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RESEARCH ARTICLE

STUDYING THE RELATION BETWEEN IRON DEFICIENCY ANEMIA & FEBRILE SEIZURES.

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Abstract

Objective:The aim of this study was to evaluate iron deficiency anemia as a risk factor for febrile seizures in pediatrics.

Background: Febrile seizures are a form of acute symptomatic seizures. Being one of the most important pediatric health problems in developing and developed countries. Also, iron deficiency anemia is a major health problem in young children.

Methods:This study was conducted on 80 infants and children aged 6 months to 6 years old. They were divided into two groups: group (A) it included 50 infants and children suffering from febrile seizures with mean age 23.6±15.84; (6-72) months. Group (B): it included 30 infants and children suffering from fever without any neurological problems, with mean age 16.89±13.15; (6-60) months. 25 infants were from rural areas and 25 infants were from urban areas in group (A); while 18 infants were from rural areas and 12 infants were from urban areas in group (B). All enrolled children were subjected to: history taking, clinical examination. Complete blood count was done with measures of serum iron, serum ferritin levels , total iron binding capacity and Transferrin saturation.

Results: Iron deficiency anemia was present in 72% of group A (36) and 50% of group B(15). There was statistical significant difference between studied groups regarding the presence of iron deficiency anemia with OR of 2.57 95% CI (0.90-7.34). There was negative significant correlation between temperature and Serum ferritin in Group A, positive significant correlation between temperature and TIBC in Group A and negative significant correlation between temperature and Transferrin saturation in both Group A and Group B.

Conclusion: Children with iron deficiency anemia were found to be more susceptible to have febrile convulsions compared to non-anemic children.

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Introduction:-

Seizures are one of the most common neurological symptoms that occur in infancy and childhood. They represent many different disorders with many different causes. Neonatal seizures occur in ~1.5% of neonates, febrile seizures in 2-4% of young children, and epilepsy in up to 1% of children and adolescents. [1].

Febrile convulsion is the most common convulsive disorder in children which occurs in 2-5 % of them. This seizure happens in children aged between 6 months and 5 years, with a core temperature higher than 38 ˚C without a central nervous system infection or an acute brain insult. [2]

Iron deficiency is one of the most common nutrition-related problems in the world, with an appraised 5 billion people (including the human infants especially between 6 and 24 months of age) so afflicted. In developing countries, 46–66% of the children under the age of four are anemic, half having iron deficiency anemia. [3]

Iron deficiency anemia and febrile seizures are two common diseases in children worldwide as well as in our country. Iron insufficiency is known to cause neurological symptoms like behavioral changes, poor attention span and learning deficits in children. Therefore, it may also be associated with other neurological disturbances like febrile seizures in children. [4]

We aimed to evaluate iron deficiency anemia as a risk factor for febrile convulsions in infants and children.

Patients and Methods:-

This was a cross-sectional study that conducted at Pediatrics department, Benha University hospitals and Benha Teaching hospital. Two groups of infants and children were enrolled; **group A:**who developed febrile seizures, it included 50 infants and children (6-72) months with mean age 23.6±15.84 months ,there were 29 males (58.0 %) and 21 females (42.0 %);**Group (B):**admitted with febrile illness including respiratory tract infections or acute gastroenteritis but without seizures, it included 30 infants and children without any neurological problems, (6-60) months with mean age 16.89±13.15 months and there were 18 males (60.0 %) and 12 females (40.0 %). The exclusion criteria were children younger than 6 months or older than 5 years, children with any CNS infection or any other defined cause of seizure , children with disturbed conscious level and children receiving iron supplement. The study gained the approval of local ethical committee of the Pediatric Department, Benha University and the Pediatric Department, Benha teaching hospital. Informed written consent was obtained from the parents or caregivers of enrolled children after explanation of the study.

Methods:-

Enrolled children were subjected to full history. Clinical examination (both general and neurological examinations) searching for the cause of febrile illness, clinical assessment of conscious level and type of seizure. Laboratory investigations were done for all children by taking venous blood samples (5 ml) that were obtained under complete aseptic technique. Each sample was divided into two sterile tubes: one tube (2 ml) was put in an EDTA tube for complete blood count analyzed by Sysmex Kx-21N and peripheral blood smear (PBS) [Hemoglobin level < 11 g% was considered low [5].The other tube (3 ml) was put in plain vacutainers for serum iron,total iron binding capacity (TIBC) that were detected using Biosystem BTS-350 . Reference ranges for serum iron were 40–100 μg/dl for infants and 50–120 μg/dl for children. For TIBC, reference ranges were 100–140 μg/dl for infants and 250–400 μg/dl for children [6].Serum ferritin was detected using Biosystem BTS- 350: (Spectrum Diagnostic Ferritin Turbi Latex).Transferrin saturation was calculated using the following formula: transferrin saturation = iron level/TIBC×100 (normal value = 20–45%) for [7] C-reactive protein more than 6 mg/dl was considered positive. In group A, Considering the fact that infection can affect iron panel studies by increasing serum ferritin level (usually by more than 50 μg/l if no iron deficiency) and decreasing serum iron level and TIBC. The diagnosis of IDA in Febrile seizure patients was made when at least three of the below parameters were present :(1) Hypochromia and microcytosis saw in blood smear (2) Low mean corpuscular volume (MCV) (specificity around 96%) (not affected by infections).(3) Red cell distribution width greater than 14.5(sensitivity of 92.1% and specificity of 90.9%).(4) Mentzer index greater than 13.5 (with around85% specificity and sensitivity).The Mentzer index was calculated using the following formula: Mentzer index = mean corpuscular volume/red blood cell count.(5) Transferrin saturation less than 10% (with a specificity of 85% if below 15% and sensitivity around 80%)[8]. In group B IDA was diagnosed when serum ferritin was less than 10 ng/ml [7], or when serum iron was lower than 50 μg/dl and serum TIBC was higher than 400 μg/dl [6].

Statistical analysis:-

The collected data were summarized in terms of mean ± Standard Deviation (SD) and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the Chi-square test (χ^2) and Fisher's Exact Test (FET) to compare proportions as appropriate and Odd Ratio (OR) and 95% Confidence Interval (95% CI) were estimated. The Pearson correlation coefficient (r) was used test for the correlation between estimated parameters. Receiver Operator Characteristic (ROC) analysis was carried out for potential diagnostic variables and the Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and the Area Under the Curve (AUC) were estimated. The corresponding P-values were obtained. A P-value < 0.05 was considered statistically significant (S), a P-value < 0.001 was considered statistically highly significant (HS), while a P-value > 0.05 was considered statistically non-significant. The statistical analysis was conducted using STATA/SE 11.2 for Windows (STATA Corporation, College Station, Texas).

Results:-

Table (1):- Comparison between Group A and Group B: age, sex, residence, Family history, Temperature, Seizure characters, CNS infection and Iron supplementation:-

Variable		**Group A (No.=50)**		**Group B (No.=30)**		**Test**	**P**
		No.	**%**	**No.**	**%**		
Age (months)	Mean ±SD; (range)	23.6±15.84; (6-72)		16.89±13.15; (6-60)		t= 1.95	0.054
Sex	Males	29	58.0	18	60.0	χ^2= 0.03	0.86
	Females	21	42.0	12	40.0		
Residence	Rural	25	50.0	18	60.0	χ^2= 0.75	0.38
	Urban	25	50.0	12	40.0		
Family history	Negative	17	34.0	30	100.0	χ^2= 33.70	<0.001 (HS)
	Positive	33	66.0	0	0.0		
Temp.	Mean ±SD; (range)	39.22±1.04; (38-42)		38.62±0.73; (38-40)		t= 2.79	0.007 (S)
Febrile convulsion characters	Atypical	14	28.0	-	-	-	-
	Typical	36	72.0	-	-		

Table (2):-Comparison between Group A and Group B regarding laboratory parameters (HB, RBCs count, MCV, MCH, MCHC, RDW-CV%, Serum iron, Serum ferritin, TIBC and Transferrin saturation).

Variable	**Group A (No.=50)**			**Group B (No.=30)**			**Test**	**P**
	Mean	**±SD**	**Range**	**Mean**	**±SD**	**Range**		
HB (g/dl)	9.34	1.85	6.1-13.5	10.42	1.03	8.5-12.6	t= 2.89	0.005 (S)
RBCs (million /ml)	3.72	0.83	2.1-5.8	4.34	0.45	3.71-5.29	t= 3.78	<0.001 (HS)
MCV(fL)	72.66	9.29	45.9-90	71.84	10.45	26.1-88.2	Z= 0.26	0.80
MCH(pg)	24.58	3.86	11-33	24.66	3.2	19-32.3	Z= 0.23	0.82
MCHC(g/dL)	29.75	4.01	22-36	32.54	1.17	29-35.1	t= 3.71	<0.001 (HS)
RDW-CV (% age)	18.18	5.01	11-30	14.9	2.79	11-20	t= 3.29	0.001 (S)
Serum iron (µg/dL)	39.21	23.53	11-110	113.47	35.0	57-176	t= 11.34	<0.001 (HS)
Serum ferritin(ng/mL)	38.72	39.14	1.2-157	102.87	46.22	45-200	t= 6.63	<0.001 (HS)
TIBC (µg/dL)	423.82	142.99	121-700	255.03	55.48	155-356	t= 6.18	<0.001 (HS)

Transferrin saturation (%)	11.63	10.47	2-36	46.4	16.44	16-85	t= 11.57	<0.001 (HS)

Table (3):-Comparison between Group A and Group B regarding presence of iron deficiency anemia(IDA).

IDA	**Group A (No.=50)**		**Group B (No.=30)**		**Test**	**P**	**OR (95% CI)**
	No.	**%**	**No.**	**%**			
IDA	36	72.0	15	50.0	χ^2= 3.93	0.048 (S)	2.57 (0.90-7.34)
Not IDA	14	28.0	15	50.0			

Table (4):-Correlation of hemoglobin and iron profile (iron level, ferretin, TIBC and transferrin saturation) with temperature in C.

Variable	**Group A (No.=50)**		**Group B (No.=30)**	
	Pearson correlation coefficient (r)	P	Pearson correlation coefficient (r)	P
HB (g/dl)	-0.15	0.29	-0.08	0.66
Serum iron (µg/dL)	0.05	0.75	-0.34	0.06
Serum ferritin (ng/mL)	-0.33	0.02 (S)	-0.19	0.30
TIBC (µg/dL)	0.35	0.01 (S)	0.32	0.08
Transferrin saturation (%)	-0.29	0.04 (S)	-0.42	0.02 (S)

Figure (1):- Roc curve (cut off) point for temperature as Sensitivity 82.0% & Specificity 50.0%.

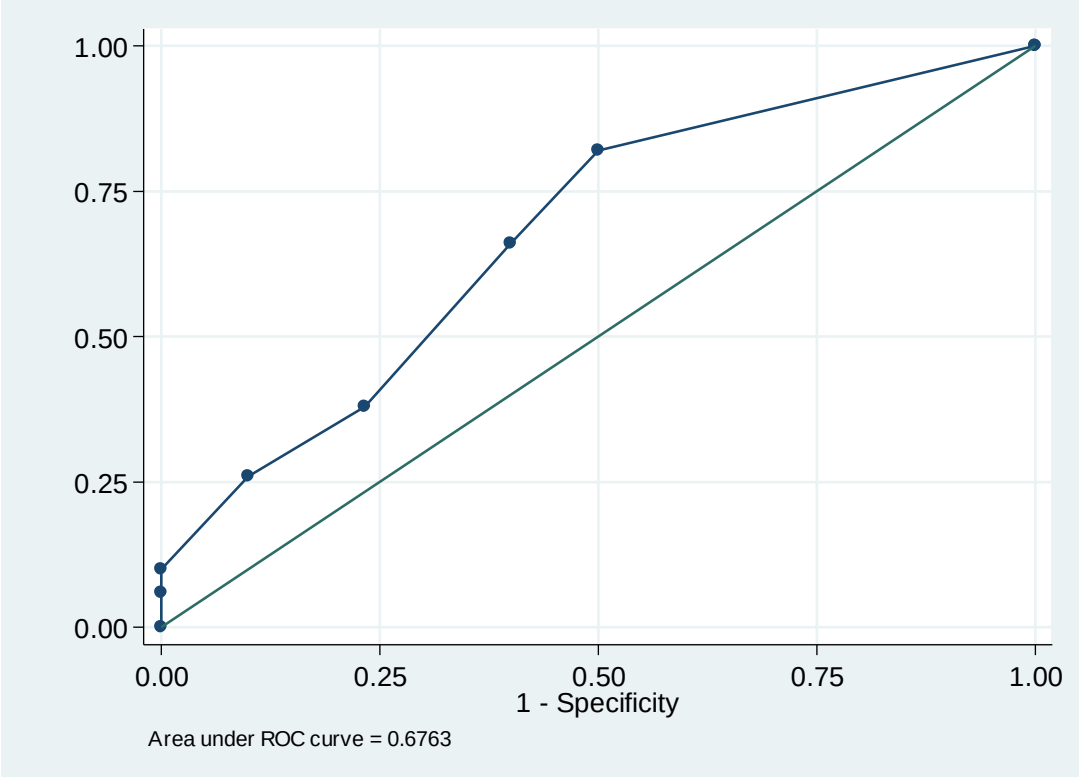


Figure (2):- Roc curve (cut off) point for TIBC as Sensitivity 84.0% & Specificity 83.33%**.**

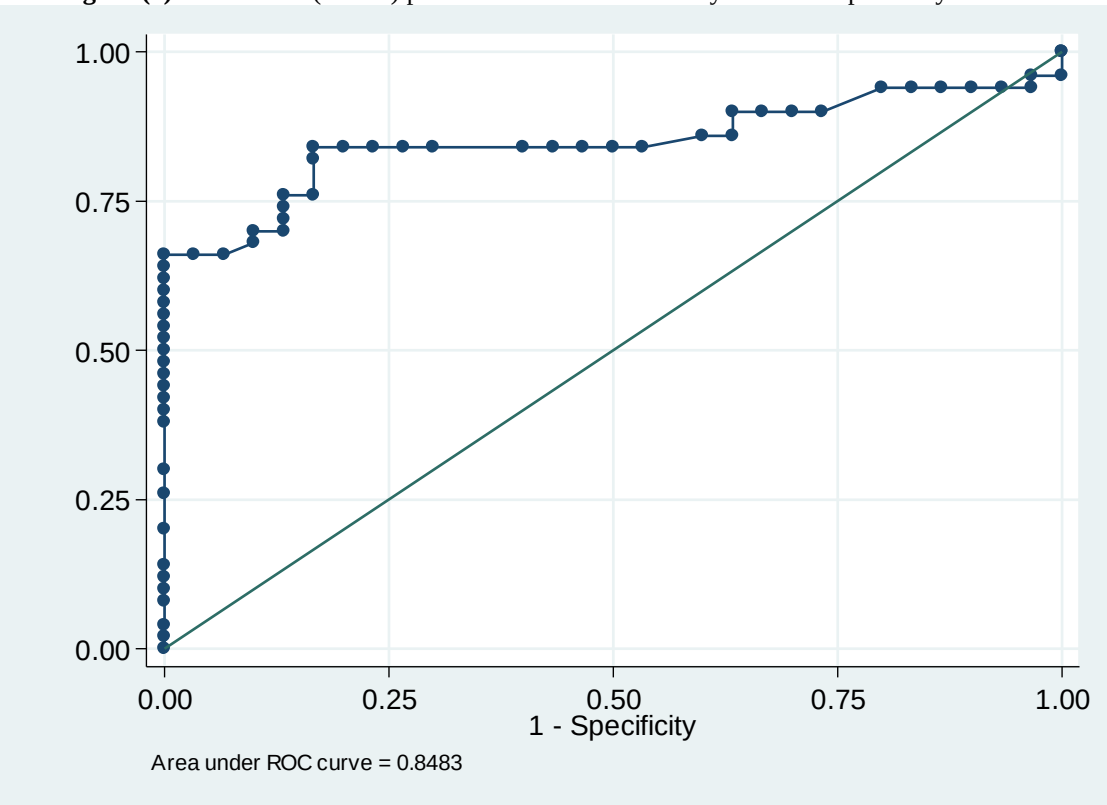


Figure (3):- Roc curve (cut off) point for serum ferritin as Sensitivity 72.0% & Specificity 100.0%**.**

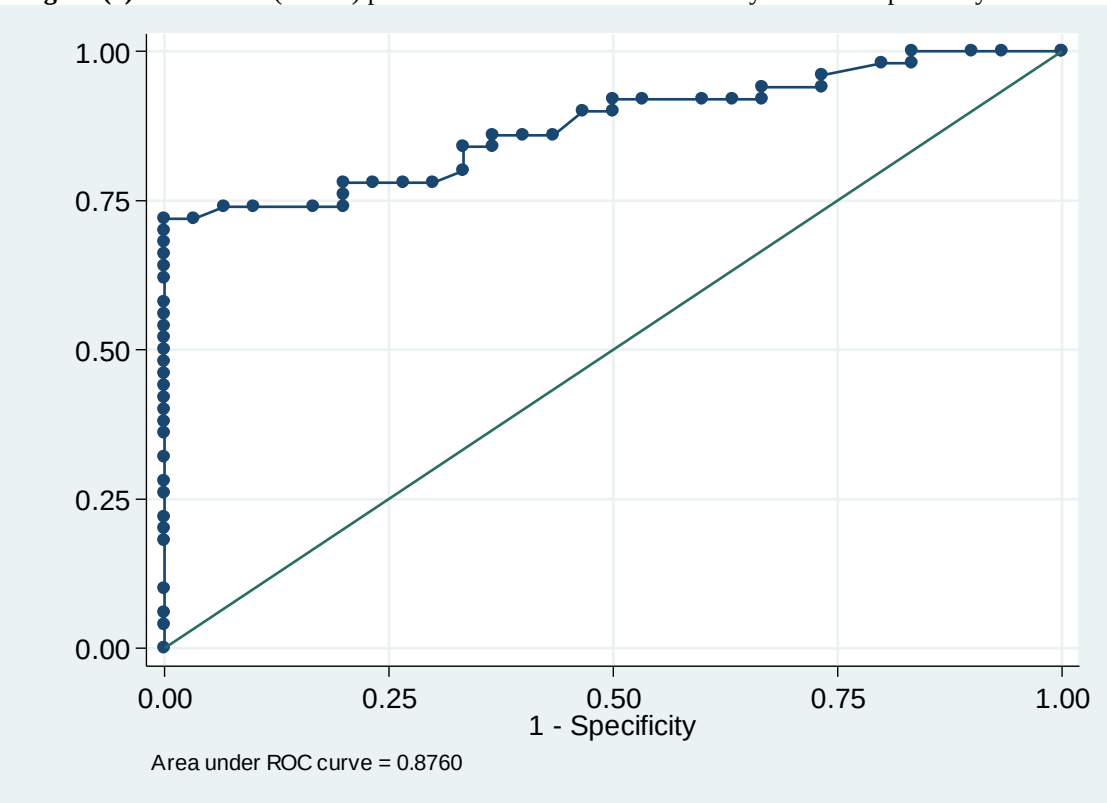
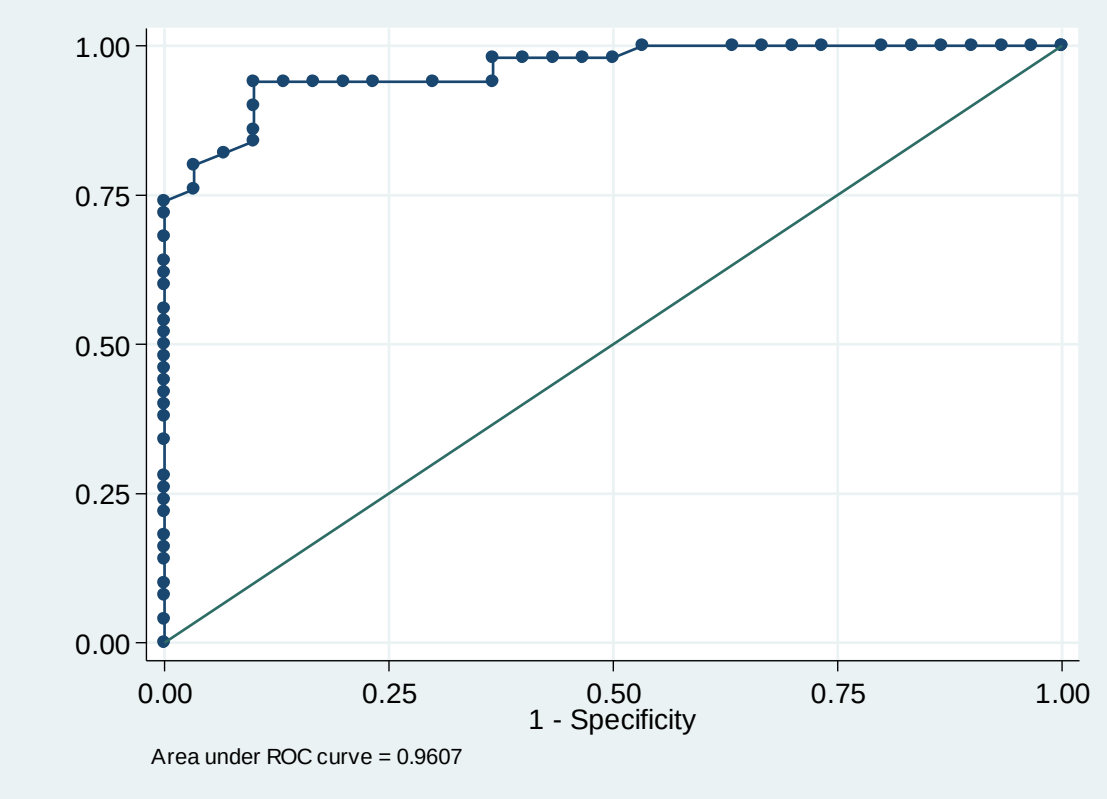


Figure (4):- Roc curve (cut off) point for serum ironas Sensitivity 90.0% & Specificity 90.0%.



Discussion:-

In our study regarding to iron profile among group A and group B there was highly statistical significant difference in laboratory parameters (serum iron, serum ferritin, TIBC and Transferrin saturation).

Regarding serum iron the mean level was 39.21±23.53 ;(11-110) µg/dL in group A and 113.47 ±35.0;(57-176) µg/dL in group B as P value was (<0.001), and there was high significant statistical difference between anemic group A and anemic group B as mean Serum iron was 31.63±16.83;(11-70.5) µg/dL in anemic group A and was 107.73±11-70.5;(57-167) µg/dL in anemic Group B**.** This agrees with the study of ***Akbayram et al. ,*** who indicated that in children with febrile convulsions, serum iron levels were lower than those in the control febrile group but without febrile convulsions[7]. Also, ***Gencer et al.,*** found a statistically significant difference (p=0.03) between the cases and control group at mean serum iron level [8]. ***Raju and Kumar*** , and ***Modaresi et al.,*** found that there was no significant difference in Serum Iron levels between cases and control groups as p value was (P>0.05)[9,10].

In our study there was highly statistical significant difference between group A and group B as the mean serum ferritin level in group A was 38.72±39.14 ;(1.2-157) ng/mL and in group B was 102.87±46.22;(45-200) ng/mL, either there was highly statistical significant difference between anemic group A and anemic group B as in anemic group A the mean serum ferritin level was 32.59±40.95;(1.2-157) ng/mL and in Anemic Group B was 110.07 ±47.3;(50-200). This agrees with study done by ***Vaswani et al.,*** as fifty children between 6 months to 6 years with first febrile seizure (Cases) and 50 children with febrile illness but without convulsions (Controls) were enrolled from the pediatric ward of a tertiary care hospital in India , 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)[11]**.** In the study of ***Chandrasekhar et al .,*** The mean and standard deviation value of serum ferritin showed that measurements were lower among cases compared to control and it was statistically significant as the mean serum ferritin level in the cases was 29.5 mcg/L, much lower than the values in the controls (53.5 mcg/L)[12]. ***Naseer et al.,*** also found that low serum ferritin, in cases than in controls; concluding that low body iron plays an important role in brain metabolism, can down regulate halting many substantial functions of brain and could lead to febrile seizures[13]. On the Contrary, ***Derakhshanfar et al.,*** and ***Bidabadi et al.,*** found that Serum plasma ferritin was significantly higher among the cases than in the controls. The

protective effect of iron deficiency against febrile convulsions was not confirmed. The study by reported that the amount of plasma ferritin was significantly higher among the cases with febrile convulsion than the controls[14,15].

According TIBC there was highly statistical significant difference between group A and group B as the mean level of TIBC as in group A was 491.81 ±142.99;(121-700) µg/dL and in group B the mean TIBC was 256.67 ±55.48;(155-356) µg/dL either in anemic patients in group A and group B there is highly statistical significant difference as the mean TIBC in anemic group A was 491.81±102.12;(200-700)µg/dL and in anemic group B was 256.67±58.76;(155-356) µg/dL and the mean Transferrin saturation in group A is 11.63 6.58±10.4;(72-36)% and in group B was 46.4±16.44;(16-85) showing highly significant difference between cases and controls ,either in anemic patients in group A and group B the mean Transferrin saturation in anemic group A was 6.58±3.82; (2-15) % and in anemic group B was 43.93±14.12; (16-71) with highly statistical significant difference between group A and group B. These results agree with the result in the study of ***Derakhshanfar et al.,*** who proved that the amount of TIBC was significantly lower among the cases with febrile convulsion than the control without febrile convulsions[14]. The results of ***Bidabadi et al.,*** study demonstrated the significantly lower amount TIBC among the cases than in the controls[15], While the mean TIBC 423.82% for group A and 255.03% for group B and mean Transferrin saturation 11.63% for group A and 46.4% for group B***. Miri-Aliabad et al.,*** study showed that the mean value of Transferrin saturation in patients with febrile seizure were lower than the control group, but the difference was not statistically significant[16].

Regarding the presence of iron deficiency anemia in group A and group B, anemia was diagnosed in 72.0% of group A while in group B anemia was diagnosed in 50.0% there was statistical significant difference between group A and group B presence of iron deficiency anemia with OR of 2.57, 95% CI (0.90-7.34) .These results agree with ***Singh et al.,*** who found that IDA was 1.9 times more common with patients of febrile convulsion this has also been reported by ***Idro et al.,*** [17,18]. In ***Raju and Kumar*** Iron deficiency was found to be a significant risk factor for Febrile seizures in children of age group 6 months to 5 Years with (P value 0.0008)[9]. ***Shah et al.,*** found a strong association of iron deficiency anemia as a risk factor for simple febrile seizure (p value<0.001), they have observed that iron deficiency anemia was present in 63.3% of patients with simple febrile seizures[19]. Similar association was observed previously in ***Khurram et al., Malla et al., Akbar et al ,. and Kumari et al., 2011*** they have similar observation that IDA was present in simple febrile patients[20,21,22,23]. On the other side ***Gencer et al.,*** found that the anemia ratio in the case group was consistent with that found in literature (26.3%), there was no statistically difference with that in the control group[8]. The incidence of iron deficiency anemia was significantly higher in controls compared with the cases as results of another study by ***Yousefichaijan et al.,*** showed 22.5% of the children in the febrile convulsion group suffered from anemia, while 34.0% of the children in the control group were afflicted with it (P <0.001)**[24].**

Diagnostic performance of Iron, ferritin, TIBC and temperature for predicting of febrile seizures. Cut off point for Serum iron, serum ferritin, TIBC and temperature were 70.5(µg/dL), 45 (ng/mL), 298.5(µg/dL) and 38.5% respectively. Sensitivity of Serum iron, serum ferritin, TIBC and temperature were 90.0%, 72.0%, 84.0% and 82.0% respectively .Specificity of Serum iron, serum ferritin, TIBC and temperature were 90.0%, 100.0%, 83.33% and 50.0% respectively. Positive predictive value (PPV) for Serum iron, serum ferritin, TIBC and temperature were 93.8%, 100.0%, 89.4% and73.2% respectively. Negative predictive value (NPV) of Serum iron, serum ferritin, TIBC and temperature were 84.4%, 68.2%, 75.8% and 62.5% respectively. Area under the curve (AUC) of Serum iron, serum ferritin, TIBC and temperature were 0.9607, 0.8760, 0.8483 and 0.6763 respectively and the correctly diagnosed of Serum iron, serum ferritin, TIBC and temperature were 90.0%, 82.5%, 83.75% and 70.0% respectively, so according to our results ferritin was with highest specificity for prediction of febrile convulsions. This was the same as in the study of ***Daoud et al.,*** who found that mean Ferritin levels were significantly less in study group with febrile seizures 29 ng/ml than in the controls 53.3ng/ml. They observed a significantly lower ferritin level in the first febrile seizures group than in the reference group proving that serum ferritin is a sensitive, specific and reliable measurement for determining iron deficiency at an early stage, and it may be the best indicator of total body iron status

Conclusion:-

Children with anemia and those with iron deficiency anemia were found to be more susceptible to have febrile when compared to children without iron deficiency anemia. Hence, early detection and timely correction of anemia may be helpful for prevention of febrile convulsions in children in this age group.

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