron is a basic element of haemoglobin, myoglobin, cytochromes and many other enzymes. ID has been associated with different neurological problems including: restless leg syndrome (31), impaired auditory or visual evoked potentials (32), breath-holding spells (33), strokes (34) and attention deficit hyperactivity disorder (ADHD) (35). Iron participates in cerebral energy production and is important for myelin formation by oligodendrocytes (36), for the metabolism inhibitory neurotransmitter GABA (37) and for the metabolism of monoamines-neurotransmitters (dopamine, nor-epinephrine, serotonin), acting as a co-factor of tyrosine hydroxylase, tryptophan hydroxylase and aldehidoxidase (38). A reduction of neurotransmitter release (selectively GABA) is postulated to predispose to a situation of hyper-excitability (39), and thus, may account for the

pathophysiologic association of ID to the occurrence of seizures.

The diagnosis of ID in the presence of fever/infection can be challenging. Haematological parameters (like Haemoglobin, Haematocrit, MCV, RDW), microscopic examination of blood smear, plasma iron, TIBC, transferrin saturation, plasma ferritin, sTfR and free erythrocyte protoporphyrin may assist the diagnosis. Bone marrow examination is considered to be the "gold standard" method, but it is a traumatic and painful method and, therefore, was not used in the present study.

Plasma ferritin levels are a reliable method to examine the iron status of the body. Levels ≤12ng/ml are indicative of ID (40). In the presence of infection/inflammation diagnostic levels may be raised up to ≤30ng/ml (41). In our study the cut-off level of 30 ng/ml was used in order to diagnose ID. The disadvantage of ferritin is that it belongs to acute phase proteins and rises non-specifically with inflammation. In the present study fever/infection was present both in cases and controls, so any difference in ferritin levels among cases and controls could not be attributed solely to fever.

The main limitation of our study is the use of hospital controls, which may have introduced a selection bias, since this group of patients show higher levels of ID than does the reference population. Using community controls would be better but there are ethical difficulties in taking blood in well children, unless there is a programme of screening for ID with appropriate treatment in toddlers. In the light of the meta-analysis published after our study closed (24), an additional weakness is the lack of data on temperature on admission, previous anaemia, family history of anaemia, and estimated dietary intake of iron. There appears to be an association between iron deficiency and febrile convulsions in areas of low, but not in high, prevalence of iron deficiency, possibly suggesting a protective effect of maternal iron deficiency. However, in most of the studies which reported a protective effect, the diagnosis of iron deficiency was based on haemoglobin and/or haematocrit (24), which may be discrepant when compared to Ferritin measurement. Whether or not Ferritin values are lower in case does appear to be related to temperature on admission (24). All these data should be available in future prospective studies.

Our study has several strengths: 1) it is prospective (most reports are retrospective) 2) we used multiple laboratory parameters (Haemoglobin, Haematocrit, MCV, RDW, plasma iron, TIBC, plasma ferritin, transferrin saturation, sTfR) simultaneously which reflects a better image of iron status, 3) we defined as ID the presence of plasma ferritin levels ≤30ng/dl and 4) it is only the second to be published from Europe.

The literature regarding the association between ID and FS is fairly limited and there is considerable

controversy. Pisacane et al. (9), reported that ID was more frequent in Italian children with first episode of FS, as did Daoud et al. (14), Zareifar et al. (16), Naveed-ur Rehman and Billoo (17), Sherjil et al (19) and Akbayram et al. (41) . Hartfield et al. (20) suggested that Canadian children with FS were twice as likely to be iron deficient in comparison to controls. Vaswani et al. (18) reported that plasma ferritin levels are lower in children with FS. Our study is in agreement to the above mentioned studies, with plasma ferritin significantly lower and TIBC significantly higher for the whole group of children with FS and for the subgroup with complex FS.

However, there are data showing the opposite. Kobrinsky et al. (13) in a small study of 26 children suggested that ID may act as a protection for FS. Bidabadi et al. (42) also reported that iron and ferritin levels are significantly higher and TIBC significantly lower in children with FS. Heydarian et al. (21), found the haemoglobin concentration to be lower, but did not make other measurements.

The two recent meta-analyses concluded that there appeared to be an association of ID and FS and considered that factors contributing to the controversial results included the sample size, the different age groups, the different diagnostic criteria used in each study for the diagnosis of ID and the background prevalence of iron deficiency (23, 24). Including all the cases in the other 2 meta-analyses, other data published since (43-45) and our data, the pooled odds ratio for an association between iron deficiency and febrile convulsions is 1.788 (95% confidence intervals1.325-2.413). This strongly suggests an association but it would be of interest to estimate the effect of ID on complexity of the initial seizure and risk of recurrence of FS before considering a trial of therapeutic iron supplementation to prevent recurrence in those with a first febrile seizures. Further exploration is also warranted of the effect on the brain of erythropoiesis in the context of iron deficiency as it is possible that gene expression is altered in this situation and alters the seizure threshold. Measuring iron levels in cerebrospinal fluid in children with FS, reflecting more accurately the local CNS environment, would also be of interest.

Conclusions: Children with FS have lower levels of plasma ferritin and higher levels of TIBC, implying an association between iron deficiency and FS. In complex FS also, the levels of plasma ferritin are significantly lower and TIBC significantly higher, which reinforces our primary conclusion. Those with recurrent febrile convulsions appear to have higher haemoglobin and MCHC despite indices consistent with iron deficiency. The exact explanation for the differences of iron status between children with FS and their controls is unknown. However, since ID seems to be related to the pathogenesis of FS, early prevention and detection

could reduce the frequency of FS. Therefore, iron status work-up could be established as a routine screening for all children who are in high risk to have FS or for preventing a recurrence. Iron seems to be related to the pathogenesis of FS, but other mechanisms are also implicated, since ID was not found in all cases with FS and not all the iron deficient patients had FS.

References

1. Berg A. Febrile seizures and epilepsy the contributions of epidemiology. Pediatr Perinat Epidemiol. 1992;6:145–52.

2. Freeman J. Febrile seizures: a consensus of their significance, evaluation, and treatment. Pediatrics. 1980;66:109.

3. Waruiru C, Appleton R. Febrile seizures: an update. Arch Dis Child. 2004;89:751–6.

4. Verity C, Golding J. Risk of epilepsy after febrile convulsions: a national cohort study. BMJ. 1991; 303: 1373-1376.

5. Berg A, Shinnar S, Shapiro E, Salomon M, Crain E, Hauser W. Risk factors for a first febrile seizure: a matched case-control study. Epilepsia. 1995;36:334–41.

6. Nelson K, Ellenberg J. Prenatal and perinatal antecedents of febrile seizures. Ann Neurol. 1990;27:127–31.

7. Clark D, Kidd I, Collingham K, Tarlow M, Ayeni T, Riordan A, et al. Diagnosis of primary human herpesvirus 6 and 7 infections in febrile infants by polymerase chain reaction. Arch Dis Child. 1997;77:42–5.

8. Ganesh R, Janakiraman L. Serum zinc levels in children with simple febrile seizure. Clinic Pediatr. 2008;47:164–6.

9. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. BMJ. 1996;313:343

10. Agarawal KN. Iron and the brain: neurotransmitter receptors and magnetic resonance spectroscopy.Br J Nutr 2001; 85 (Suppl. 2): 147-50

11. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006 May;64(5 Pt 2):S34-43; discussion S72-91.

12. Yager JY, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. Pediatr Neurol. 2002 Aug;27(2):85-92.

13. Kobrinsky N, Yager J, Cheang M, Yatscoff R, Tenenbein M. Does iron deficiency raise the seizure threshold? J Child Neurol. 1995;10:105–9.

14. Daoud A, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron status: a possible risk factor for the first febrile seizure. Epilepsia. 2002;43:740–3.

15. Kumari PL, Nair MK, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures-a case control study. Indian Pediatr 2012; 49: 17-19

16. Zareifar S, Hosseinzadeh H, Cohan N. Association between iron status and febrile seizures in children. Seizure. 2012;21:603–5.

17. Naveed-ur-Rehman, Billoo A. Association between iron deficiency anemia and febrile seizure. J Coll Physicians Surg Pak. 2005;15:338–40.

18. Vaswani R, Dharaskar P, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr. 2010;47:437–9.

19. Sherjil A, us Saeed Z, Shehzad S, Amjad R. Iron deficiency anaemia- a risk factor for febrile seizures in children. J Ayub Med Coll Abbottabad. 2010;22:71–3.

20. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. Clin Pediatr (Phila) 2009 May;48(4):420-6.

21. Heydarian F, Vatankhah H. The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old. Neurosciences (Riyadh). 2012;17:226–9.

22. Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anemia and febrile seizure in children.Med Glas (Zenica). 2012;9:239-42

23. Idro R, Gwer S, Williams T, Otieno T, Uyoga S, Fegan G, et al. Iron deficiency and acute seizures: results from

children living in rural Kenya and a meta-analysis. PloS one. 2010;5:e14001.

24. Habibian N, Alipour A, Rezaianzadeh A. Association between Iron Deficiency Anemia and Febrile Convulsion in 3- to 60-Month-Old Children: A Systematic Review and Meta-Analysis. Iran J Med Sci. 2014 Nov;39(6):496-505.

25. Phiri K, Calis J, Siyasiya A, Bates I, Brabin B, Van Hensbroek M. New cut-off values for ferritin and soluble transferrin receptor for the assessment of iron deficiency in children in a high infection pressure area. J Clin Path. 2009;62:1103–6.

26. Paul SP, Chinthapalli R. Rational approach to management of febrile seizures. Indian J Pediatr. 2013;80:149-50

27. Ozaydin E, Arhan E, Cetinkaya B, Ozdel S, Degerliyurt A, Guven A, et al. Differences in iron deficiency anemia and mean platelet volume between children with simple and complex febrile seizures. Seizure 2012 Apr;21(3):211-4.

28. Sadeghzadeh M, Khoshnevis AP, Mahboubi E. Iron status and febrile seizure- a case control study in children less than 3 years. Iran J Child Neurol 2012;6(4):27-31.

29. World Health Organization. Iron Deficiency. Assessment, Prevention, and Control: A Guide for Programme Managers. World Health Organization: Geneva, 2001.

30. Dowling P, Klinker F, Stadelmann C, Hasan K, Paulus W, Liebetanz D. Dopamine d3 receptor specifically modulates motor and sensory symptoms in iron-deficient mice. J Neurosci. 2011;31:70–7.

31. Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res. 2003; 53: 217 –23.

32. Zehetner A, Orr N, Buckmaster A, Williams K, Wheeler D. Iron supplementation for breath-holding attacks in children. Cochrane Database Syst Rev. 2010;12:CD008132.

33. Swann I, Kendra J. Severe iron deficiency anaemia and stroke. Clin Lab Haematol. 2000;22:221–3.

34. Lahat E, Heyman E, Livne A, Goldman M. Iron deficiency in children with attention deficit hyperactivity disorder. Isr Med Assoc J. 2011;13:530–3.

35. Badaracco M, Siri M, Pasquini J. Oligodendrogenesis the role of iron. Biofactors. 2010; 36: 98–102

36. Taneja V, Mishra K, Agarwal KN. Effect of early iron deficiency in rat on the gamma-aminobutyric acid shunt in brain. J Neurochem. 1986 Jun;46:1670–4.

37. Dallman P. Biochemical basis for the manifestations of iron deficiency. Ann Rev Nutr. 1986;6:13–40.

38. Youdim M, Yehuda S. The neurochemical basis of cognitive deficits induced by brain iron deficiency: involvement of dopamine-opiate system. Cell Mol Biol (Noisy-le-grand). 2000;46:491–500.

39. Ali M, Luxton A, Walker W. Serum ferritin concentration and bone marrow iron stores: a prospective study. Can Med Assoc J. 1978;118:945–6.

40. Goodnough L, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood. 2010;116:4754–61.

41. Akbayram S, Cemek M, Büyükben A, Aymelek F, Karaman S, Yilmaz F, et al. Major and minor bio-element status in children with febrile seizure. Bratisl Lek Listy. 2012; 113: 421–3.

42. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. Seizure. 2009;18:347–51.

43. Fallah R, Tirandazi B, Ferdosian F, Fadavi N. Iron deficiency and iron deficiency anemia in children with first attack of seizure and on healthy control group: a comparative study. Iran J Child Neurol 2014;8(3):18-23.

44. Ghasemi F, Valizadeh F, Taee N. Iron-deficiency Anemia in Children with Febrile Seizure: A Case-Control Study. Iran J Child Neurol 2014;8(2):38-44.

45. Yousefichaijan P, Eghbali A, Rafeie M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anemia and simple febrile convulsion in children. J Pediatr Neurosci 2014 May;9(2):110-4.

Table Legends.

Table 1. Demographic data and details of personal history among cases and controls (p-value as a result of χ^2 test ^ as a result of Fisher's exact test)

Table 2. Haematology data among cases and controls (^p-value as a result of t-test * p-value as a result of Mann-Whitney test)

Table 3. Haematology data among cases with complex FS and controls (^p-value as a result of t-test * p-value as a result of Mann-Whitney test)

Table 4. Univariate logistic regression analysis of factors predisposing to FS.

Table 1.

		Cases (n=50)	Controls (n=50)	p-value
Age		25.6±13.2	25.1±14.2	0.87
Sex	*Male*	22 (44%)	22 (44%)	
	Female	28 (56%)	28 (56%)	1.00
Causes of fever				
	Respiratory tract infection	18 (36%)	16 (32%)	
	Tonsillitis	9 (18%)	2 (4%)	
	Otitis media	6 (12%)	4 (8%)	
	Urinary tract infection	2 (4%)	13 (26%)	
	Viral syndrome	11(22%)	11 (22%)	
	Gastroenteritis	2 (4%)	-	
	MMR	2 (4%)	-	
	Bronchiolitis	-	3 (6%)	
	Osteomyelitis	-	1 (2%)	
Smoking during pregnancy		8 (16%)	4 (8%)	0.22
Prematurity		14 (28%)	11 (22%)	0.49
Caesarian section		25 (50%)	20 (40%)	0.32
Pregnancy problems		10 (20%)	14 (28%)	0.35
Perinatal problems		14 (28%)	12 (24%)	0.65
Positive family history for FS		23 (46%)	2 (4%)	**<0.001**
Positive family history for Epilepsy		4 (8%)	1 (2%)	0.18^
Vaccination status				
	Complete	41 (82%)	35 (70%)	
	Incomplete	9 (18%)	15 (30%)	0.16
Breast-feeding > 6 months		13 (26%)	11 (22%)	0.64
Birth weight (gr)		3035.7±560.3	3198.5±537.0	0.14

p-value as a result of χ^2 test ^ as a result of Fisher's exact test

Table 2.

	Cases Mean [SD]	Cases Median [Range]	Controls Mean [SD]	Controls Median [Range]	p
Haemoglobin concentration (g/dl)	11.82 (1.01)	11.85 (9.1-13.5)	11.44 (1.00)	11.40 (9.3-13.5)	0.059
Haematocrit (%)	35.35 (3.21)	35 (28-41)	34.85 (3.18)	35.00 (29-41)	0.4
Red blood cells (*10^9/L)	4.48 (0.40)	4.47 (3.45-5.49)	4.43 (0.36)	4.44 ((3.65-5.16)	0.5
Mean Cell Volume (fl)	79.11 (3.70)	79.55 (65.6-88.3)	78.82 (4.00)	79.50 (68.1-86.8)	0.7
Mean Cell Haemoglobin (pg/cell)	26.47 (1.39)	26.50 (21.4-29.6)	25.87 (1.38)	25.95 (22.3-28.3)	0.031
Mean Cell Haemoglobin Concentration (g/dl)	33.46 (0.82)	33.60 (31.7-35.4)	32.83 (1.03)	32.60 (31.5-37.2)	0.001
Red Cell Distribution Width (%)	51.42 (1.60)	15.35 (12.2-21.4)	15.79 (1.57)	15.70 (13.2-20.2)	0.3
Ferritin (ng/mL)	53.65 (44.35)	53.63 (3.0-285.7)	74.03 (38.04)	58.3 (21.4-195.3)	0.015
Iron (µg/dl)	43.00 (30.37)	37.5 (4-128)	36.72 (25.09)	30.0 (6-92)	0.3
Total iron binding capacity (µg/dl)	267.60 (58.91)	260 (124-391)	243.54 (58.45)	232.50 (125-443)	0.043
Transferrin saturation (%)	17.98 (16.56)	14 (1-90)	16.18 (12.30)	12.00 (2-46)	0.5
Soluble transferrin receptor	25.35 (5.77)	25.55 (15.00-39.10)	27.33 (6.31)	26.45 (15.4-42.9)	0.1

Table 3.

	Controls (n=50)		Simple febrile seizures (n=36)		Complex febrile seizur	
	Mean [SD]	Median [Range]	Mean [SD]	Median [range]	Mean [SD]	Medi
Haemoglobin (g/dl)	11.44 (1.00)	11.40 (9.3-13.5)	11.93 (1.03)	12.10 (9.1-13.5)	11.55 (0.93)	11.30
Haematocrit (%)	34.85 (3.18)	35.00 (29-41)	35.52 (3.34)	35.95 (28-41)	34.93 (2.92)	34
Red blood cells (*10^9)	4.43 (0.36)	4.44 ((3.65-5.16)	4.47 (0.21)	4.49 (3.45-5.49)	4.50 (0.36)	4.43
Mean Cell Volume (fl)	78.82 (4.00)	79.50 (68.1-86.8)	79.68 (3.81)	79.70 (65.6-88.1)	77.65 (3.03)	77.30
Mean Cell Haemoglobin (pg/cell)	25.87 (1.38)	25.95 (22.3-28.3)	26.78 (1.38)*	26.80 (21.4-29.6)	25.67 (1.08)	26 (
Mean Cell Haemoglobin Concentration (g/dl)	32.83 (1.03)	32.60 (31.5-37.2)	33.61 (0.80)*	33.70 (32.2-35.4)	33.08 (0.77)	32.2
Red Cell Distribution Width (%)	15.79 (1.57)	15.70 (13.2-20.2)	15.05 (1.25)	14.70 (12.2-18.1)	16.36 (2.03)	15.95
Ferritin (ng/dl)	74.03 (38.04)	58.3 (21.4-195.3)	55.57 (47.34)*	44.40 (14.1-285.7)	48.61 (36.63)*	30.25
Iron (µg/dl)	36.72 (25.09)	30.0 (6-92)	44.22 (32.74)	37.50 (4-128)	39.86 (24.00)	36.
Total iron binding capacity (µg/dl)	243.54 (58.45)	232.50 (125-443)	261.11 (55.09)	253.00 (124-391)	284.29 (67.04)*	286.5
Transferrin saturation (%)	16.18 (12.30)	12.00 (2-46)	19.40 (18.01)	15.00 (1-90)	14.31 (9.53)	12.
Soluble transferrin receptor	27.33 (6.31)	26.45 (15.4-42.9)	24.54 (5.10)	25.15 (15.00-33.80)	27.42 (6.99)	27.85

Table 4.

	OR	Lower 95% CI	Upper 95% CI	p
Family history	1.83	0.57	5.87	0.3
Complex	2.62	0.62	11.04	0.2
Ferritin	0.98	0.16	1.01	0.13
TIBC	1.01	0.999	1.021	0.071
Haemoglobin	2.51	1.23	5.12	0.011
MCHC	2.46	1.08	5.61	0.03