



The Role of Iron Deficiency as a Risk Factor for Febrile Seizures

Authors

Dr Kuppusamy¹, Dr Shiv Narayan Panda^{2*}, Dr S S Dalal³, Dr Vandana Negi⁴

¹Resident, Department of Pediatrics, CHAF, ²Asst. Prof., Department of Pediatrics, CHAF

^{3,4}Prof., Department of Pediatrics, CHAF

Corresponding Author

Dr Shiv Narayan Panda

Assistant Professor, Department of Paediatrics, Command Hospital Air Force, Bangalore-560007, Karnataka, India

Abstract

Introduction: Iron plays an important role in synthesis of various neurotransmitters in the brain. Iron deficiency, by altering neurotransmitter levels, may predispose children with iron deficiency to increased risk of febrile seizures.

Aims and Objectives: To study the role of iron deficiency as a risk factor for febrile seizures in children 6 to 60 months of age and to identify the peak age group of febrile seizures.

Methods: Case control study conducted in a tertiary care hospital in South India from October 2016 to children between 6 to 60 months of age admitted with febrile seizure were included as cases (n=50) and age matched children admitted with short febrile illness without seizures as controls (n=50). Complete haemogram, serum iron and ferritin levels were compared between the cases and controls. Iron deficiency was defined as Hb < 11g/dl and serum ferritin < 30ng/ml in the presence of fever (as per WHO guidelines).

Results: 74% of the cases had low serum ferritin levels compared to 20% among the controls (p=0.001). Mean serum ferritin levels were significantly low in cases compared to controls (28.6ng/ml Vs 92.1µg/L). Also mean haemoglobin concentration (11.2 Vs 12.1, P value 0.004), mean MCV (67.9 Vs 77.8, P value 0.000) were significantly low and mean TIBC levels were significantly high (468.3 Vs 315.2, P value 0.002) in febrile seizure group than in the control group. The febrile seizures were common in the age group between 1 year and 3 years.

Conclusion: Children with low iron stores are at higher risk for febrile seizures.

Keywords: Iron Deficiency, Febrile Seizures.

Introduction

Febrile seizures are defined as the seizures that occur between the age of 6 and 60 months during febrile illness with a temperature of 38°C (100.4°F) or higher, in the absence of central nervous system infection or any metabolic imbalance, and previous history of afebrile seizures. It occurs in 2% to 5% of neurologically healthy infants and children. Recurrence of febrile

seizures is 30% after single episode, 50% after 2 or more episodes and 50% when febrile seizures occurs in infants^[1].

Various risk factors such as first or second-degree relative with history of febrile and afebrile seizures, developmental delay, Influenza-A viral infection, Human herpesvirus-6 infection, Metapneumovirus, and iron deficiency anaemia

are associated with the occurrence of first febrile seizures in children^[2].

Iron deficiency is the most common nutritional disorder all over the world. It is estimated that 30% of global population suffers from iron deficiency anaemia, and most of them live in developing countries^[3]. Iron is a cofactor for several enzymes in the body and has a role in the production and function of neurotransmitters, hormonal function and DNA duplication^[4]. Iron is involved in several essential processes of brain such as neuro-metabolism, myelination, and neurotransmitter function. In patients with iron deficiency, reduced metabolism of several neurotransmitters and monoamine and aldehyde oxidases was observed. It has also been suggested that fever aggravates the negative effects of iron deficiency on the brain because of which the iron deficient children may have a lowered threshold for and an increased risk of febrile seizures^[5].

As iron deficiency and febrile seizures are common during early childhood, it was postulated that some association may exist between these two clinical conditions. To establish some correlation among them, various studies were undertaken with majority of the studies concluding that iron deficiency is common in febrile seizure patients^[6-8], few studies concluded that iron status has no role in febrile seizures^[9,10] and a few studies concluded that iron deficiency raises seizure threshold thereby it protects children from seizures^[11,12].

In view of high prevalence of iron deficiency in children less than 5 years of age in our country and conflicting results from previous studies, we planned this research to study the role of iron deficiency as risk factor for febrile seizures in children. Findings from the study will help in reducing or preventing the occurrence of febrile seizures in community.

Materials and Methods

This study is a hospital based cross sectional analytical study done in the Department of Paediatrics of tertiary care referral hospital from

October 2016 to September 2018. The cases are children aged between 6 months and 5 years admitted with febrile seizures in paediatric ward and controls are children presenting in paediatric ward and in OPD with short febrile illness without seizures. Sample size was calculated using Epi Info program based on the assumptions that alpha error 5%, β error 20% i.e. power of study 80%, Odds ratio 2.8, and prevalence of exposure (iron deficiency) in the control group 30%. Accordingly sample size of 100 children which include 50 children with febrile seizures as cases and 50 age matched children with short febrile illness without seizures as controls was taken for this study.

All eligible children aged 6 months to 60 months reported or admitted with short febrile illness (≤ 5 days) in Paediatric OPD/ ward of the study hospital during the study period. Cases were the children with febrile seizures and control group included children presented with short febrile illness without seizures.

Inclusion Criteria: Children from the age of 6 month- 60 months presenting with short febrile illness (≤ 5 days) with or without febrile seizures.

Exclusion Criteria: Children with known neurological problems, developmental delay, CNS infections, malignancy, electrolyte imbalance, decreased glucose, haematological disorders, past history of febrile seizures, who received iron supplementation in past 3 months were excluded from the study.

Method of collection of data: After obtaining informed consent from their parents, patient details were recorded in a pre-designed proforma. With all aseptic precautions, 3ml blood was collected and transported in EDTA vials for CBC estimation and iron free tubes for iron studies. All cases and controls were subjected to haematological investigations – Complete blood count (CBC), Serum Iron, TIBC (Total iron binding capacity) and Serum ferritin. Samples for haematological indices were run on same day in automated Haematology analyser (Sysmex XP-100). Serum iron and TIBC were measured by ferene method (Dimension EXL 200- Siemens).

Ferritin levels were assessed by Access 2 chemiluminescence analyser (Beckman Coulter). As per WHO guidelines 2001 on Iron Deficiency Anaemia, Assessment, Prevention and Control cut-offs were used. (Iron deficiency – serum ferritin <30ng/ml, Iron deficiency anaemia - serum ferritin <30ng/ml, haemoglobin <11g/dl). Although iron deficiency was defined as serum ferritin < 12ng/ml, a higher cut -off value (<30ng/ml) of serum ferritin was used in view of infection. Chi square test and t-test were used to compare the categorical and continuous variables respectively. Level of confidence was taken as 95% and P values of < 0.05 was taken for statistical significance.

Results

Fifty children aged 6 months to 60 months, who met the clinical definition of febrile seizures, and the inclusion and exclusion criteria of the study were enrolled as cases in the study. A total of 50 age matched children who had short febrile illness but no seizures were enrolled as controls. In our study we found that 54% of children with febrile seizures were in the age group between 1 year and 3 years. The body temperature of the febrile seizure group was significantly higher than that of control group. There was no statistically significant difference between the case and

control groups in terms of age, sex and family history of febrile seizures. Out of the 50 febrile seizures cases, 20 (40%) children had simple febrile seizures and the remaining 30 (60%) had complex febrile seizures.

Mean TLC was significantly high in febrile seizure group than in control group. The mean haemoglobin concentration (11.2 ± 1.3 vs 12.1 ± 1.8 , P value 0.004), mean MCV (67.9 ± 5.6 vs 77.8 ± 7.8 , P value 0.000) were significantly low in febrile seizure group than control group. There was no statistically significant difference between case and control groups in mean values of MCH and MCHC (TABLE 1). The mean serum ferritin levels were significantly low (28.7 ± 20.1 vs 92.1 ± 86.2 , P value 0.001), serum TIBC levels were significantly high (468.3 ± 321.8 vs 315.2 ± 84.7 , P value 0.002) in febrile seizure group than in the control group. However no significant difference was observed in mean serum iron levels between febrile seizure group and control group (TABLE 2). The proportion of iron deficiency with low serum ferritin (<30ng/ml) was significantly higher ($P < 0.000$) in cases (37, 74%) than in controls (10, 20%) (TABLE 3, Fig 1). The proportion of iron deficiency anaemia as defined in the study was present in more number of cases (15, 30%) than controls (5, 10%) with P value 0.045 (TABLE 4, Fig 2).

Table 1: Comparison of haematological parameters among the study subjects

Variable	Cases (N=50)	Controls (N=50)	P value
Hb (g/dL)	11.2 ± 1.3	12.1 ± 1.8	0.004
MCV (fL)	67.9 ± 5.6	77.8 ± 7.8	0.000
MCH (pg)	27.3 ± 7.6	27.1 ± 3.6	0.853
MCHC (g/dL)	31.4 ± 3.2	31.0 ± 3.4	0.601

Table 2: Comparison of iron status indices among the study subjects

Variable	Cases (N=50)	Controls (N=50)	P value
Serum Iron ($\mu\text{g/dL}$)	65.2 ± 61.6	57.3 ± 25.3	0.369
TIBC ($\mu\text{g/dL}$)	468.3 ± 321.8	315.2 ± 84.7	0.002
Serum Ferritin (ng/ml)	28.7 ± 20.1	92.1 ± 86.2	0.001

Table 3: Proportion of iron deficiency (SF <30 ng/ml) among study subjects

Serum Ferritin	Cases (N=50)	Controls (N=50)	P value
Low (<30 ng/ml)	37 (74%)	10 (20%)	0.000
Normal (≥ 30 ng/ml)	13 (26%)	40 (80%)	

Figure 1: Proportion of iron deficiency (SF <30 ng/ml) among study subjects

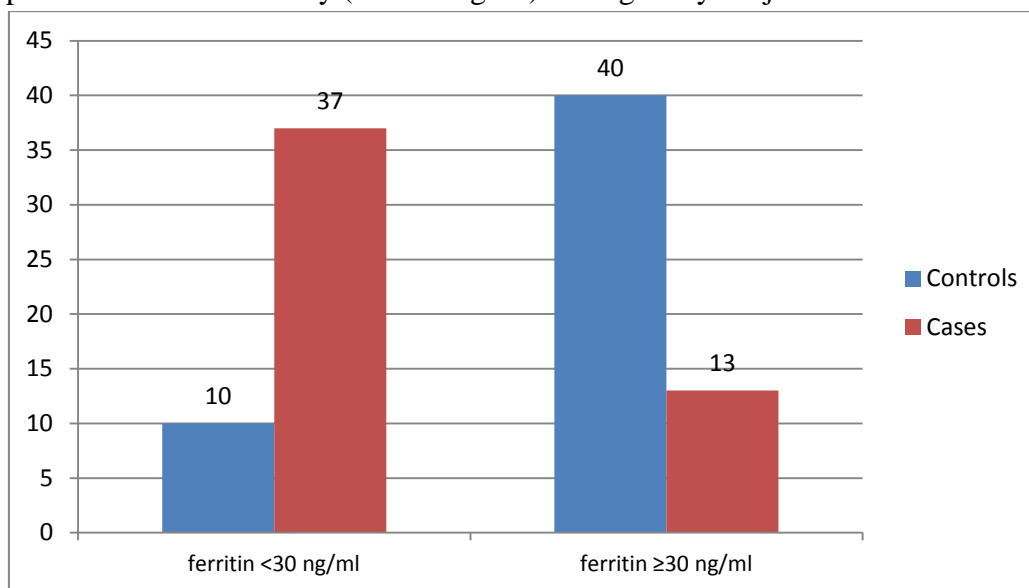


Table 4: Proportion of children with iron deficiency anaemia (Hb< 11g/dL and SF <30ng/ml) among study group.

Iron Deficiency Anaemia		Cases (N=50)	Controls (N=50)	P value
n(%)	Absent	35 (70%)	45 (90%)	0.045
	Present	15 (30%)	5 (10%)	

Figure 2: Proportion of iron deficiency anaemia (Hb< 11g/dL and SF < 30 ng/ml) among study group

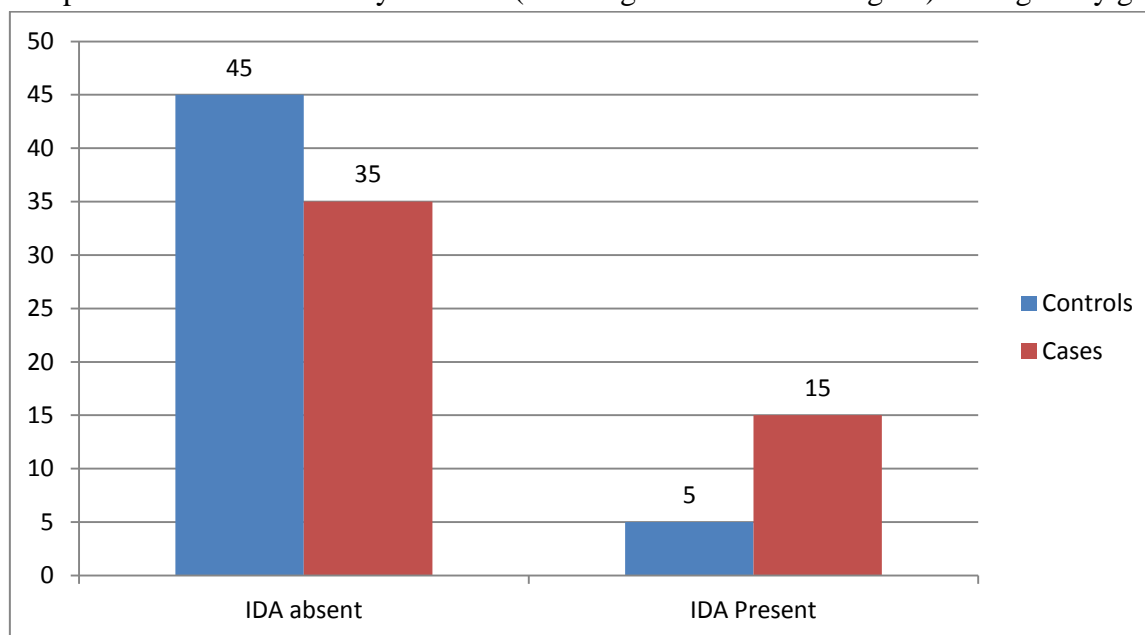


Table 5: Adjusted odd ratio of iron deficiency (serum ferritin <30ng/ml) among the study subjects

	Adjusted odd ratio (95% confidence interval)*
Controls	1
Cases	10.6 (3.8 – 29.4)

*adjusted for family history, temperature

Discussion

In this study, we compared iron status between children with febrile seizures (cases) and an age matched control group with febrile illness without seizures in order to determine the relationship between iron status and febrile seizures in paediatric patients in southern India. In our study we enrolled 50 cases of febrile seizures aged 6 months to 60 months after meeting the clinical definition of febrile seizures, and the inclusion and exclusion criteria of the study. A total of 50 age matched children who had febrile illness but no seizures were enrolled as controls.

In the current study, iron status in the form of low serum ferritin and iron deficiency anaemia was found as a significant risk factor for febrile seizures in children of age group 6 month to 5 years in our study. We found iron deficiency anaemia is more common in febrile seizure group (30% vs 10%) than in control group (P value 0.045). Odds of iron deficiency (serum ferritin < 30 ng/ml) among the cases was 10.6 times (95% CI 3.8-29.4) more than the controls (TABLE 5). We also observed statistically significant lower mean serum ferritin level (mean serum ferritin level in cases was 28.7 ± 20.1 vs 92.1 ± 86.2 ng/ml in controls, P value 0.001) and lower mean Hb levels (11.2 ± 1.3 vs 12.1 ± 1.8 , P value 0.004) in children with febrile seizure than in controls. Since fever was present in all the study subjects, the differences in ferritin concentration between the two groups cannot be explained by presence of infection / fever. In a study by Daoud, et al [13] the significance of iron status as a possible risk factor for febrile seizures was evaluated. The mean serum ferritin level in the cases (29.5 ± 21.3 µg/L) was much lower than the values in the controls (53.3 ± 37.6 µg/L) (P=0.0001). The mean serum ferritin level was significantly low in children with first febrile seizures (31.9 ± 31.0 µg/L) as compared to controls (53.9 ± 50.5 µg/L) (P=0.003). However, no significant difference was noted in the mean haemoglobin value of cases (9.4 ± 1.2 g/dL) and controls (9.5 ± 1.0 g/dL) (P=0.7), or in the mean value of blood indices. A

Kenyan case-control study as well as the meta-analysis of eight case-control studies have examined the relationship between febrile seizures or acute seizures and iron deficiency found their results suggested that iron deficiency may be associated with an increased risk of febrile seizures in children^[5]. Derakhshanfar et al^[14] studied the relationship between iron deficiency anaemia and febrile convulsion. They found that the level of iron deficiency and iron deficiency anaemia in the control group were significantly higher than those in the febrile seizure group, and concluded that the risk of febrile convulsion in children suffering from iron deficiency was less than the risk in iron sufficient children. They attributed the probable reason for the protective role of iron deficiency to the role iron plays in the activity of excitatory neurotransmitters such as monoamine oxidase and aldehyde oxidase. They added that the lack of iron leads to a reduction in the excitation power of the neurons and decline in the probability of excitation and convulsion in iron deficiency anaemia, although their results contradict those obtained in other studies. Kobrinsky et al^[12] found a higher level of iron deficiency anaemia in the control group and concluded that anaemia raises the threshold for febrile seizure and iron deficiency may protect against the development of febrile convulsions.

In our study, we found 54% of cases and 50% of controls were in the age group of 1–3 years. In a study, Kumari et al^[7] reported 55.8% of cases and 56.5% of controls were in the age group less than 17 months. Higher prevalence of febrile seizure in younger age group could be because of immaturity of the brain as maximum hippocampal growth is noted to occur in the period 15-36 months, this is the period of normal brain maturation which is thought to have enhanced neuronal excitability^[15]. Both cases and the controls had a similar proportion of males (54% vs. 52%) and females (46% vs. 48%).

In our study the mean of temperature peak on admission was significantly higher in the febrile seizure group (39.1 ± 0.1 C) than in the controls

($38.8 \pm 0.4C$) (P value 0.01). This finding is in agreement with a study conducted by Berg A Tet al^[16] which revealed that increasing peak temperature has been reported to increase the risk of febrile seizures progressively. But a study conducted by Daoud et al^[13] showed no marked differences in mean peak temperature at admission between cases and controls. Probable explanation for this observation is that fever can worsen the effects of anaemia or Iron Deficiency on the brain therefore causes convulsions. In addition, anaemia can be associated with the severity of febrile disease, and patients with more severe symptoms may be affected by convulsions. But, febrile convulsions usually occur at the onset of a febrile disease, before the reduction in Hb is not due to the infectious disease^[17]. Complex febrile seizures were the most frequent (60% vs 40%) type of seizures in our study. This is in contrast with other studies which concluded simple febrile seizures are the most common type. The possible explanation for the discrepancy is that our institute being a tertiary referral centre, more cases of complex febrile seizures are referred here for admission whereas most of the simple febrile seizure cases are handled at periphery hospitals as OPD patients.

In this study, family history of febrile seizures were higher among cases than controls (16% vs 10%) but the difference was not statistically significant (P=0.277). This difference could be due to firstly recall bias as parents of the children with febrile seizures are more likely to look for or remember the history of febrile seizures in their family members, secondly children with positive family history of febrile seizures are more likely to have febrile seizures.

A study conducted by Daoud et al^[13] also concluded that family history of febrile seizures was higher among cases than controls, but the differences were not statistically significant. Family history of febrile seizures most likely represents a genetic susceptibility to seizures with fever^[16].

In our study, the mean of haemoglobin concentration (11.2 ± 1.3 vs 12.1 ± 1.8 , P value 0.004) and MCV (67.9 ± 5.6 vs 77.8 ± 7.8 , P value 0.000) were significantly low and serum TIBC levels were significantly high (468.3 ± 321.8 vs 315.2 ± 84.7 , P value 0.001) in febrile seizure group than in the control group. Pisacane et al^[17] studied the level of HB, MCV, and serum iron and found that in children younger than 2 years from Naples, 30% of febrile seizures children had anaemia compared with 14% in the controls, but plasma ferritin level was not measured in their study. Fallah et al^[18] from Iran showed low Mean HB (11.46 ± 1.18 gm/dL) in case group as compared to control group (11.9 ± 0.89 g/dL) which was significant.

In the current study, we noticed that mean TLC of cases is significantly higher than that of controls (10841 ± 5082 vs 7561 ± 2299 , P=.000). This observation could be attributable to more severe febrile illness in cases which could have caused higher TLC in cases.

Conclusion

There was a significant association between iron deficiency (low serum ferritin levels) and febrile seizure among children. Children with febrile seizures should be screened for iron deficiency. The percentage of children with febrile seizures was more in the age group 1 to 3 years.

Acknowledgements: None

Funding: Nil

Conflict of Interest: None

References

1. Mikati MA, Hani AJ. Febrile Seizures. In: Kliegman RM, Stanton BF, Schor NF, St. Geme JW (eds.). *Nelson Textbook of Paediatrics*, 20th edition Philadelphia: Elsevier; 2016. p.2829.
2. Jones T, Jacobsen SJ. Childhood Febrile Seizures: Overview and Implications. *Int J Med Sci*2007; 4(2): 110-14.
3. Richard Sills. Iron-Deficiency Anaemia. . In: Kliegman RM, Stanton BF, Schor NF,

- St. Geme JW (eds.). *Nelson Textbook of Paediatrics*, 20th edition Philadelphia: Elsevier; 2016. P.2323
4. Hartfeld D. Iron deficiency is a public health problem in Canadian infants and children. *Paediatr Child Health*. 2010;15(6):347-50. PubMed PMID: 21731416; PubMed Central PMCID: PMC2921732.
 5. Idro R, Gwer S, Williams TN, Otieno T, Uyoga S, et al. (2010) Iron Deficiency and Acute Seizures: Results from Children Living in Rural Kenya and a MetaAnalysis. *PLoS ONE* 5(11): e14001. doi:10.1371/journal.pone.0014001
 6. Gupta S, Agarwal N, Maheshwari M: Iron Deficiency as a Risk Factor for Febrile Seizures – A case Control Study. *People's Journal of Scientific Research*.2015;8(2):37-40.
 7. Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron Deficiency as Risk factor for Simple Febrile Seizures- A case control study. *Indian Paediatrics*. 2012 Jan; 49(1): 17-19.
 8. Rajwanti KV, Praveen GD, Swati K, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. *Indian Pediatrics*. 2010;47:437-9.
 9. Waheed N, Butt MA. Iron status: is there a role in febrile seizures? *J Ayub Med Coll Abbottabad*. 2012 Jul-Dec;24(3-4):128-30. PMID: 24669632
 10. Heydarian F, Vatankhah H. The role of anaemia in first simple febrile seizure in children aged 6 months to 5 years old. *Neurosciences (Riyadh)*. 2012 Jul; 17(3):226-9.
 11. Yousefichaijan P, Eghbali A, Rafeie M, Sharafkhah M, Zolfi M, Firouzifar M. The relationship between iron deficiency anaemia and simple febrile convulsion in children. *J PediatrNeurosci*. 2014 May-Aug; 9(2): 110–114. doi: 10.4103/1817-1745.139276. PubMed ID:25250062
 12. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does Iron Deficiency raise the seizure threshold? *J Child Neurol*.1995; 10(2):105-109
 13. Daoud A S, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron Status: A Possible Risk Factor for the First Febrile Seizure. *Epilepsia*. 2002 Jul; 43(7):740-3. PMID: 12102677
 14. Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anaemia and febrile seizure in children. *Med Glas (Zenica)*. 2012 Aug; 9(2):239-42.
 15. Vestergaard M, Obel C, Henriksen TB, Christensen J, Madsen KM, Ostergaard JR, Olsen J. The Danish National Hospital Register is a valuable study base for epidemiologic research in febrile seizures. *J ClinEpidemiol*.2006; 59(1): 61-6.
 16. Berg A.T., Shinnar S., Shaprio E.D., et al.: Risk factors for a first febrile seizure: A matched case-control study. *Epilepsia*, 1995; 36: 334-41.
 17. 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 (7053):343.
 18. Fallah R, Trinandazi B, Ferdoian F, Fadavi N. Iron deficiency and iron deficiency anaemia in children with first attack of seizures and in healthy control group; a comparative study. *Iran J Child Neurol* 2014; 8(3):18–23.