International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 1; Issue 5; December 2015; Page No. 35-39

Iron deficiency anemia and vulnerabilities to febrile seizure among Sudanese children

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Abstract
Febrile seizures are the most common seizure disorder in childhood, affecting 2-5% of children. Research of the association between iron deficiency and seizures has shown conflicting results. No previous study had been conducted in Sudan. So the present study was carried out to compare the IDA rates in FS children with those in the febrile children without seizure. A total of 148 patients fulfilled the study criteria of febrile seizure or any febrile illness. These were divided into two groups with children having febrile seizures comprised the cases while those having only febrile illness with no seizures comprised the controls. Both groups had equal number of children matched for age and gender. Workup for seizures and iron deficiency anemia was done and data was analyzed using SPSS version 10. At P≤0.05 body temperature were statically significant P value 0.001 with mean (39.07±0.60, 38.70±0.59) for case and control. Iron deficiency anemia found in 62.7% of the cases and 34.2% of the control group OR=3.2. Mean level of HB, MCV, MCH, SF, SI were lower in cases than in controls with significant Odd Ratio and Relative Risk. Hb (9.98±1.85) and (11.14±1.81) OR 3.26 RR 1.4.MCV (70.06±8.10) and (75.94±8.88) OR3.2 RR1.77. MCH (22.74±3.67) and (25.41±4.95) OR 3.41 RR1.83.SF (16.75±13.89) and (19.76±10.45) OR 2.73 RR 1.63.SI (38.97±32.92) and (52.39±30.40) OR 3.2 RR 1.77.TIBC (4.17±8.66) and (3.69±9.00) OR 0.31 RR 0.56 in cases and controls respectively. Lower hematological indices were found in anemic patients with simple seizure than those who are anemic with complex seizure with differences statistically significant in MCV, RDW, SF, SI and TIBC. HB 28 (52.8%) and 25(47.2%) P= 0.221. MCV 27(57.4%) and 20(42.6%) P=0.001. MCH 27 (56.2%) and 21(43.8%) P=0.064.SF 25(56.8%) and 19 (43.2%) P=0.012. SI 27(57.4%) and 20 (42.6%) P=0.001.TIBC 27(57.4%) and 20 (42.6%) P=0.001 for participants with simple and complex seizure respectively. Generalized seizure was found in 43.7% of patients with iron deficiency compared to 56.4% of control group. Partial seizure 51.7% and 48.3% Simple seizure 57.4%and 42.3% Complex seizure 42.9% and 57.1%. Duration of seizure in minutes (7.52 ± 3.77) and (5.17 ± 2.95) for patients with iron deficiency and those without iron deficiency respectively. Iron deficiency anemia is more in children with simple than complex seizure with lower hematological indices in cases with simple than with complex seizures with statistically significant MCV, SF, SI and TIBC. Children with risk factors of Iron Deficiency Anemia should be identified, screened and treated.

Keywords: Iron deficiency anemia, febrile seizure, Sudanese children

Introduction

Febrile seizure was defined as seizures associated with fever (temperature ≥38 °C) in the absence of central nervous system infection or acute electrolyte imbalance in a young child (Komi, *et al.,* 2015 [16] & Patterson, *et al*., 2013 [21]) that occurs in infants and children 6 through 60 months of age." It is classified as simple or complex (Adhikari, *et al.,* 2013 & Patterson, *et al*., 2013 [21]). While, the National Institute of Health defined as "an event in infancy or childhood usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause for the seizure (Dawn, *et al*., 2009 [9] & Azhar, *et al*., 2002 [2]). It is the most common convulsive disorder in children, which affects 2-5% (Ostergaard, 2009) [31]. Although FS is benign and rarely leads to brain damage, it causes emotional, physical, and mental damages, which are stressful for parents, and affects families' quality of life (Jones, *et al*., 2007 & Flury, *et al.,* 2001) [33]. The risk of subsequent epilepsy following simple febrile seizures is no greater than that for the general population (Camfield, *et al*., 2002) [7]. The etiology is complex with strong evidence for a heterogeneous genetic predisposition interacting with fever of any cause, with certain viral infections having a greater effect. A large amount of literature has established that febrile seizures have no long-term consequences on cognition or behavior. Unfortunately, about 40% of children with a first febrile seizure will have a recurrence. The strongest predictor of recurrence is age <14-16 months at the time of the first febrile seizure. Epilepsy follows febrile seizures in ~3% cases, with the concepts of simple and complex febrile seizures providing relatively weak prediction. Very prolonged febrile seizures may lead to mesial temporal sclerosis and temporal lobe epilepsy although the degree of risk remains uncertain (Camfield, and Camfield, 2015) [6]. In addition to genetic predisposition, febrile seizures are generally thought to be induced by elemental changes such as iron deficiency (Derakhshanfar, *et al*., 2012) [11].

Iron has been found to act as a cofactor in a number of enzymatic reactions at the cellular level, and it effects neurotransmitter production and function, hormone function, and DNA replication (Beard, 2001 [4] & Ghosh, 2006 [27]). Monoamine and aldehyde oxidases are reduced in iron-deficiency anemia, which is common during the second and third years of life, and has variably been associated with behavioral and developmental disturbances (Azhar, *et al*., 2002) [2]. The most clinically obvious consequence of Iron deficiency is anemia, but virtually every organ system is affected, resulting in change in cognitive and behavioral performance, impaired physical growth, and impairment of immune function (Ghosh, 2006) [27]. Neurological problems in young children, including developmental delay, stroke, breath-holding spells, and pseudotumorcerebri (Yager, 2002) [29]. Several lines of evidence led to the hypothesis that iron may have a role in the onset of a convulsion (Feteme, *et al*., 2014 & Poudel, *et al.,* 2013 [22]).

Iron deficiency (ID) is present in most of the pre-school children and pregnant women in developing countries and at least 30–40% of the children aged between 0 and 4 years and 48% of the children aged between 5 and 14 years are anemic (Nihal, *et al*., 2015 & WHO, 2001) [20]. Some recent studies have reported that iron-deficiency anemia (IDA) could be a risk factor for FS, because the latter is more common in children under two years of age and IDA is also common in children of the same age (Feteme, *et al*., 2014). Four small studies have been published investigating a possible relationship between ID and febrile seizures, with varying results. Three of the studies found that ID was associated with febrile seizures whereas the fourth found that those with ID were less likely to have a febrile seizure. These contrary results include small patient numbers and different diagnostic criteria for the diagnosis of ID in the setting of a febrile illness (Dawn, *et al*., 2009) [9]. Since the relationship between IDA and FS is not yet determined, chance or other unknown factors can be considered as causes (Bidabadi, and Mashouf, 2009) [5]. Considering the above controversial results and since no study has been conducted in Khartoum state on the mentioned relationship, the present study was carried out to compare the IDA rates in FS children with those in the febrile children without seizure.

Patients and Methods

In this prospective case control study 148 children with febrile seizure who were admitted to GafarIbnOuf pediatric specialized Hospital and Omdurman Emergency pediatric Hospital during the period from Jan- March 2015 were considered for inclusion for this study. Children who were aged six months to six years presented with simple febrile seizures (FS).

FS is classified as simple and complex. Simple febrile seizures are single, brief, and generalized or single seizure of <15 minutes duration in the presence of fever without focal feature and those with febrile illness without seizures. Complex FS is defined as a seizure lasting more than 15 minutes and recurring within 24 hours or focal seizure that includes more than one seizure. The peak age of febrile seizures is 18 months, with recurrent episodes occurring in one third of patients (Shinnar, and Glauser, 2002 [30] & Azhar, *et al.,* 2002 [2] & Fallah, *et al*., 2014 [13] & Daoud, *et al*., 2002 [2]).

The control group consists 73 of children with minor febrile illness without seizures.75 children with febrile seizures were defined as (case). Age of cases and controls were (24.36±17.01) and (25.19±17.97) months. Consanguinity was found in 48(55.5%) and 38(44.2%) in cases and controls respectively. Children with seizure due to Central Nervous System infection, metabolic cause, with afebrile seizure, on recent iron therapy, or have other causes of anemia the presence of any chronic systemic diseases and having neurodevelopmental delay, previous afebrile seizure, or acute central nervous system infection (meningitis, encephalitis) were excluded. Parents of children in the study were told briefly about the importance, the aims of this study and the procedures that will be done for their children such as clinical examination and blood samples and a written consent was obtained from all of them. The ethics committee at two hospitals approved the study.

Blood investigations were done to diagnose iron-deficiency in both cases and controls. Iron deficiency was diagnosed as per WHO criteria (hemoglobin value <11 g%, red cell distribution width of >15% and serum ferritin value <12 ng/mL). Other explanatory variables, which can be the potential confounders were also included in the study and considered for analysis.

Body weight, height, temperature were measured. Blood samples were collected from all participants for hemoglobin (HB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), serum ferritin (SF), serum iron (SI), and total iron binding capacity (TIBC). HB, MCV, MCH, MCHC, RDW were part of a complete blood count done on the lab of each hospital. SF, SI, TIBC were done on the referral lab at Khartoum Teaching Hospitals'. SF level was measured by using the IMx Ferritin assay. In micro particle enzyme immunoassay (MEIA) for quantitative determination of human SF. SI, and TIBC were measured by using analyzer, spectrophotometer (BT5- 305).

The data was processed statistically by using statistical package for social science (SPSS). Results were expressed in frequency and percentage, OR and RR. P. value < 0.05 was considered to indicate significant.

Results

At P≤0.05 body temperature were statically significant P value 0.001 with mean (39.07±0.60, 38.70±0.59) for case and control. While, body weight and height showed no variances between both groups P values 0.233 and 0.702 with Mean (10.42±3.09, 11.03±3.10) and (82.96±1.18, 83.72±1.2) respectively (Table 1). Iron deficiency anemia found in 47(62.7%) of the cases and 25(34.2%) of the control group OR=3.2. Mean level of HB, MCV, MCH, SF, SI were lower in cases than in controls with significant Odd Ratio and Relative Risk. Hb (9.98±1.85) and (11.14±1.81) OR 3.26 RR 1.4.MCV (70.06±8.10) and (75.94±8.88) OR3.2 RR1.77. MCH (22.74±3.67) and (25.41±4.95) OR 3.41 RR1.83.SF (16.75±13.89) and (19.76±10.45) OR 2.73 RR 1.63.SI (38.97±32.92) and (52.39±30.40) OR 3.2 RR 1.77.TIBC (4.17±8.66) and (3.69±9.00) OR 0.31 RR 0.56 in cases and controls respectively Table (2)

Table 1: Body Temperature, Weight and Height among study participants

	Case Mean± SD	Control Mean± SD	P. Value
Temperature °C	39.07±0.60	38.70±0.59	0.001
Weight	10.42±3.09	11.03±3.10	0.233
Height	82.96±1.18	83.72±1.2	0.702

Table 2: Comparison of Frequency of Iron Deficiency and Iron Deficiency Anemia among study population

	Case Mean±SD	Control Mean ±SD	OR	RR
Hb *g/dl*	9.94±1.85	11.14±1.81	3.26	1.4
MCV fl	70.06±8.10	75.94±8.88	3.22	1.77
MCH pg	22.74±3.67	25.41±4.06	3.41	1.83
MCHC g/dl	28.54±4.78	31.12±4.95	2.73	1.63
RDW %	16.22±3.61	13.94±3.67	0.31	0.56
Platelet	424.57±136.21	363.31±91.84	0.24	0.54
SF ng/ml	16.57±13.84	19.76±10.45	2.73	1.63
SI mcg/dl	38.97±32.92	52.39±30.40	3.22	1.77
TIBC mcg/dl	4.17±8.66	3.69±9.00	0.31	0.56

Distribution of IDA among patients with Simple and Complex Seizures

Lower hematological indices were found in anemic patients with simple seizure than those who are anemic with complex seizure with differences statistically significant in MCV, RDW, SF, SI and TIBC. HB 28 (52.8%) and 25(47.2%) P= 0.221.MCV 27(57.4%) and 20(42.6%) P=0.001. MCH 27 (56.2%) and 21(43.8%) P=0.064.SF 25(56.8%) and 19 (43.2%) P=0.012. SI 27(57.4%) and 20 (42.6%) P=0.001.TIBC 27(57.4%) and 20 (42.6%) P=0.001forparticipants with simple and complex seizure respectively Table (3).

Generalized seizure was found in 31 (43.7%) of patients with iron deficiency compared to 40 (56.4%) P= 0.46. Partial seizure 15(51.7%) and14 (48.3%) P 0.93. Simple seizure 27(57.4%) and 24(42.3%) P=0.001. Complex seizure 16(42.9%) and 12(57.1%) P=0.001. Duration of seizure in minutes (7.52 ± 3.77) and (5.17 ± 2.95) P=0.01 for patients with iron deficiency and those without iron deficiency respectively Table (4).

Table 3: Incidence of Iron deficiency anemia between simple and complex Seizure

	Simple seizure				Complex seizure				Pvalue
	Anemia		No anemia		Anemia		No anemia		
	NO	%	NO	%	NO	%	NO	%	
Hb g/dl	28	52.8	15	68.2	25	47.2	7	31.8	0.221
MCV fl	27	57.4	16	57.1	20	42.6	12	42.9	0.001
MCHpg	27	56.2	16	59.3	21	43.8	11	40.7	0.064
MCHCg/dl	26	59.1	17	59.8	18	40.9	14	45.2	0.134
RDW %	27	57.4	16	57.1	20	42.6	12	42.9	0.001
Platelet	23	62.2	20	52.6	14	37.8	18	47.4	0.696
SF ng/ml	25	56.8	18	58.1	19	43.2	13	41.9	0.012
SI mcg/dl	27	57.4	16	57.1	20	42.6	12	42.9	0.001
TIBC mcg/dl	27	57.4	16	57.1	20	42.6	12	42.9	0.001

Table 4: Comparison of Type and Duration of Seizure in Children with and without Iron Deficiency

Group		With iron deficiency	Without iron deficiency	P. value
Type of seizure	Generalized	31 (43.7%)	40 (56.4%)	0.46
	Partial	15(51.7%)	14 (48.3%)	0.93
	Simple	27(57.4%)	24(42.3%)	0.001
	Complex	16(42.9%)	12(57.1%)	0.001
Duration of seizure in minute (mean ±SD)		7.52 ± 3.77	5.17 ± 2.95	0.01

Discussion

Iron deficiency may develop in the absence of anemia and the tissues may be affected from this condition. Iron deficiency is manifested in different stages. If iron requirement is below intake, iron stores are reduced primarily. After the iron stores are reduced, hemoglobin levels may stay normal for a while which means that iron deficiency is observed in the absence of anemia. At this time, only plasma ferritin level and plasma transferrin saturation are reduced. Negative iron balance which continues after iron stores are exhausted is manifested with decreased hemoglobin. Conclusively, reduced body iron stores has been defined as Iron deficiency and worsening of this condition and development of anemia is defined as Iron deficiency anemia (Nihal, 2015) [20]

The Association between febrile seizure and Iron Deficiency Anemia has been described in the last decade with conflicting results. This is the first study to find out this Association in Sudan.

Significant differences between case and control group in Hb Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration. (MCHC) Serum Ferritin (SF) and Serum Iron (SI) While, Red Distribution width (RDW) Platelet Total Iron Binding Capacity (TIBC) were significantly higher among case group, with prevalence of iron deficiency anemia obviously emerged in case group this could be reflecting their nutritional status and their depending on breast feeding and unfortified cow milk, and their need additional source of iron, like complementary food or iron supplement. Overlap of the peak age between FS and IDA suggesting an association between them. In this study, the mean plasma ferritin concentration in the healthy group was lower than that in control group, but there was no significant difference. In studies by Daoud *et al.* (2002) [2], Rehman and Billoo, (2005) [28] and Moeman *et al.,* (2010) & Fallah, *et al*., (2014) [13] the mean plasma ferritin level in the febrile convulsion group was significantly lower than the control group, which led them to the conclusion that it can demonstrate the role of IDA in the incidence of febrile seizure It is indeed evident that ferritin is an acute phase reactive substance in nonspecific response to any febrile disease. This can be confirmed by the higher plasma ferritin levels in the patient groups than in the healthy group, and fever can cause the lack of difference in ferritin levels between the two patient groups. In any case, the use of plasma ferritin cannot simply be an efficient criterion for the diagnosis of ID in febrile children feteme, *et al.,* (2014). In contrast, study done, by Bidabadi, and Mashouf (2006) who studied 200 cases and controls. IDA was less frequent in cases than in controls. The total amount of SF, SI were significantly higher and TIBC was significantly lower among cases than controls. The amount of HB, MCV, MCH, MCHC were also higher in cases than control and the

differences were not statistically significant.31.85% of cases had iron deficiency anemia whereas, 19.6% of controls were found to have iron deficiency anemia as revealed by low levels of haemoglobin level, serum ferritin level. Mean Corpuscular Haemoglobin Concentration and Mean Corpuscular Volume Sherjil, *et al,* (2010) & Derakhshanfar, *et al.,* 2012 [11] reported. This study revealed significant inference in body temperature which is high among case group febrile with seizure compared to those who ha febrile illness without seizure. On the other hand both groups showed high incidence of 24hrs fever attack. Increasing peak temperature has been reported to increase the risk of FS., Daoud *et al*, (2005) found no marked differences in mean peak of temperature on presentation 38.9 and 38.6. Nor in the mean peak temperature on admission between the cases and the controls in (Daoud, *et al.,* 2002) Another study done by Bidabadi, *et al,* (2009) [5] showed the mean of core temperature is significantly higher in cases compared with controls. The majority of children have their febrile seizures on the first day of illness and in some cases, it is the first manifestation that the child is ill. The degree of fever associated with febrile convulsions is variable, and approximately 25 percent of events occur when the temperature is between 38 ºC and 39 ºC. Also this parallel that obtained by Derakhshanfar, *et al.,* (2012) [11] the mean of temperature peak on admission was significantly higher in the febrile convulsion group than controls. The results of this study suggest that the risk of febrile seizure occurrence in anemic children is less common as compared to non-anemic ones.

IDA was more prevalent among cases with febrile seizure (62.7%) as compared to the controls (34.2%) OR 3.2. We found iron deficiency anemia a modifiable risk factor for febrile seizure among Sudanese children. IDA was more in patients with simple febrile seizure compared to complex seizure with statistically significant differences The total amount of HB, MCV, MCH and SF were lower in simple than in complex seizure differences statistically significant for MCV, RDW, SF, SI and TIBC. In contrast to the study done by Daoud. *et al.* (2010) who found lower mean level of HB, MCV and SF in children with complex than with simple febrile seizure. The differences were statistically significant for SF and MCH. Iron deficiency was found as a significant risk factor for simple febrile seizures in the study done by Pisacane, *et al.* among children of the same age group, similar results were noted and the odds ratio was 3.3 (95% CI of 1.7-6.5). Iron status was measured by hemoglobin, MCV and serum iron in that study. Plasma ferritin level was significantly lower in cases as compared to controls suggesting that iron deficient children are more prone to febrile seizures. (Naveed-ur-Rehman, and Billoo, 2005) [19]. This study in concordance with Study done by Hartified *et al.* (2009) who found children with febrile seizures were nearly twice to be iron deficient compared to those with febrile illness alone. LeelaKumari, *et al*. (2011). Highly significant associationfound between IDA and febrile seizures. Naveed-Ur-Rehman, *et al,* (2001) & Daoud *et al,* (2000) &Vaswani, *et al.* (2009) & Piscane, *et al,* (1996)

This study showed that higher prevalence of simple seizure compared to complex seizure with 93.33% had generalized seizure compared to 6.67% had focal seizure. Highly significant association was found between iron deficiency and simple febrile seizures. So Iron deficiency is a significant risk factor for simple febrile seizures in children. This is similar to that obtained by Kumari, *et al.,* (2012) [17] &. Shrestha, *et al.,* (2014) [24] & Komi, *et al.,* (2015) [16] Simple febrile seizure and complex febrile seizure were observed in 76.7% and 23.3% of patients respectively. Majority of children had generalized tonic clonic seizure followed by tonic seizures. Most of children who developed first episode of seizure were below 24 months of age with the mean age of 20.7 (±12.1) months. Overall 33% of patients developed recurrence of febrile seizure and first episode of febrile seizure at age one year or below was associated with the seizure recurrence. Febrile seizure was observed predominantly in children below age of two years and simple febrile seizure was the commonest variety.

Conclusion

A febrile seizure is dominated by generalized tonic-clonic seizures. Iron deficiency anemia is more prevalent in children with simple febrile seizure than in children with febrile illness without seizure. The peak mean of body temperature at presentation is statistically significant between the cases and controls. An interventional prospective cohort study should be done for those children presenting with febrile seizure.

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